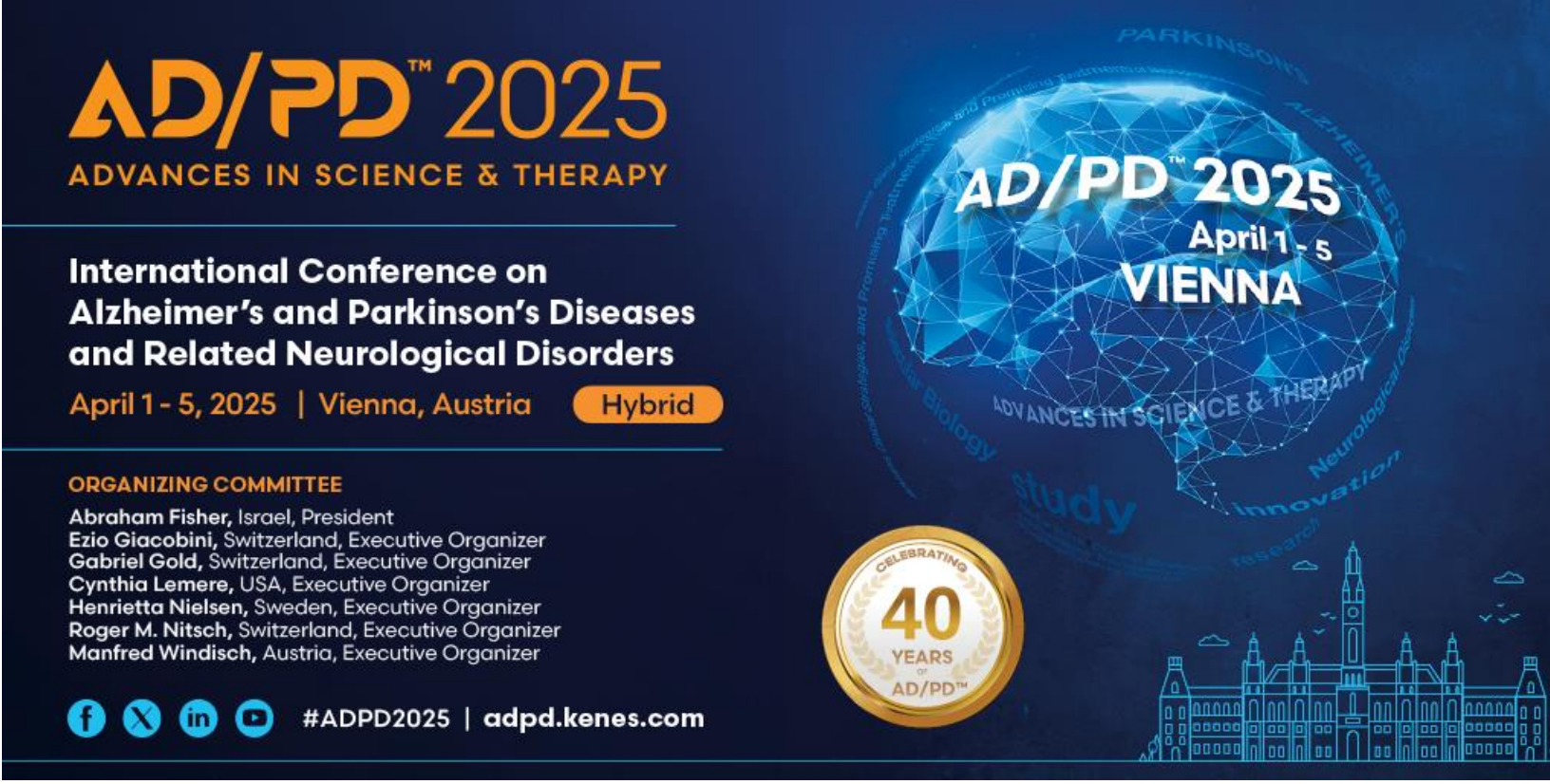

Posters on Board

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Those presenters who are registered for onsite participation are entitled to bring a poster on board to hang in the poster hall.

Poster on boards will be hung in shifts. The shift information and board number appear above each abstract title.

Shift 1: April 2-3

- **Mounting time** April 1, during welcome reception, April 2 from 08:00 will 10:00
- **Dismounting time** April 3 from 17:30 till 18:30

Shift 2: April 4-5

- **Mounting time** April 3 from 17:30 till 18:30, April 4 from 08:00 till 10:00
- **Dismounting time** April 5, from 17:30 till 18:30

To search for a specific abstract, please use CTRL+F to search by last name.

Posters on Board

Shift 01

2 – 3 April 2025

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SHIFT 01-002

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / ANIMAL MODELS: PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS
2-3 April 2025

OBSERVATION OF A-SYNUCLEIN PROPAGATION AND PATHOLOGICAL STRUCTURE IN HUMAN BRAIN ORGANOIDS BY ELECTRON MICROSCOPY

Yeojin Kim[1], Minkyo Jung[1], Min-Kyoung Shin[2,3], Junghyun Jo[2,3,4], Ji Young Mun[1]
[1]Korea Brain Research Institute, Neural Circuits Research Group, Daegu, Korea, Republic of, [2]Ajou University School of Medicine, Department Of Pharmacology, Suwon, Korea, Republic of, [3]Ajou University School of Medicine, Center For Convergence Research Of Neurological Disorders, Suwon, Korea, Republic of, [4]Ajou University School of Medicine, Department Of Biomedical Sciences, Suwon, Korea, Republic of

Aims: The aim of this study was to observe the connectivity of neuron and glia in brain organoids and to investigate the propagation and structural changes of α-synuclein.
Methods: The sample was first cut into 150 μm thick sections, followed by primary fixation, secondary fixation, and dehydration processes, and then was plasticized with infiltrating resin. The sample was cut into 100 nm sections and mounted on ITO-coated glass, and immunostaining was performed to confirm SNCA expression, and then SEM images were taken. Images were acquired using ZEISS atlas5 software for gemini 300 SEM. Image resolution in the x-y plane was 5nm/pixel.
Results: The interconnectivity between each cells was validated by SEM images, which also allowed the observation of α-synuclein within each cell by CLEM technique. Furthermore, the structures of Lewy bodies and alpha-synuclein aggregates showed different characteristics. (e.g., astrocytes, microglia, and oligodendrocytes).
Conclusions: In this study, we propose that CLEM technique can be used to analyze wide-area SEM images, resulting in a more detailed examination of the structural changes of α-synuclein and Lewy bodies.

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SHIFT 01-004

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / A-SYNUCLEIN
2-3 April 2025

DECOUPLING MOTOR DYSFUNCTION FROM A-SYNUCLEIN OLIGOMERS: THE ROLE OF AGING IN PD MICE

Verena Bopp[1], Jaehyun Lee[2], Patrick Oeckl[2], Julia Kühlwein[1], Veselin Grozdanov[1], Martin Kiechle[1], Benjamin Mayer[3], Bettina Möhrle[4], Hartmut Geiger[4], Karin Danzer[2]
[1]Universitätsklinikum Ulm, Department Of Neurology, Ulm, Germany, [2]German Center for Neurodegenerative Diseases (DZNE), Ulm, Germany, [3]Ulm University, Institute Of Epidemiology And Medical Biometry, Ulm, Germany, [4]Ulm University, Institute Of Molecular Medicine, Ulm, Germany

Aims: Aging is a major risk factor for Parkinson's disease (PD), yet the relationship between aging, PD symptoms and the role of α-synuclein (α-syn) oligomers is poorly understood. This study investigates whether aging increases vulnerability to PD or if prolonged exposure to α-syn oligomers drives disease progression, using a mouse model of α-syn oligomerization.
Methods: We used an inducible murine α-syn model of PD and turned on expression for either five months at different ages (short expression) or from birth on (long expression). Motor abilities were compared using Rotarod analysis and size-exclusion chromatography assessed α-syn oligomer load. To investigate underlying mechanisms, single-nucleus RNA sequencing (snRNA-seq) and protein degradation studies were performed.
Results: The findings revealed that motor decline in our α-syn PD model is primarily influenced by age rather than the duration of α-syn exposure. Despite similar oligomer levels at different ages, significant motor impairments were only seen in older mice. SnRNA-seq identified 35 distinct cell types and demonstrated early impairments in cAMP signaling pathways, with downstream effects on axonal transport and protein degradation becoming more pronounced later. Proteasomal dysfunction, validated experimentally, was identified as a key mechanism in PD progression. Aging and PD were found to share several dysfunctional pathways, including calcium signaling, proteasome activity and axon/actin function, with six central "Pathological Aging" genes (Calm3, Ubb, Actb, Dynll1, Tubb5 and Acp1) highlighting the intersection between aging and PD pathology.
Conclusions: α-syn oligomer formation precedes motor deficits, with age being the primary factor influencing severity. The lifelong presence of oligomers reduces cAMP signaling activity, triggering downstream dysfunctions that culminate in motor impairments. Six "Pathological Aging" genes were identified in PD and aging, as a link between aging and PD pathology.

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SHIFT 01-006

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
2-3 April 2025

PROFILING NEURAL PROTEIN DOPAMINYLATION WITH AGE AND IN PARKINSON'S DISEASE

Winnie Chen, Ian Maze
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Aims: Dopamine is historically believed to function exclusively via membrane bound receptors and plays critical roles in neuronal networks that regulate cognition, reward, and motor learning, among other processes. More recently, dopamine has been shown by our lab to serve a chemical donor for a novel class of post-translational modification, termed dopaminylation – i.e. the covalent modification of proteins by dopamine. Dopaminergic neuron firing and dopamine levels decrease with normal aging in the substantia nigra, and drastic declines in dopamine signaling have been linked to a range of age-related disorders, including Parkinson's Disease (PD). Given the importance of dopamine to both aging and PD, we aim to profile the dopaminylation landscape utilizing both mouse models and postmortem human brain tissues.
Methods: Here, we utilize a novel bioorthogonal tagging approach, which allows for enrichment of dopaminylated proteins, coupled with LC MS/MS to profile alterations of the protein "dopaminylome" with age and in PD across various brain regions.
Results: From postmortem human PD brain samples and aged mouse brain, we have identified a general trend towards global reductions in protein dopaminylation. Of interest, there is a loss of neural Histone 3 glutamine 5 dopaminylation (H3Q5dop), as well as the associated combinatorial mark H3K4me3Q5dop, without global reductions in H3K4me3 within the substantia nigra of subjects with PD.
Conclusions: Interestingly, enhancing H3K4me3 mediated transcription is known to have neuroprotective effects in PD rodent models, and the deposition of H3Q5dop stabilizes and potentiates H3K4me3 to increase permissive gene expression. Thus, ongoing experiments aim to implement a dominant negative mouse model to identify the impact of H3Q5dop reductions on the epigenomic landscape and motor learning behavior.

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SHIFT 01-008

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES
2-3 April 2025

DISCOVERING A NOVEL ROLE FOR FBXO7/PARK15 IN INTRACELLULAR TRAFFICKING

Hanna Bjone[1], Maria Pereira[2], David Gershlick[2], Heike Laman[1]
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Aims: Pathogenic variants in Fbxo7, a subunit of the Skp1-Cullin1-F-box protein (SCF)-type E3 ubiquitin ligase complex, are associated with autosomal recessive early-onset parkinsonism. Mutations in *FBXO7/PARK15* disrupt functions such as regulation of the proteasome and mitophagy. In a high-throughput screen for SCF(Fbxo7) substrates, 338 substrates were identified. Gene ontology analysis showed that 70 of these targets are involved in transport. We hypothesise that mutation of Fbxo7 impairs its ability to regulate intracellular trafficking thereby contributing to PARK15 pathology. We aim to validate novel protein substrates involved in transport, for Fbxo7 interaction and ubiquitination, and investigate the effect of Fbxo7 mutations on intracellular trafficking.
Methods: Co-immunoprecipitation and *in vivo* ubiquitination assays were used to test interactions between Fbxo7 and substrates involved in trafficking. We investigated the impact of Fbxo7 disruption on both the retrograde and secretory trafficking pathways by kinetic trafficking assays, immunofluorescence analysis, flow cytometry, and western blotting.
Results: Fbxo7 was found to interact with and ubiquitinate proteins involved in intracellular trafficking, and we are mapping the sites of ubiquitination required for this. Knockout (KO) of Fbxo7 caused no significant effect in retrograde trafficking assays. However, we observed decreased secretion measured by a kinetic secretion assay and also reduced IgG secretion in B cells with Fbxo7 KO. We also identified sites of cargo accumulation by IF.
Conclusions: We identify a new role for Fbxo7 in regulating intracellular transport through the ubiquitination of proteins involved in membrane trafficking. This function may contribute to PARK15 pathology, suggesting an important link between Fbxo7 and intracellular trafficking in maintaining neuronal health.

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SHIFT 01-009

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES
2-3 April 2025

STUDY OF PARKIN FUNCTION IN COGNITIVE ASPECTS IN PARKINSON'S DISEASE

Gwendoline Fremont[1], Eric Duplan[2], Fanny Eysert[2], Mounia Chami[1], Frédéric Checler[2], Cristine Alves Da Costa[1]
[1]Ipmc - Institut De Pharmacologie Moléculaire Et Cellulaire, Valbonne, France, [2]CNRS, Ipmc, Valbonne, France

Aims: Parkinson's disease (PD) is a major public health problem that mainly affects the elderly. It is a slowly progressing, irreversible, and currently incurable disease. Its precise etiology remains unknown, but it is inevitably associated with an exacerbated death of neurons in a brain region involved in controlling movement. Nevertheless, PD also concerns multiple non-movement symptoms including cognitive decline. The mechanisms responsible for this decline remain unknown.
This study aimed to study the implication of the PD causative gene, parkin (PRKN) in the cognitive decline observed in the late stages of the disease. PRKN is a pleiotropic protein implicated in numerous functions, including apoptosis control, tumor suppression, mitophagy, and neuroplasticity. Notably, it has been shown that invalidation of the PRKN gene alters behavior, dopaminergic neurotransmission, and glutaminergic synaptic transmission in the hippocampus of PRKN knockout mice (KO-PRKN mice) corroborating the hypothesis that the PRKN is involved in cognitive aspects of PD.
Methods: To address this hypothesis, we first assessed the contribution of PRKN in cognitive aspects with primary cultures of KO-PRKN mouse neurons. We then identified targets regulated by PRKN by RNA-seq studies and analyzed their involvement in this cognitive aspect related to Parkinsonian pathology.
Results: Experiments performed in primary cultured neurons of WT and KO-PRKN show a significant regulation of numerous genes involved in neuroplasticity. Analysis of the number of synaptic boutons and the shape of dendritic spines in this model shows an impact of PRKN in neuroplasticity. RNAseq studies in the hippocampus indicate the contribution of PRKN transcriptional factor function in these phenotypes.
Conclusions: Overall our data clearly show an implication of PRKN in cognitive function. Experiments aiming at the molecular characterization of this phenotype are ongoing.

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SHIFT 01-011

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
2-3 April 2025

METABOLOMIC DISCOVERY OF SYSTEMATIC XANTHINE PATHWAY DYSREGULATION IN PARKINSON'S DISEASE

Elisa Gómez De Lope[1], Rebecca Loo[1], Armin Rauschenberger[1], Muhammad Ali[1], Pavelka Lukas[2], Tainá Marques[3], Clarissa Gomes[1], Rejko Krüger[4], Enrico Glaab[1]
[1]University of Luxembourg, Esch-sur-Alzette, Luxembourg, [2]Luxembourg Institue of Health, Luxembourg, Luxembourg, [3]Luxembourg Institute of Health, Luxembourg, Luxembourg, [4]Luxembourg Centre for Systems Biomedicine, University of Luxembourg, Luxembourg, Luxembourg

Aims: To identify new blood-based metabolic signatures in Parkinson's disease (PD) through comprehensive plasma metabolomics profiling, with a focus on treatment-independent changes in *de novo* patients. The study aimed to detect disease-associated alterations at both individual metabolite and pathway levels, examine correlations with motor impairment scores, and integrate findings with transcriptomics data to reveal coordinated molecular network changes that could provide insights into disease mechanisms.
Methods: Blood plasma samples from 549 PD patients (including 56 *de novo* cases) and 590 controls from the Luxembourg Parkinson's Study were analyzed using liquid chromatography-mass spectrometry metabolomics profiling. Statistical analyses identified differentially abundant metabolites in both *de novo* and all PD patients versus controls, adjusting for confounders and treatment effects. In addition, we performed pathway enrichment analyses and applied machine learning to assess the metabolites' predictive value for disease status and motor severity. Finally, by integrating metabolomics with transcriptomics data we determined coordinated enzyme-metabolite network alterations.
Results: Multiple metabolites showed significant abundance changes in PD, with particularly pronounced alterations in xanthine metabolism. Four xanthine pathway metabolites displayed consistently increased abundance in *de novo* PD. The integrated network analysis revealed decreased expression of the enzyme *HPRT1* as a potential key regulator of these changes, mechanistically linking them to cellular ATP deficiency in PD. Additional significant alterations were observed in fatty acid β-oxidation and retinal metabolism.
Conclusions: The study revealed significant PD-associated metabolome alterations, highlighting coordinated changes in xanthine metabolism that were mechanistically consistent across metabolomics and transcriptomics data. The enzyme *HPRT1* emerged as a potential key regulator of these network alterations, suggesting it as a candidate target for preclinical intervention studies. The findings provide new insights into disease mechanisms and identify promising directions for biomarker and therapeutic development.

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SHIFT 01-012

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
2-3 April 2025

EXPLORING SYNAPTIC DYSFUNCTION IN GLUCOCEREBROSIDASE DEFICIENCY AND A-SYNUCLEIN OVEREXPRESSION USING HUMAN MIDBRAIN ORGANOIDS

Min-Kyoung Shin[1,2], Zacharie Taoufiq[3], Jestlin Ng[4,5], Hwang-Soo Kim[1,2], Seongeun Gu[1,6], Minju Kim[1,6], Eunho Cha[1,6], Sungsoo Lee[1,6], Haerim Kim[1,2], Su Bin Lim[4,5], Junghyun Jo[1,2,3,6]
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Aims: Glucocerebrosidase (GCase) deficiency and α-synuclein (SNCA) overproduction are key risk factors for Parkinson's disease (PD), but their effects on synaptic dysfunction remain unclear. This study aims to investigate the molecular mechanisms of trans-synaptic transmission in α-synuclein propagation using human midbrain organoids with depletion of GCase and SNCA overexpression. Synaptosomes were isolated and analyzed via proteomics to identify key molecular contributors to synaptic dysfunction, offering insights into the pathogenesis of PD.
Methods: We generated GBA1 knock out (KO) and SNCA overexpressing isogenic (G/S) human embryonic stem cells (hESCs). Synaptosomes were isolated from human midbrain organoids (hMOs), generated from the wild type (WT) and G/S hESCs. Peptides were analyzed using a quadrupole-orbitrap LC-MS system. And then, protein identification was conducted using Proteome Discoverer software v2.1 and Mascot 2.6. Additional statistical analyses were performed using R software.
Results: Preliminary data indicate differentially expressed proteins involved in synaptic transmission in GBA-deficient organoids with α-synuclein aggregation. Proteomic analysis identified candidate molecules potentially contributing to synaptic dysfunction in the context of GCase deficiency and α-synuclein pathology.
Conclusions: This study provides novel insights into the molecular pathways underlying mechanism of synaptic dysfunction in Parkinson's disease. The findings highlight the complex interplay between GCase deficiency and α-synuclein aggregation in disrupting trans-synaptic transmission factors, offering potential targets for future therapeutic interventions.

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SHIFT 01-013

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS
2-3 April 2025

IDENTIFICATION AND ROLE OF COMMON PROTEIN PARTNERS OF DISTINCT ALPHA SYNUCLEIN STRAINS

Milena Giromini[1], Ronald Melki[1], Virginie Redeker[1,2], Nolwen Rey[1]
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Aims: Synucleinopathies are neurodegenerative diseases characterized by the misfolding and aggregation of α-synuclein in the brain. Misfolded α-synuclein can form fibrillary polymorphs (strains) that differ in conformation and present both common and distinct surfaces, likely interacting with different proteins partners. These proteins partners could be involved in synucleinopathy development. This study aims to identify the common α-synuclein strains interactome to uncover shared molecular features in synucleinopathies and explore the role of selected protein partners.
Methods: We generated different well-charaterized α-synuclein strains (F75, F91 and Ribbons) by modifying the assembling conditions *in vitro*. We then incubated these α-synuclein strains with proteins extracted from mouse neurons, and we covalently immobilized protein-protein interactions by cross-linking. The interactome of α-synuclein strains was pulled-down, and identified by mass-spectrometry and bioinformatics analysis. Finally, the functional effect of selected protein partners is investigated by modulating their expression in Neuro2A cells.
Results: Among 2054 proteins identified as interactors of α-synuclein strains in the presence of the cross-linker, we selected a few common protein partners to all three strains. For this selection, different criteria were used, such as a fold change above 4 between strains and controls. We also performed enrichment analyses on partners identified in cross-linked versus non-crosslinked conditions. We then set up a cell model to modulate selected partners expression and investigate the consequences on α-synuclein internalization, expression level, aggregation and clearance.
Conclusions: We identified the interactome of α-synuclein strains and selected a few protein partners common to all three strains for further investigation, *in cellulo*. Our results will enhance understanding of the pathological mechanism underlying synucleinopathies and help identify new therapeutic targets for all synucleinopathies.

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SHIFT 01-014

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2-3 April 2025

ASTROCYTIC DYSFUNCTION IN ALPHA-SYNUCLEIN PATHOLOGY: DEGRADATION PATHWAYS, SECRETOME ALTERATIONS, AND IMPLICATIONS FOR DOPAMINERGIC NEURONAL HEALTH AND FUNCTION

Indrani Datta[1], Aishwarya Raj[1], Roon Banerjee[1], Vikram Holla[2], Nitish Kamble[2], Ravi Yadav[1], Pramod Pal[1]
[1]National Institute of Mental Health and Neurosciences, Biophysics, Bengaluru, India, [2]National Institute of Mental Health and Neurosciences, Neurology, Bengaluru, India

Aims: Aims: This study aims to elucidate how astrocytes engage distinct protein degradation mechanisms to handle monomeric and aggregated forms of wild-type (WT) and mutant α-synuclein. We focus on how these mechanisms respond when protein degradation efficiency begins to decline. Additionally, we aim to assess α-synuclein release into the astrocytic secretome at this critical juncture and examine its impact on the survival and function of surrounding healthy dopaminergic-neurons.
Methods: Methods: We used rat primary astrocytes and healthy control hiPSC-derived astrocytes under extracellular α-synuclein insult to assess the subsequent impact on primary rat dopaminergic-neurons and SH-SY5Y cells. Degradatory pathways—matrix-metalloprotease MMP9, ubiquitin proteasome system (UPS), and autophagy-lysosomal pathway (ALP)—were analyzed using confocal-imaging, flow-cytometry and Western-blotting. Secretome was evaluated for α-synuclein release by α-synuclein exposed astrocytes and pro-inflammatory cytokines through ELISA. Dopaminergic-neuron health, neurite stability, and function were also evaluated under astrocytic secretome influence.
Results: Results: Initially, astrocytes managed monomeric α-synuclein via UPS and larger aggregates through MMP9 and autophagy, clearing extracellular α-synuclein and preserving neuronal health. However, prolonged exposure to α-synuclein inhibited UPS and MMP9, destabilizing autophagy and transforming astrocytes from protectors to contributors of neurodegeneration. This shift led to α-synuclein release, inflammatory cytokine secretion, and decreased neurotrophic factors, inducing dopaminergic neuron apoptosis, neurite collapse, impaired Ca^{2+} response, and diminished dopamine release from dopaminergic neurons. The presence of phosphorylated and nitrated α-synuclein in astrocytes also suggests they may modify both α-synuclein forms.
Conclusions: Conclusion: Astrocytes initially protect dopaminergic neurons by clearing extracellular α-synuclein, but prolonged exposure induces dysfunction, impairing neuron-glia cross-talk. This shift highlights the pivotal role of astrocytes as emerging hubs for propagating α-synuclein pathology via their secretome, disrupting crucial glia-neuron communication and exacerbating neurodegeneration. Integrating astrocytes into synucleinopathy treatment paradigms may be thus essential.

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SHIFT 01-017

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

MUTATION-DEPENDENT SEEDING AND NEURONAL TOXICITY OF A-SYNUCLEIN AGGREGATES IN AN IN VITRO CORTICAL MODEL

Lotta Agholme[1], Elin Allgén[2], Olivia Borg[2], Marziyeh Ghaeidamini[2], Maitrayee Sardar Sinha[1], Albin Skilje[1], Fritjof Havemeister[2], Johan Pihl[1], Elin Esbjörner[2]
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Aims: Parkinson's disease is defined by the formation of Lewy bodies composed of aggregated α-synuclein (α-syn). Point mutations in the SNCA gene result in diverse α-syn variants including A30P, E46K, H50Q, and A53T, each exhibiting unique self-aggregation tendencies, and varying abilities to initiate endogenous α-syn aggregation in neurons. This study investigates how different mutated forms of α-syn pre-formed fibrils (PFFs) induce aggregation in mouse and rat cortical neurons, and how this impacts neuronal function and viability. By exploring the cellular uptake and trafficking of α-syn PFFs, we seek to establish links between their structural features (such as size, shape, and secondary structure) and their biological effects in neuronal cell models.
Methods: All α-synuclein variants were expressed in E. coli and purified. PFFs were prepared following the Michael J. Fox Foundation protocol for reproducibility in PD research, sonicated to ~100 nm for high uptake, and characterized biophysically. Mouse and rat E18 cortical neurons were seeded in 384-well plates, and sonicated PFFs were added at 7DIV, followed by a 7-day incubation. At 14DIV, cells were fixed, stained for α-syn pS129, NeuN, and MAP2, then imaged.
Results: Our study shows that both wild-type and mutated alpha-syn PFFs promote endogenous α-syn aggregation in mouse and rat cortical neurons, with significant variation in aggregate structure between variants. While overall neuronal viability was unaffected, mutations like A53T and H50Q caused marked dendritic disruption, suggesting potential neurotoxicity. These findings highlight how specific α-syn mutations drive distinct aggregation patterns and contribute differently to neurodegenerative processes in Parkinson's disease.
Conclusions: This study reveals that α-synuclein variants drive distinct aggregation patterns and neurotoxic effects, enhancing our understanding of mutation-specific contributions to Parkinson's disease pathology.

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SHIFT 01-018

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

INCREASED SOLUBLE HIGH- AND LOW-MOLECULAR WEIGHT ALPHA-SYNUCLEIN OLIGOMERS IN DEMENTIA WITH LEWY BODIES

Mia Antorini[1], Emil Gregersen[1], Lasse Reimer[1], Ludovica Zaccagnini[2], Dennis Selkoe[3], Tim Bartels[2,4], Poul Henning Jensen[1]
[1]Aarhus University, Dept. Of Biomedicine, Aarhus C, Denmark, [2]UK Dementia Research Institute, Neurology, London, United Kingdom, [3]Brigham and Women's Hospital-Harvard Medical School, Neurology, Boston, United States of America, [4]UK DRI, Neurology, London, United Kingdom

Aims: We aim to investigate the molecular size distribution of soluble a-synuclein (a-syn) oligomers in cytosol extracts from brains affected by dementia with Lewy bodies (DLB) by combining size exclusion chromatography (SEC) with the MJFR14-6-4-2 a-syn aggregate-specific ELISA.
Methods: Frontal cortex grey matter from *post-mortem* brains of eight neurologically healthy controls and eight DLB patients were homogenized, and cytosol extracts isolated[1]. Extracts were resolved by size-exclusion chromatography and fractions analysed for total a-syn and MJFR14-6-4-2 positive aggregates using ELISA[2]and by immunoblotting. 1 Sanderson, J. B. *et al.* (2020) *Brain Commun* **2**, fcaa010. 2 Lassen LB, *et al.* (2018) *PLoS One.* 13(4): e0196056. doi: 10.1371
Results: Total presumably native a-syn eluted as a single peak with max in fraction 11 in DLB and controls. In DLB patients, the majority of MJFR14-6-4-2 immunoreactive oligomers peak in fraction 9, corresponding to a molecular size of 120-250 kDa, and as a minor high-molecular weight component in fraction 3 and 4, corresponding to a size of >1800 kDa. Western blotting of total a-syn validated a shift to fractions corresponding to larger molecular sizes.
Conclusions: Soluble a-syn oligomers in cytosol extracts of DLB patients are dominated by lower-molecular weight 120-250 kDa species and a smaller fraction of large >1800 kDa species. These observations will help understand the physiological landscape of a-syn oligomers and how it changes during disease. The two pools may present difference pathogenic properties and may need to be targeted by different neuroprotective strategies.

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SHIFT 01-019

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

BIOPHYSICAL CHARACTERISATION OF (PYROGLUTAMATE) ALPHA-SYNUCLEIN – INSIGHTS INTO THE AGGREGATION MECHANISM VIA A DIMERIC INTERMEDIATE

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Aims: Alpha-synuclein (aSyn) aggregation represents a key event in the neurodegenerative cascade of synucleinopathies. Here, we present new insights into structural characteristics of aggregated full-length (FL-) aSyn and, for the first time, of recently discovered pathological pyroglutamate (pE-) aSyn variants of different lengths. The generation of pE-aSyn post-translational modifications (PTM) requires two enzymatic activities for: (i) N-terminal truncation of aSyn and (ii) the subsequent cyclisation of the resultant N-terminal glutamine to pE by glutaminyl cyclase (QC).
Methods: To initiate aggregation, recombinant FL- and pE-aSyn variants were agitated with 900 rpm, at 37°C for 5 h. To gain insights into structural properties of monomeric and oligomeric states, size exclusion chromatography coupled small angle X-ray scattering (SEC-SAXS) were performed at SOLEIL synchrotron (France). Those results were orthogonally complemented with results obtained from analytical ultracentrifugation (AUC) and intrinsic viscosity measurements by SEC coupled with multi-angle light scattering (MALS) performed at Institut Pasteur (France).
Results: The interdisciplinary approach showed an elongated, unfolded monomeric state of all proteins analyzed, consistent with the known intrinsically disordered nature of FL-aSyn. In addition, a more structured amyloid pore, which was described for the FL-aSyn oligomer, was detected. Furthermore, shapes of oligomeric pE-aSyn variants were bioinformatically modeled and differed from FL-aSyn. Surprisingly, the data suggest the formation of dimers as the initial aggregation state for all proteins studied.
Conclusions: Understanding the complexity and the influence of PTMs on protein aggregation is important for developing disease-modifying interventions. We here investigated the 3D-shape of the dimeric state as a key intermediate in the aSyn aggregation/oligomerisation process. Additionally, our results suggest a role of QC as aSyn-modifying enzyme and highlight it as a potential target for treatment of synucleinopathies.

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SHIFT 01-020

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

BRAIN-DERIVED EXTRACELLULAR VESICLES HARBOR ALPHA-SYNUCLEIN SEEDS

Maria Bregendahl[1,2], Ayman Faroqi[1,2], Marissa Russo[1,2,3], Zeynep Bengisu Kaya[2], Zhengrong Zhang[2], Yang You[2], Tsuneya Ikezu[1,2], Suelen Boschen[1,2], Michael Deture[2], Dennis Dickson[2], Pam Mclean[1,2]
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Aims: Dementia with Lewy Bodies (DLB) is a primary synucleinopathy characterized neuropathologically by intraneuronal aggregates of alpha-synuclein (aSYN) called Lewy bodies. Due to clinical overlap with other dementias and absence of distinct biomarkers, DLB diagnosis typically occurs post-mortem. To address this diagnostic challenge, our study aims to identify disease-specific signatures in brain-derived extracellular vesicles (EVs) from neuropathologically confirmed post-mortem brain tissue. By profiling aSYN and additional relevant markers in EVs, we aim to develop antemortem diagnostic tools capable of distinguishing DLB-specific profiles from those of Alzheimer's Disease (AD) and non-Lewy body dementias.
Methods: EVs were enriched from post-mortem brain tissue of patients with neuropathologically confirmed DLB, AD, and non-Lewy body control cases through differential centrifugation and size exclusion chromatography (SEC). EVs were subsequently analyzed for particle concentration and biochemical composition. Total aSYN levels were quantified by immunoassays, while the seeding potential was evaluated using a seed amplification assay (SAA), specifically real-time quaking-induced conversion (RT-QuIC) assay, which measures the templated conversion of monomeric aSYN to fibrils by seeds via Thioflavin T incorporation.
Results: Using RT-QuIC, aSYN seeds were detected in SEC fractions enriched from DLB cases. EV fractions represent subpopulations of EVs separated by size and density. In contrast, no aSYN seeds were detected in EVs enriched from AD, corticobasal degeneration, or control cases. These findings suggest a DLB-specific seeding profile within EV-containing fractions, which could be potentially applied to EVs from antemortem plasma-derived EVs for biomarker development.
Conclusions: These preliminary findings suggest that RT-QuIC can differentiate DLB-specific EV profiles, demonstrating potential as a diagnostic tool. Future work will expand this approach to brain-derived EVs from plasma, with the goal of developing a readily accessible antemortem diagnostic method for DLB.

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SHIFT 01-021

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

EXPRESSION OF LINGO1 AND POTASSIUM CHANNELS IN ALPHA-SYNUCLEIN PATHOLOGY MODELS

Fred Jonathan Edzeamey[1], Éanna Ryan Ryan[1], Carmen-Jeanette Stepek[1], Rachel Stewart[1], Orla Watters[1], Niraj Khemka[1], Sharada Baindoor[1], Ronald Melki[2], Ayse Ulusoy[3], Donato A. Di-Monte[3], Mark A. Hollywood[4], Niamh M. Connolly[1], Jochen H. M. Prehn[1]
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Aims: LINGO1 is a regulator of large conductance potassium (BK) channels, that functionally inhibits BK channels and may contribute to the pathophysiology of Parkinson's Disease and Essential tremor. This study aimed to characterise the transcriptional expression of LINGO1 and potassium channel subunits using *in vivo* and *in vitro* models of alpha-synuclein (aSyn) pathology
Methods: For the *in vivo* model of aSyn overexpression, the substantia nigra (SN) of adult female mice was stereotaxically injected with an AAV6 capsid carrying human SNCA DNA. Mice were sacrificed 3 or 8 weeks later and midbrain sections were collected. Spatial transcriptomics was performed on the SN using the Nanostring GeoMX platform. *In vitro*, mouse primary cortical neuron cultures were exposed to pre-formed aSyn (p91) fibrils on DIV7 to induce aSyn aggregation and downstream assays were performed between DIV18-21. Model pathology was assessed by immunofluorescence (*in vivo* model), pS129-aSyn immunocytochemistry and western blot. RNA was isolated and subjected to RNA-sequencing and qRT-PCR
Results: Loss of tyrosine hydroxylase-positive (Th+) neurons in the *in vivo* model was observed 8 weeks after induction of aSyn-overexpression. Spatial transcriptomic data revealed a downregulation of Lingo1 and several potassium channel subunits (*e.g.,* Kcna2, Kcnc1/3/4, Kcnn3), but not BK channel transcripts in SN tissue of SNCA-overexpressing mice compared to controls. aSyn aggregation was confirmed in the primary cortical neuron model. In this *in vitro* model, little alterations was observed in LINGO1 or the potassium channel subunits measured, either by RNA-Seq or qRT-PCR
Conclusions: Our *in vivo* aSyn-overexpression model showed a downregulation of LINGO1 and several potassium channel subunits. We will next modulate LINGO1 expression in primary neurons to investigate its effects on potassium channel expression and function.

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SHIFT 01-022

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

INVESTIGATION INTO THE POLYMORPH LANDSCAPE OF ALPHA-SYNUCLEIN AMYLOIDS

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Aims: Aggregation of intrinsically disordered proteins is associated with several neurodegenerative diseases, however, the polymorphic nature of their amyloid fibril structures complicates disease-relevant in vitro studies. Our goal is to understand the factors influencing α-synuclein polymorph selection in order to reproduce the disease-relevant structures in vitro.
Methods: We studied α-synuclein fibrils derived from protein of different degrees of purity, under various physiological enviroments and in the prescence of a library of compounds using cryo-Electron Microscopy helical reconstruction. In combination with HPLC and LC-MS analysis we use a high-throughput approach to understand the formation of distinct polymorphs in vitro.
Results: We found that in the physiological pH range (5.8-7.4), polymorph selection between type 1, 2 and 3 fibrils is pH dependent. In addition, two new polymorphs were discovered at pH 7.0 in phosphate-buffered saline: a monofilament type 1 fibril resembling the fibrils obtained from patients with juvenile-onset synucleinopathy and a type 5 polymorph similar to those found in disease seed studies.
Conclusions: These results highlight the sensitivity of α-synuclein amyloid polymorphs to environmental conditions, particularly pH, and suggest the potential for replicating disease-relevant structures in vitro. We are currently working on replicating in vivo polymorphs of Parkinson's disease, juvenile-onset synucleinopathy and multiple system atrophy in an in vitro setting.

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SHIFT 01-023

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

IMPORTANCE OF ATP13A2 IN PREFORMED FIBRILS-INDUCED A-SYNUCLEIN AGGREGATION MODELS

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Aims: ATP13a2 is a lysosomal transmembrane transporter that has been genetically associated with several neurological conditions including spastic paraplegia, neuronal ceroid lipofuscinosis, and rare cases of a Parkinson syndrome called Kufor-Rakeb Syndrome. The latter is characterized by loss of dopaminergic neurons and motor dysfunction suggesting nigrostriatal pathology similar to idiopathic Parkinson's disease. However, the mechanism of action by which ATP13a2 leads to dopaminergic neuron degeneration is unclear. Several reports in literature have mixed conclusions on the impact of ATP13a2 on a-synuclein (α-syn) pathology. In this study, we aimed at testing the impact of ATP13a2 reduction on α-syn pathology using preformed fibrils (PFFs)-induced a-syn aggregation models *in vitro* and *in vivo*.
Methods: *In vitro;* WT and ATP13a2-KO primary neuronal cultures, generated from E19 mouse embryos, were treated with a-syn PFFs on DIV9, followed by immunocytochemical analysis of phosphorylated (P-S129) a-syn on DIV20. *In vivo;* following histopathological characterization of ATP13a2 mice (WT, HZ, and KO) at 2.5, 6 and 12 months of age, 15 months old mice were bilaterally injected with α-syn PFFs in the dorsal striatum. One month after injection, mouse brains were collected to quantify a-syn aggregation using biochemical analysis.
Results: As previously published, ATP13a2-KO animals display increased lipofuscin-induced autofluorescence in a genetic and age dependent manner. Additionally, histological analysis of the brain does not reveal any impact of ATP13a2 constitutive absence on dopaminergic neuron density and phosphorylated (P-S129) α-syn levels. Finally, we did not observe any potentiation of PFF-induced a-syn aggregation *in vitro* nor *in vivo* in conditions of ATP13a2 hypofunction.
Conclusions: Altogether, our findings in our ATP13a2-KO models do not support the hypothesis that ATP13a2 dysfunction potentiates a-syn aggregation and may suggest that other mechanisms are at play in dopaminergic neurodegeneration.

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SHIFT 01-024

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
2-3 April 2025

DISEASE-SPECIFIC CELLULAR IMPACT OF ALPHA-SYNUCLEIN AGGREGATE STRAINS FROM PARKINSON'S DISEASE AND MULTIPLE SYSTEMS ATROPHY

Hjalte Gram[1], Anissa Hammi[1], Nanna Møller Jensen[1], Juliana Zink Pedersen[2], Vasileios Theologidis[3,4], Mohammad Shahnawaz[5], Claudio Soto[5], Poul Henning Jensen[1]
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Aims: Parkinson's Disease (PD) and Multiple system atrophy (MSA) present different disease courses, symptoms and neuropathology, and contain structurally different alpha-synuclein (a-Syn) folding strains. We aim to compare the cellular impact of patient-derived PD and MSA a-Syn aggregate strains.
Methods: From the cerebrospinal fluid of PD and MSA patients, we amplified a-syn aggregates using seed amplification assay. These validated a-syn aggregate strains were used to investigate cellular templated aggregate formation in two different cell-type models of a-syn aggregation: a-syn overexpressing oligodendrocyte cell line and induced pluripotent stem cell derived neurons. We studied inclusion pathology by immunocytochemistry with antibodies towards p-S129 and aggregated a-Syn (MJFR-14-6-4-2). To study non-inclusion pathology, we utilized a proximity ligation assay with two anti-aggregated a-syn antibodies (MJFR-14-6-4-2). To selectively investigate endogenously formed aggregates we developed a single-amino acid modified a-syn aggregate that cannot bind the anti-aggregated a-syn antibody (MJFR-14-6-4-2). Additionally, oxidative stress in response to a-syn aggregate strain treatment was measured in the cell models using the H2DCFDA probe.
Results: Our results show that PD-derived and MSA-derived aggregates differ in cellular impact in our two cell model systems. PD-derived and MSA-derived aggregates resulted in markedly different and cell-type specific inclusion pathology and oxidative stress. Using proximity ligation assay, we observed seeded non-inclusion aggregates in both PD and MSA treated cells, that did not correlate to the level of inclusion pathology.
Conclusions: We show that aggregates from PD and MSA have a distinct cellular impact, implicating that conformational differences in aggregate structure may be involved in the pathophysiology of a-syn aggregate-dependent neurodegenerative diseases.

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SHIFT 01-026

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
2-3 April 2025

RELATIONSHIP OF ASYN PATHOLOGY AND THE LYSOSOMAL CATHEPSINS D, B, AND L IN MODELS OF PARKINSON´S DISEASE

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Aims: Pathological amount and forms of aSyn present in Parkinson´s disease (PD) can severely impair the activity of lysosomal enzymes, resulting in the worsening of aSyn pathology. These findings imply a vicious cycle between lysosomal dysfunction and aSyn aggregation. Our aim is to gain a better understanding of the interplay of aSyn pathology and lysosomal dysfunction, with the hope of identifying molecular targets to interfere this self-perpetuating process.
Methods: We study the effect of aSyn accumulation on the trafficking, maturation, and activity of lysosomal proteins, among them some of the most abundant lysosomal proteases: cathepsin D, B, and L. We use human induced-pluripotent stem cell-derived dopaminergic neurons carrying copy number variations (triplication) or pathogenic point mutation (A53T) of the *SNCA* gene as models of PD. The techniques we use involve lysosomal pH determination, in vitro and live-cell enzymatic assays, estimation of protein levels by western blot, and immunofluorescence staining for colocalization detection. Furthermore, in order to restore the observed enzymatic alterations, we utilize pharmacological treatment such as the farnesyltransferase inhibitor (FTI) LNK-754.
Results: Ours findings show aSyn-related lysosomal dysfunction in the utilized PD models as it is reflected by the observed inverse relation between aSyn levels and impaired proteolytic activity of the investigated lysosomal enzymes. We found that these alterations are a consequence of defective maturation and lysosomal trafficking of the enzymes. The alterations in lysosomal enzyme levels/activities can be restored by treatment with FTI, which, as a consequence, leads to a decrease in aSyn levels.
Conclusions: Our results explore an approach for breaking the vicious cycle of aSyn pathology and lysosomal dysfunction in PD models, and by this offering a novel avenue for further research in this direction.

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SHIFT 01-027

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
2-3 April 2025

THE INFLUENCE OF CTSB ON GBA1 DEFICIENCY-ASSOCIATED PHENOTYPES IN VITRO

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Aims: The lysosomal protease cathepsin B (CTSB) has recently been identified as a potential risk factor for Parkinson's disease (PD) and modifier of penetrance of *GBA1*-related diseases like PD and Lewy Body Dementia. CTSB can cleave alpha-synuclein (αSyn) at several sites and suppression of the enzyme can prevent pre-formed αSyn fibrils from inducing aggregation of the endogenous protein *in vitro*. This study aims to further elucidate how CTSB is involved in αSyn metabolism, as well as how CTSB may modify *GBA1*-related disease penetrance.
Methods: Using CRISPR/Cas9, we have generated isogenic lines of wild-type and *GBA1*-heterozygous null cells with complete *CTSB* knockout to observe how the loss of CTSB affects αSyn metabolism and lysosomal function, particularly in the context of *GBA1* deficiency. Label-free quantitative proteomics, immunoblotting, and confocal microscopy were performed to evaluate the downstream consequences.
Results: We observed mechanistically distinct alterations in the protein levels of several lysosomal cathepsins in response to CTSB loss with and without *GBA1* deficiency. Additionally, *GBA1* protein levels were significantly decreased by *CTSB* knockout in *GBA1*-deficient cells compared to those with *GBA1* intact. Proteomic analyses suggest that most proteins are unaltered by CTSB loss in the context of *GBA1* heterozygosity, highlighting a potential discrete and disease-relevant interplay between the two proteins.
Conclusions: These observations demonstrate a novel deleterious consequence of decreased CTSB in the context of *GBA1* haplotype insufficiency and suggest that CTSB may have an important role in stabilizing *GBA1* protein under disease conditions. Further work will determine how these changes impact αSyn metabolism.

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SHIFT 01-028

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
2-3 April 2025

LYSOSOMAL DYSFUNCTION MAY BE AN EARLY DRIVER FOR DYSREGULATED NEURONAL ACTIVITY AND NEURODEGENERATION IN PARKINSON'S DISEASE

Katelin Ennis, Michael Lamorte, Anna Blazier, Iqra Pervaiz, Arissa Pounall, Dimitry Ofengeim, Nellwyn Hagan
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Aims: Parkinson's disease (PD) is a multifactorial complex neurodegenerative disease, recent genome-wide association studies (GWAS) have identified risk loci harboring disease-susceptibility variants in addition to causative genes driving pathogenesis. A number of these causative genes have implicated both alpha synuclein aggregation (SNCA) and endo-lysosomal pathways (LRRK2 and GBA) as critical determinants of disease onset and progression.
Methods: To model the complex CNS micro-environment *in vitro*, a human tri-culture system consisting of iPSC derived neurons, microglia, and astrocytes, was developed. These tri-cultures were then treated with α-synuclein pre-formed fibrils (PFFs) to simulate PD pathogenesis *in vitro*. Dopaminergic tri-cultures were imaged with a neuronal specific genetically encoded calcium indicator (Neuroburst) over time to characterize neuronal activity. In addition to the *in vitro* disease- relevant model, an *in vivo* MPTP mouse model of PD was characterized to understand alterations in neuroinflammatory, lysosomal, and mitochondrial pathways with the onset of disease.
Results: Following PFF treatment, a robust signature of neuroinflammation, cytokine signaling, and phagosome formation was observed in the tri-culture after 24-hours. Comparison of identified RNA-Seq signatures from PFF treated tri-cultures identified similar pathway changes to bulk RNA-Seq data from the midbrain of human PD patients. Following acute administration of MPTP, substantia nigra and striatum tissue was profiled over time to reveal robust changes in lysosomal markers and activity, mitochondrial dysfunction, and neuroinflammatory activation at transcriptomic levels. Neuronal synchronicity was significantly decreased and dysregulated following treatment with PFFs, and dopaminergic tri-cultures showed alterations in mean burst duration and strength.
Conclusions: Taken together, PD-relevant *in vitro* and *in vivo* models show early robust alterations in lysosomal pathways and altered neuronal activity suggesting lysosomal dysfunction may be an earlier driver for dysregulated neuronal activity, neuroinflammation, and neurodegeneration pathology in PD.

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SHIFT 01-029

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
2-3 April 2025

CBE-INDUCED GCASE ACTIVITY INHIBITION ON LYSOSOMAL ACTIVITY AND AUTOPHAGY BIOMARKERS

Bruno Igreja[1], André Marques[2], Luísa Dória[1], Otília Vieira[2], Christian Czech[1], Nuno Pires[1]
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Aims: Objectives: Conduritol-β-epoxide (CBE) is an inhibitor of glucocerebrosidase (GCase) enzyme commonly used to model hereditary deficits of GCase in animals. The aim of this study was to characterize the effect of CBE-induced GCase inhibition on lysosomal activity and autophagy in mice.
Methods: Methods: C57Bl/6J mice were treated with CBE at either 30 or 100mg/Kg/day or vehicle for 12-days by intraperitoneal injection. Brain tissue and plasma were collected from these mice to analyze protein levels and enzyme activity of lysosomal hydrolases. The GCase substrate glucosylsphingosine levels were also assessed.
Results: Results: No or marginal effects on lysosomal activity and autophagy were observed at CBE 30mg/Kg/day dose. LAMP1, total cathepsin D and prosaposin levels were increased in brains of mice treated with CBE 100mg/kg/day compared to vehicle-treated animals, a readout of lysosomal mass increase. There was no change in mature-to-total cathepsin D ratio, indicating regular lysosome function. Autophagy markers LC3II/LC3I ratio and p62 were increased in brain tissue after CBE 100mg/Kg/day treatment as compared to vehicle group, showing an autophagy upregulation. Enzyme activity of lysosomal hydrolases cathepsin D, B, L, HEXB and LAL were increased in brain tissue of mice treated with CBE 100mg/Kg/day, as compared to vehicle group. Levels of brain glucosylsphingosine were found to increase CBE-dose dependently. In plasma, there was an increase in soluble LAMP1 and glycoprotein non-metastatic melanoma protein B (GPNMB) levels in mice treated with CBE 100mg/Kg/day, as compared to vehicle-treated animals, indicating an increased exocytosis and lysosomal stress.
Conclusions: Conclusions: CBE-mediated GCase inhibition, at 100mg/kg/day, leads to lysosomal stress in mice leading to *de novo* lysosomal biogenesis and upregulation of autophagy in brain tissue. Soluble LAMP1 and GPNMB plasma levels were increased suggesting their potential use as lysosome-related biomarkers.

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SHIFT 01-033

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

CHEMICAL INDUCERS AND INHIBITORS OF FERROPTOSIS CAN ALTER THE PATHOLOGICAL EFFECTS OF ALPHA-SYNUCLEIN OLIGOMERS.

Omer Wisam Mohammed Salih Al-Ani[1], David Smith[2]
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Aims: To investigate the effect of ferroptosis induction and inhibition on the seeding capacity of alpha-synuclein oligomers in a cell line model.
Methods: Alpha-synuclein oligomers type C were prepared according to Danzer et al (1). The ferroptosis inducer erastin, and the ferroptosis inhibitor ferrostatin-1, were used to evaluate the effect of ferroptosis induction and inhibition in HEPG2 cells. Cells were treated with either erastin or ferrostatin-1 one hour before treatment with oligomers and compared to cells treated with oligomers alone and control cells treated with PBS. Cells were visualized using fluorescent microscopy. The alpha-syn 211 antibody was used to detect total alpha-synuclein seeding and the amytracker 680 reagent was used to detect the formation of amyloid-like aggregates. The MTT assay was used to evaluate cell toxicity.
Results: HEPG2 cells pretreated with ferrostatin-1 before oligomer treatment demonstrated less seeding than cells without pretreatment. On the other hand, cells treated with both erastin and oligomers showed a higher Amytracker 680 signal than cells treated with oligomers alone. Neither erastin nor oligomers demonstrated significant cell death at the used concentrations.

Conclusions: Our results demonstrate that ferroptosis inhibition may decrease the seeding capacity and the prion-like propagation effect of alpha-synuclein oligomers. Also, the induction of ferroptosis may facilitate the formation of amyloid-like aggregates in cell models even at subtoxic concentrations. These results show that ferroptosis can contribute to disease pathology through different mechanisms and that the manipulation of ferroptosis can be a viable option in developing disease-modifying treatments for Parkinson's disease and other synucleinopathies. Reference: 1. Danzer KM, Haasen D, Karow AR, Moussaud S, Habeck M, Giese A, et al. Different species of alpha-synuclein oligomers induce calcium influx and seeding. J Neurosci. 2007 Aug 22;27(34):9220–32.

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SHIFT 01-034

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

THE IMPACT OF PARKINSON'S DISEASE-ASSOCIATED LIPID ALTERATIONS ON A-SYNUCLEIN RELEASE.

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Aims: The intercellular transmission of misfolded α-synuclein has been proposed to play a role in the progression of Parkinson's disease. Alongside this, dysregulated lipid metabolism has recently emerged as a significant factor. However, the mechanisms behind α-synuclein spread, and the role of lipid alterations in this process, remain poorly understood. The goal of this project is to investigate the impact of Parkinson's disease-associated lipid alterations on α-synuclein release by extracellular vesicles.
Methods: Cortical neurons from postnatal rats and iPSC-derived dopaminergic neurons from PD patients with *GBA1* (N370S, W378G, L444P) and *LRRK2* (R1441H, G2019S) mutations, alongside isogenic controls, from male and female were studied. The membranes of these neurons were labelled by expressing mCherry-GPI or mVenus-CAAX. Cortical neurons were either treated with exogenous glucosylceramide tagged with the fluorophore nitrobenzofurazan or with conduritol-β-epoxide, a selective small molecule inhibitor of GCase, to mimic PD conditions and imaged live. Super-resolution live-cell imaging was performed alone or in combination with human α-synuclein preformed fibrils, which were generated and validated according to the MJFF protocol.
Results: We discovered that increased glucosylceramide induces the release of extracellular vesicles from primary cortical neurons and Parkinson's disease patient's dopaminergic neurons with *GBA1* and *LRRK2* mutations. These vesicles carry pathogenic α-synuclein fibrils, which are subsequently internalized by other neurons, leading to the spread of α-synuclein pathology.
Conclusions: Our findings highlight the role of extracellular vesicles as a key vehicle for α-synuclein transmission in response to lipid alterations found in Parkinson's disease.

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SHIFT 01-035

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

SPATIAL AND SINGLE CELL ANALYSIS OF A-SYNUCLEIN PROPAGATION REVEALS ASTROCYTIC NEUROTRANSMITTER PROCESSING DYSFUNCTION IN A PARKINSON'S DISEASE MOUSE MODEL

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Aims: Propagation of α-synuclein (α-syn) is considered a key element in the pathology of Parkinson's Disease (PD), yet the pathological consequences of transmitted α-syn are poorly understood. This study aims to elucidate pathways affected by the spread of α-syn using spatially resolved intrinsic and transmitted α-syn to generate transcriptional profiles via the 10X Visium and GEX platforms in a mouse model of α-syn oligomerization.
Methods: We used 20-month-old transgenic PD mice expressing α-syn oligomers based on a split Venus system (V1S/SV2) and respective single-transgenic mice as controls. Fourteen coronal brain slices of three animals per condition were analyzed using 10X Visium, and two animals per condition were included in a single-nucleus RNA sequencing (snRNA-seq) dataset.
Results: Visium analysis detected high V1S/SV2 protein and mRNA levels in the Cortex and Hippocampus. Notably, we also found close to the Substantia Nigra high protein but minute mRNA levels of V1S/SV2, pointing to transmission of α-syn to this region. Transcriptional and compositional analyses of this region revealed increased astrocyte numbers and dysregulation of astrocyte-dependent neurotransmitter cycles due to V1S/SV2 spread. Further snRNA-seq analysis confirmed astrocytic dysfunction in glutamatergic neurotransmitter processing, aligning with Visium data. In total, 22 key genes were identified as central to the dysregulation of astrocytic neurotransmitter functions. Furthermore, the transcriptional changes in the propagation region differed from those in areas with high intrinsic V1S/SV2 protein expression.
Conclusions: Spreading of α-syn oligomers is associated with the dysregulation of astrocytic functions, especially in neurotransmitter uptake and processing. We report a spreading specific, astrocytic transcriptional profile including 22 central genes. Our findings further highlight the significant role of astrocytes in PD pathophysiology, providing new insights into the mechanisms of α-syn propagation and its impact on brain function.

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SHIFT 01-038

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / DOPAMINERGIC, CHOLINERGIC
2-3 April 2025

QUANTIFICATION OF CHOLINERGIC DYSFUNCTION IN OCCUPATIONAL MANGANESE EXPOSURE USING [18F]VAT PET

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Aims: Mn is a neurotoxicant that, in excess, produces a clinical syndrome of parkinsonism and cognitive impairment. While these clinical associations are well described in Mn neurotoxicity, the underlying mechanisms are largely unknown. Our objective is to evaluate cholinergic function and its relationship with cognitive impairment in workers with occupational manganese (Mn) exposure.
Methods: We assessed brain cholinergic function using (-)-(1-(8-(2-[(18)F]fluoroethoxy)-3-hydroxy-1,2,3,4-tetrahydronaphthalen-2-yl)-piperidin-4-yl)(4-fluorophenyl)methanone (VAT) positron emission tomography (PET) in 21 Mn-exposed workers. Mn exposure was estimated from work histories and the T1-weighted magnetic resonance imaging (MRI) pallidal index. A cognitive battery consisting of the Verbal Fluency (VF), Letter Number Sequencing (LNS), Two-Back Letter Task (2B), Go-No-Go (GnG), and Simon Task (Simon) assessed cognitive control reflecting the ability to monitor, manipulate, and regulate ongoing cognitive demands.
Results: We observed inverse associations between cumulative Mn exposure as quantified by work history or T1-weighted MRI pallidal index and cholinergic VAT binding in the caudate and cortical regions including the precuneus, pars triangularis, pars opercularis, middle temporal lobe, and entorhinal cortex. Regional cholinergic function mediated the relationship between Mn exposure and both combined cognitive control performance (VF, LNS, 2B,GnG,Simon) score [β= -0.661, confidence interval (CI) -2.130, -0.032] and VF (β= -0.9443, CI -2.1574, -0.0651) in Mn-exposed workers.
Conclusions: Cholinergic function mediates the relationship between Mn exposure and cognitive control performance. Caudate and cortical cholinergic activity may be a biomarker of Mn neurotoxicity and represent an important mechanism of cognitive dysfunction in parkinsonian syndromes including Mn neurotoxicity, Parkinson's disease, and Parkinson's disease dementia.

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SHIFT 01-039

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / DOPAMINERGIC, CHOLINERGIC
2-3 April 2025

UNRAVELING THE COMPLEXITY OF ROTENONE-INDUCED PARKINSON'S DISEASE IN MICE: LONGITUDINAL EVALUATION OF DISEASE PATHOLOGY

Paula Jauregi[1], Roland Rabl[1], Magdalena Daurer[1], Livia Breznik[1], Stefanie Flunkert[1], Boris Chagnaud[2], Manuela Prokesch[1]
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Aims: Parkinson's disease (PD) is characterized by the progressive loss of dopaminergic neurons leading to motor and non-motor impairments. Animal models are a valuable tool to evaluate the physiopathology of the disease and develop novel therapies. In this study a rotenone induced mouse model of PD was longitudinally characterized to gain insights into the disease's progression and to establish the model for drug testing.
Methods: 9-week-old male C57BL/6J mice were randomly allocated to one of the following groups: 2 µg/µl, 3 µg/µl rotenone, vehicle control (DMSO) or saline. Each mouse received a 1.5 µl stereotaxic injection into the right striatum. Mice were subjected to a battery of behavioral tests at baseline (pre-injection, W0) and 2 (W2) and 4 weeks (4W) *post-injection*. In detail, beam walk, wire hanging, open field, and passive avoidance tests were used. Brains were collected at all time points for histological and biochemical analyses.
Results: Both rotenone-treated groups showed increased contralateral slips on the beam walk test at W2 and W4. Additionally, rotenone-injected mice exhibited a lower latency to fall in the wire hanging test at W2, but only the lower dose group showed continued impairment at W4. Histological analysis revealed decreased tyrosine hydroxylase levels and increased ionized calcium-binding adapter molecule 1 and glial fibrillary acidic protein expression in the ipsilateral substantia nigra (SN). Further histological and biochemical analyses are currently under investigation.
Conclusions: Intrastriatal rotenone injection can recapitulate key hallmarks of PD, including motor impairments, dopaminergic neuron loss in the SN and neuroinflammation shortly after placing the lesion, making it a valuable tool for studying the progression of the disease and testing potential therapeutic drugs.

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SHIFT 01-042

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

MICROBIOME-NEUROIMMUNE INTERACTIONS SHIFT THE BALANCE IN PARKINSON DISEASE PENETRANCE IN A MULTIGENERATIONAL ALPHA-SYNUCLEIN KINDRED

Joanna Korecka-Roet[1], Laura Cox[1], Leah Beauchamp[1], Rachel Rountree[1], Christine Chen[1], Anya Gemos[1], Lily Palumbano[1], Millicent Ekwudo[1], Danielle Leserve[1], Isabella Miller[1], Manel Boussouf[1], Kusha Chopra[1], Ane Murueta-Goyena[2], Mar Carmona-Abell´a[2], Rosario Sanchez-Pernaute[2], Juan Carlos Gómez-Esteban[2], Howard Weiner[1], Vikram Khurana[1]
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Aims: Parkinson's disease (PD) and dementia with Lewy bodies (DLB) are complex diseases involving gene-environment interactions. While it is clear that the microbiota contribute to PD and cognitive impairment, mechanistic studies that define the interaction of specific microbes with immunologic and metabolic pathways are still unknown. Studying rare kindreds with inherited forms of neurodegeneration offers a window to understanding mechanisms in a controlled genetic and environmental background. We hypothesize that specific bacteria in the gut microbiota contribute to PD dementia (PDD)/DLB by secretion of metabolites that modulate microglial function and neuronal cell death.
Methods: We investigate microbiome determinants of disease penetrance in a family harboring an alpha-synuclein E46>K mutation with highly variable PDD/DLB phonotypic outcomes. We utilize a transgenic E>K a-synuclein mutant mice (3KL) and human stem cell models to identify key microbes and metabolites.
Results: We identified bacteria associated with PDD/DLB disease penetrance, several of which are altered in sporadic PD/PDD. Transferring the PDD/DLB gut microbiota into the 3KL PD mouse model revealed worsened motor and cognitive function, outcomes linked to specific microbiota associated with familial E46K and sporadic PDD. PDD/DLB microbiome transfer increased peripheral INFg-producing T cells and activated microglial inflammatory transcriptional profiles, identifying specific microbiome-dependent immunologic pathways contributing to PDD pathogenesis. We identified specific bacteria that modulate microglial inflammatory states by conditioning human stem cell-derived microglia with supernatants from novel PDD/DLB E46K bacteria isolates. Finally, we identified potential key microbial metabolite mediators in E46K-PDD intestinal and serum samples and in mice colonized with PDD microbiota.
Conclusions: These studies uncover novel pathways by which the microbiome influences PD and PDD development and highlight the power of investigating rare but informative multigeneration kindreds.

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SHIFT 01-043

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

MODULATION OF NEURONAL ACTIVITY IN THE INSULAR CORTEX IMPROVES MOTOR SYMPTOMS AND GUT DYSFUNCTION IN PARKINSON'S DISEASE

Sun-Young Jang[1,2], Su-Yang Park[1,2], Hyowon Lee[1,3], Ju-Young Oh[1,2], Min-Ho Nam[3,4], Hi-Joon Park[1,2,4]
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Aims: Parkinson's disease (PD) is the most common neurodegenerative disorder, characterized by motor symptoms such as tremor, rigidity, bradykinesia, and postural instability, often accompanied or preceded by non-motor symptoms like gastrointestinal (GI) disorders. The insular cortex (IC), a central hub for interoception, integrates gut-related information and modulates the gut immune response. Notably, the IC has been implicated in maintaining and modulating intestinal inflammation, suggesting that targeting IC activity could influence gut health in PD. In this study, we investigated whether chemogenetic modulation of IC activity could ameliorate both motor and GI dysfunction in a PD model.
Methods: Using DREADD, we inhibited glutamatergic neuron activity in the IC of a PD mouse model. PD was induced in C57BL/6 mice by daily intraperitoneal injections of MPTP (30 mg/kg) for 5 days. Motor impairments were evaluated through rotarod and cylinder tests. Additionally, changes in tight junction proteins (zonula occludens-1 and occludin) and pro-inflammatory cytokines (tumor necrosis factor-alpha and interleukin-1 beta) were measured in the colon using immunofluorescence staining and quantitative real-time polymerase chain reaction.
Results: Chemogenetic inhibition of pyramidal neurons in IC alleviated motor symptoms and prevented the death of dopaminergic neurons in the MPTP-induced PD model. This intervention also protected the expression of intestinal tight junction proteins and reduced gut inflammation by downregulating the expression level of pro-inflammatory cytokines against MPTP.
Conclusions: The chemogenetic modulation of IC neurons effectively improved both motor deficits and GI dysfunction in the PD model. These findings suggest a novel role of the IC in PD pathogenesis and may provide a new direction for PD treatment, especially in targeting the gut-brain axis.

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SHIFT 01-044

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LRKK2, PARKIN, PINK1, DJ-1
2-3 April 2025

POST-MORTEM PARKIN AGGREGATION AND ALPHA-SYNUCLEIN HYPERPHOSPHORYLATION IN THE SUBSTANTIA NIGRA OF PARKINSON DISEASE PATIENTS.

Laura Pshevorskiy[1,2], Cyntia Tremblay[2], Hélèna Denis[1,2], Vincent Emond[2], Marc Morissette[2], Therese Di Paolo[1,2], Alex Rajput[3], Frederic Calon[1,2]
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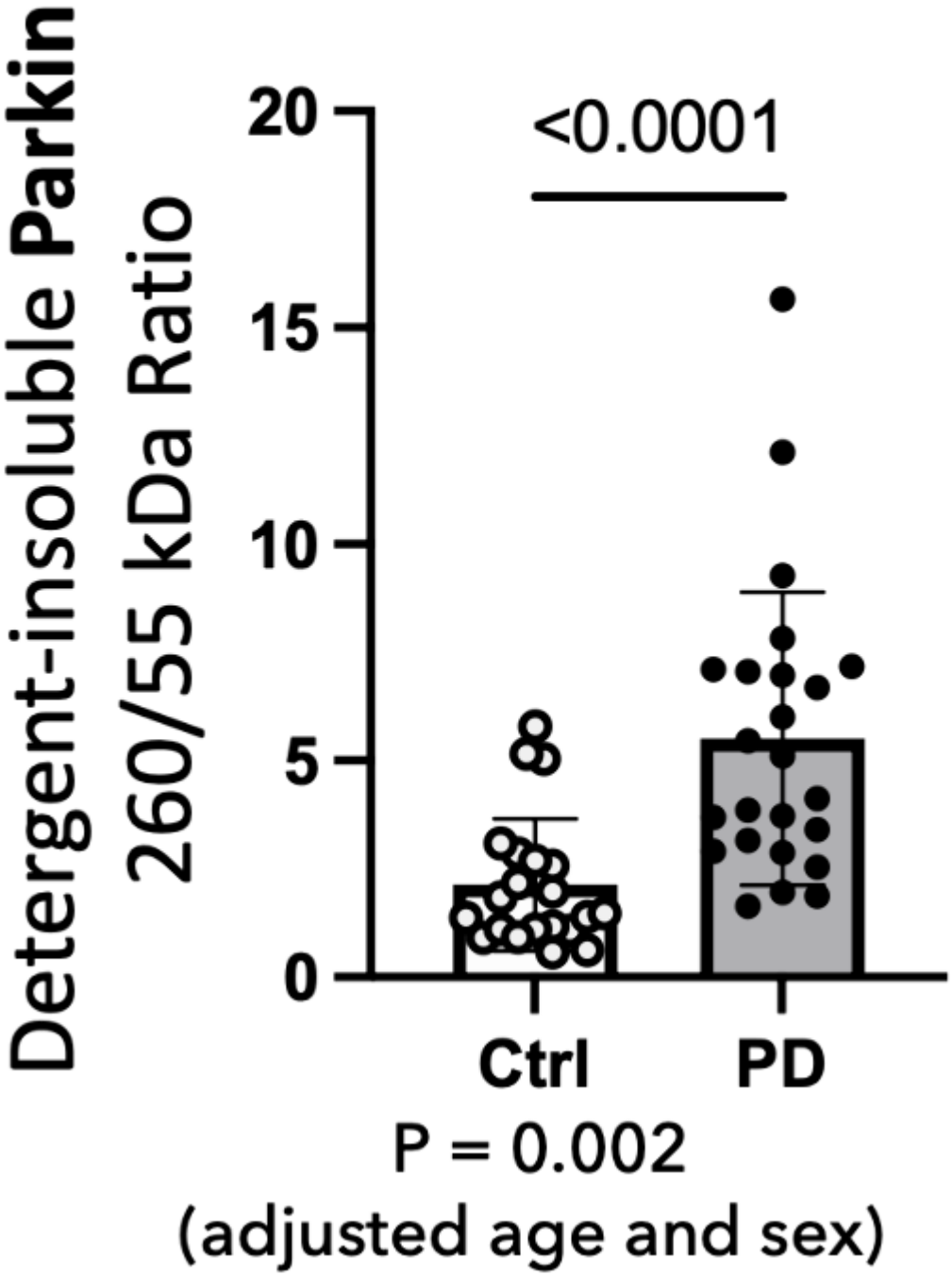
Aims: We investigated parkin and α-synuclein (α-syn) changes in the substantia nigra (SN) using a novel clinicopathology research platform comparing clinically characterized and age-matched PD patients (n= 24) with Controls (n= 21).
Methods: Two movement disorder neurologists performed clinical diagnosis. Post-mortem diagnosis was done by a neuropathologist. Data such as sex, age at onset, duration of disease, disease severity, prescribed drugs and their adverse effects (including motor complications) were available. Catecholamines were measured in the putamen using HPLC/electrochemistry. Protein levels were determined using Western immunoblots in soluble and insoluble fractions from SN, putamen, parietal cortex and cerebellum.

Substantia Nigra



Results: We first confirmed the massive loss of dopamine (DA) levels (-96%) in the putamen of PD patients, using HPLC/electrochemistry. An increase in an insoluble oligomeric form of parkin migrating at 260 kDa was observed in PD patients (+49%), alongside a decrease in the 55 kDa monomeric form (-47%). These changes in parkin (i) were specific for the SN, not present in putamen, parietal cortex and cerebellum, (ii) were associated with higher levels of phosphorylated α-syn (αsynP129) in the SN, (iii) correlated with disease duration, and (iv) were more prominent in individuals with motor complications. Analysis of parkin in animal

models of dopaminergic depletion or α-syn overproduction show that the aggregation of parkin is not a direct consequence of the death of nigral dopamine neurons.

Conclusions: In addition to dopamine loss, few other pathognomonic signs of PD have been described in the brain. The present results suggest that parkin in the SN is converted into an insoluble high molecular weight form during the course of the disease, along with dopaminergic denervation and increased α-synP129.

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SHIFT 01-045

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LRKK2, PARKIN, PINK1, DJ-1
2-3 April 2025

PERTURBED IONIC CURRENTS AND ACTION POTENTIAL FIRING IN IPSC-DERIVED CORTICAL NEURONAL MODEL OF LRRK2 G2019S PARKINSONISM

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Aims: Leucine-rich repeat kinase gene (LRRK2) mutations can lead to autosomal dominant late-onset familial Parkinson's (PD) clinically similar to idiopathic forms of the disorder; this makes it a powerful tool for assessing the pathophysiology of the disease. Previously, disease-related LRRK2 mutations, specifically G2019S knock-in mouse studies, have shown increased spontaneous and evoked glutamatergic activity in cortical neurons. Further understanding of LRRK2's role in synaptic communication represents an important route for identifying early targets in PD progression.
Methods: Changes to electrophysiological function will directly impact both motor and non-motor function. Thus, we can identify putative therapeutic targets by assessing the impact of disease-causing mutation (G2019S) and LRRK2 knockout (KO) on said function. Using the whole-cell patch clamp technique, we aim to determine the changes in action potential (AP) and ionic current properties in induced pluripotent stem cell (iPSC)-derived cortical neurons. Combined with the PatchSeq methodology, we will elucidate the channels contributing to the pathogenic alterations in electrophysiology.
Results: Preliminary data show perturbed ionic properties of G2019S and KO cortical neurons. G2019S neurons showed greater potassium (WT:54.2 ± 10.6 $pApF^{-1}$, n=6, N=2; GS: 82.2 ± 9.5 $pApF^{-1}$, n=11, N=3) and lower sodium current density (WT: -143 ± 40.7 $pApF^{-1}$, n=9, N=3; GS: -103.6 ± 16.7 $pApF^{-1}$, n=12, N=3) compared to WT. Furthermore, G2019S exhibited lower rheobase (hyperexcitability) compared to WT (WT = 38.7 ± 10.5 pA, n=8, N=3; GS = 19.3 ± 8.5 pA, n=7, N=3). G2019S neurons exhibited a greater percentage (43%) of repetitive APs than WT (25%). Meanwhile, KO exhibited an increased current density for sodium and potassium currents.
Conclusions: Our data reveal changes in the electrophysiological properties of LRRK2 mutant iPSC-derived cortical neurons that could underpin the physiological changes in PD.

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SHIFT 01-048

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

ALPHA-SYNUCLEIN – INDUCED SUBPOPULATIONS OF MICROGLIA

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Aims: Microglia is a major scavenger cell which is specialized in immunological responses in the brain. Previous transcriptome investigations of single nuclei have demonstrated that microglia are heterogeneous populations composed of numerous subpopulations with a range of functions. In Alzheimer's disease (AD) mice microglia showed higher cell heterogeneity, suggesting that in pathological conditions, microglia might differentiate into various subpopulations known as disease-associated microglia (DAM). Although these previous analyses suggested that microglia had characteristics associated with AD, an exhaustive investigation of how microglial subtypes change as Parkinson's disease progresses has not yet been addressed.
Methods: We analyzed the single-cell transcriptomes of microglia treated with neuronal cell-derived human α-synuclein in order to identify the PD-related subpopulations of microglia and clarify the early molecular features of the synuclein-specific microglia subpopulations.
Results: Human α-synuclein generated from neurons induced pro-inflammatory cytokines and signatures of cellular senescence. In single cell transcriptomic analysis, while the majority of naïve microglia comprise two discrete subpopulations exhibiting homeostatic and anti-inflammatory characteristics, microglia treated with synuclein demonstrated a significant increase in two other subpopulations exhibiting pro-inflammatory characteristics. Pseudo time analysis demonstrated that pathological α-synuclein treatment transforms resting microglia into pro-inflammatory microglia. Gene set analysis using feature genes revealed that the early-stage pro-inflammatory microglia subpopulation showed changes in transcription factors linked to macrophage polarization. We discovered that these pro-inflammatory microglia in early stage also exhibit alterations in the lipid metabolism.
Conclusions: Since lipid droplets are a major modulator of cellular senescence, these results suggested that the early transition of microglia induced by synuclein, which is mediated by transcription factors associated with macrophage polarization, may alter lipid metabolism and thus contribute to microglial senescence.

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SHIFT 01-053

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
2-3 April 2025

PARKINSON'S DISEASE – ASSOCIATIONS WITH ANXIETY, DEPRESSION, AND EXCESSIVE DAYTIME SLEEPINESS

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Aims: Published research on Parkinson's Disease (PD) has mostly focused on motor symptoms as indices for early intervention and symptom management with less focus on the non-motor symptoms. The purpose of this cross-sectional study is to examine the non-motor symptoms of anxiety, depression, and excessive daytime sleepiness as such indices, comparing their prevalences in healthy controls (HC), those with Prodromal PD (PPD), and those with PD.
Methods: This study used data from the Parkinson's Progression Markers Initiative (PPMI) database of the Michael J. Fox Foundation (MJFF) (https://www.michaeljfox.org/ppmi). The analysis was based on data from 2,241 participants enrolled between 2010 and 2023. Multinomial logistic regression was used to analyze the anxiety, depression, and excessive daytime sleepiness scores and the likelihood of being PD or having PPD compared to HC.
Results: Compared to health controls, the patient was more likely to be diagnosed with PPD (23%) or with PD (37%) per unit depression score, with PD (8%) per unit excessive daytime sleepiness score, and less likely to be diagnosed with PD (42%) if male. Neither anxiety score nor age affected the likelihood of being diagnosed with PPD or PD.
Conclusions: This study observed that, compared to healthy controls, patients with PPD are more likely to have depression and to be male, while patients with PD are much more likely to have depression and to have excessive daytime sleepiness. However, age and anxiety scores showed no association with either PPD or PD. These non-motor symptoms may also serve as indices for earlier diagnosis and treatment of the disease.

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SHIFT 01-054

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
2-3 April 2025

DEVELOPMENT OF PRE-CLINICAL MODELS FOR PATIENT STRATIFICATION IN PARKINSON'S DISEASE.

Sarah Ellwood[1], Anna Lavayssiere[1], Sally Cowley[2], Brent Ryan[1], Michele Hu[3], Richard Wade-Martins[4]
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Aims: Parkinson's Disease (PD) is the second most common neurodegenerative disease, with the majority of cases being idiopathic (iPD). iPD presentation varies between patients and the drivers behind this heterogeneity are unknown. To investigate this Lawton et al (2018) have clustered two PD cohorts into four subtypes revealing extremes of phenotype. Our aim is to test the hypothesis that pre-clinical iPSC models reflect clinical subgroups in iPD. We are generating 40 new idiopathic PD induced pluripotent stem cell (iPSC) lines for differentiation into dopaminergic neurons to explore the mechanisms behind these phenotypic differences.
Methods: Fibroblasts from iPD patients were selected for reprogramming from two clusters displaying fast motor progression and slow motor progression respectively. Fibroblasts were reprogrammed into iPSCs using Sendai virus vectors. After infection fibroblasts were plated on mouse embryonic fibroblasts to support emerging clones. Clones were picked and grown to p10 where cells should be virus free and self-sustaining. Once free of virus each cell line is expanded, banked and put through quality control steps.
Results: We have generated and banked 40 new idiopathic PD lines that have passed quality control (QC) steps. The cells were shown to be self-maintaining iPSC via FACs of pluripotency markers Nanog and Tra-1-60. All lines were tested for the presence mycoplasma and were found to be negative. SNP analysis was carried out and lines did not have any karyotypic abnormalities.
Conclusions: We have successfully reprogrammed >20 sPD fibroblasts into new iPSC lines which have been fully QC'd. These can now be utilized to investigate the mechanisms driving the phenotypic extremes of iPD, focussing on mitochondrial and lysosomal dysfunction which are common to PD.

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SHIFT 01-055

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
2-3 April 2025

MODULATING ALPHA-SYNUCLEIN PATHOLOGY IN HUMAN IPSC-DERIVED NEURONS BY SERCA INHIBITORS IN THE ABSENCE AND PRESENCE OF PRE-FORMED FIBRILS

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Aims: a-syn aggregates causes calcium dyshomesotasis by binding and activating endoplasmic reticulum calcium pump SERCA. To validate SERCA as a preclinical disease modifying drug target, we wanted to study both inclusion and non-inclusion a-syn aggregate-dependent cytopathology in human induced pluripotent stem cell (iPSC)-derived neurons and its sensitivity to treatment with SERCA inhibitors.
Methods: Human neurons were differentiated from an iPSC line carrying a doxycycline inducible A53T-a-syn-transgene. Some cultures were treated with PFF to induce templated aggregation and some with the SERCA calcium pump inhibitor cyclopiazonic acid (CPA) to normalize its overactivation. Aggregation was detected by i) immunofluorescence microscopy for pSer129-a-syn and aggregate specific epitopes, ii) proximity ligation assay (PLA)-based detection of non-inclusion a-syn aggregates, and iii) PLA detection of interactions between SERCA and a-syn aggregates.
Results: Transgenic expression of A53T-a-syn induced PLA-positive non-inclusion aggregates and interactions between SERCA and a-syn aggregates that both were reduced by treatment with inhibitors of SERCA. PFF treatment induced formation of inclusions, validated by MJF14 immunostaining, that also were reduced by treatment with inhibitors of SERCA.
Conclusions: A53T-a-syn overexpression in human iPSCs-derived neurons leads to i) formation of non-inclusion pathology, ii) interaction between a-syn aggregates and SERCA, and iii) PFF treatment induced templated inclusions. Restoration of SERCA-dependent calcium homeostasis by SERCA inhibitors reduces a-syn aggregates. Our data validates i) calcium dyshomeostasis as an important aspect of a-syn pathophysiology, and ii) SERCA as a disease modifying preclinical target in Parkinson's disease and synucleinopathies.

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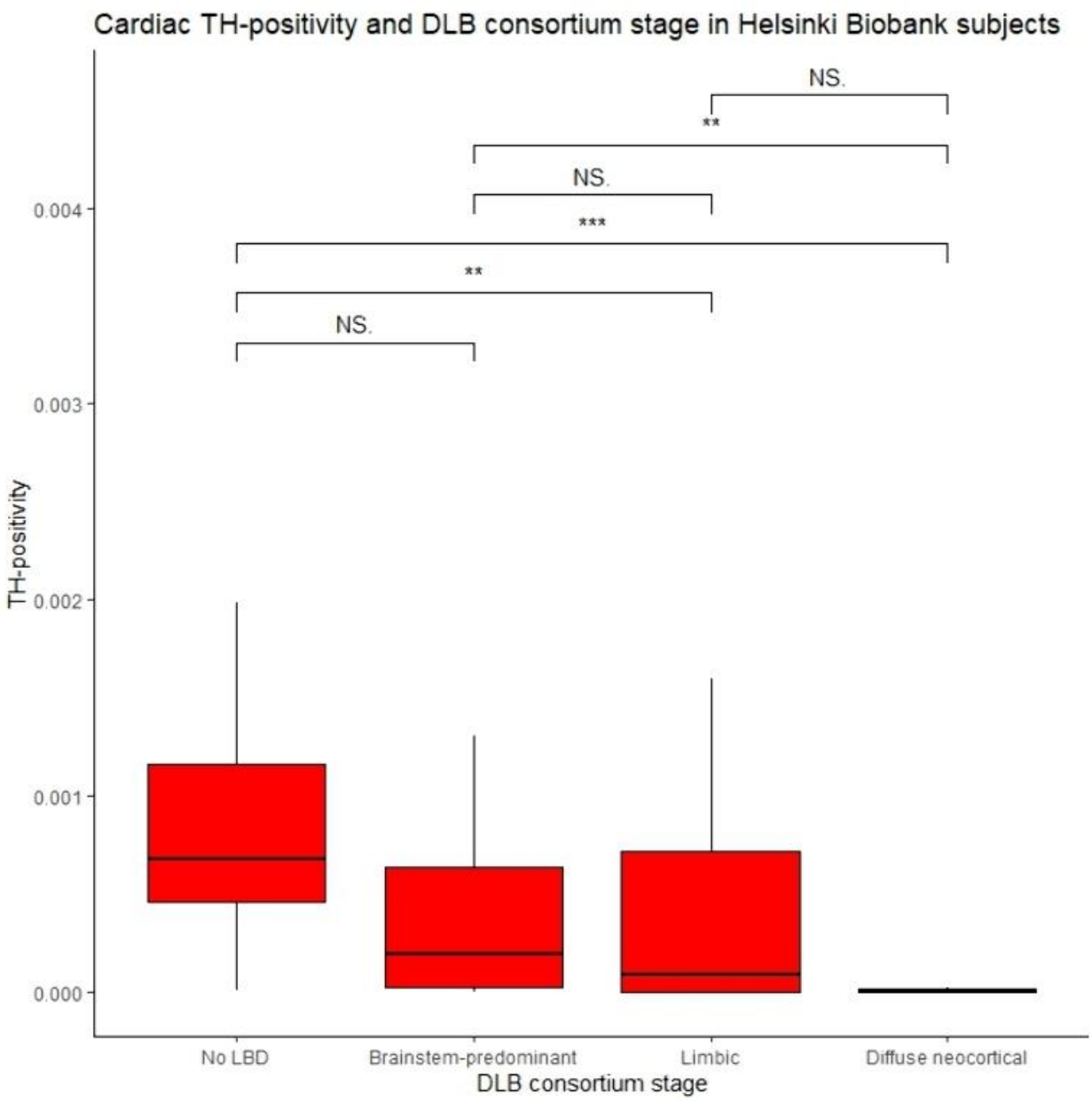
SHIFT 01-056

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
2-3 April 2025

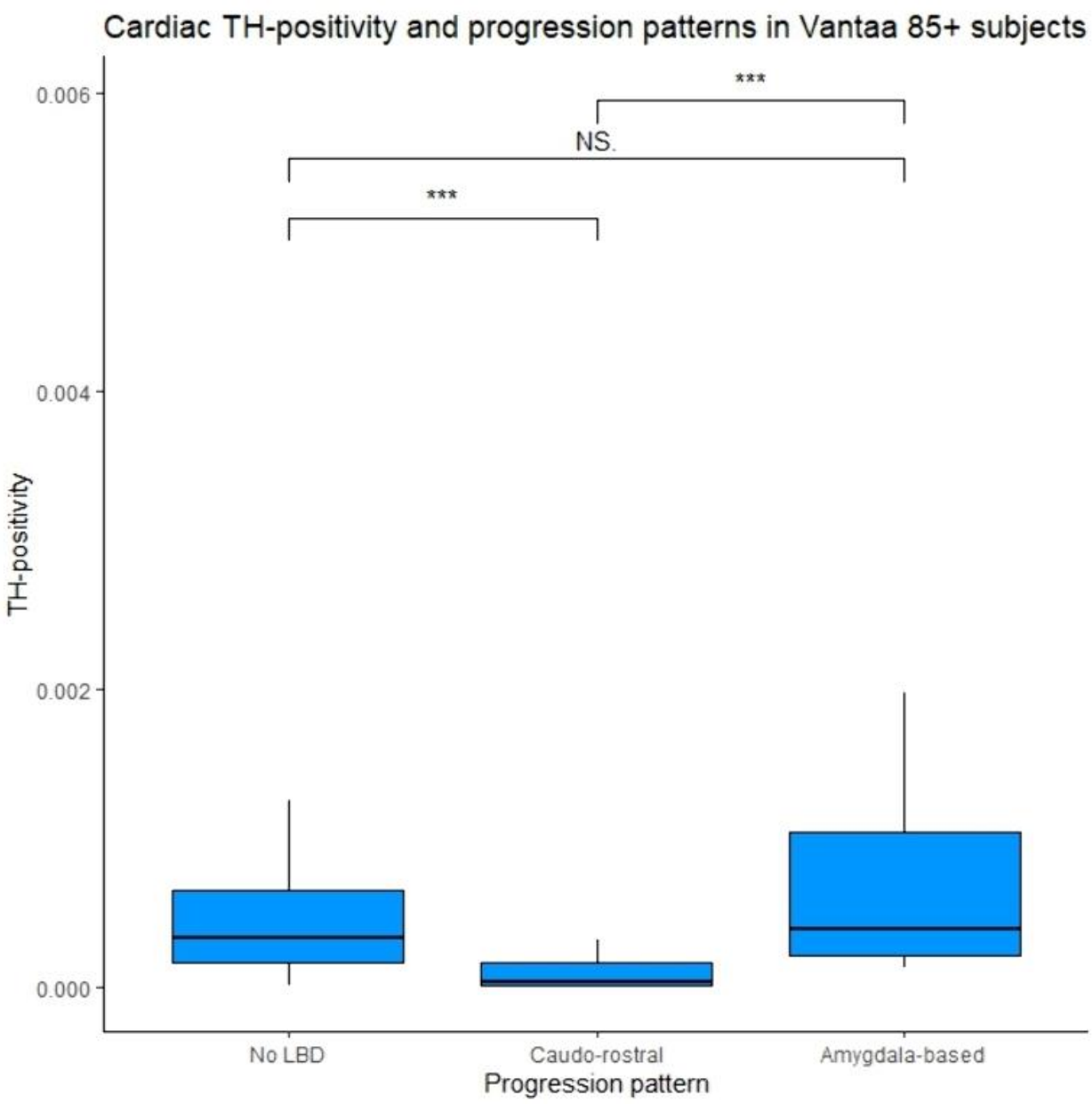
ASSOCIATION OF CARDIAC SYMPATHETIC DENERVATION WITH LEWY PATHOLOGY AND ITS PROGRESSION PATTERNS

Ville Kivistö[1], Eloise Kok[1], Mikko Mäyränpää[1,2], Tuomo Polvikoski[3], Liisa Myllykangas[4]
[1]University of Helsinki, Department Of Pathology, Helsinki, Finland, [2]HUS Diagnostic Center, Department Of Pathology, Helsinki, Finland, [3]Newcastle University, Translational And Clinical Research Institute, Newcastle upon Tyne, United Kingdom, [4]HUS Diagnostic Center, Helsinki University Hospital, Helsinki, Finland

Aims: Neuropathological and clinical data have led to hypotheses of multiple subtypes underlying Lewy pathology (LP) in Parkinson's disease and dementia with Lewy bodies. The main differentiating factor is whether the starting point is in the peripheral nervous system or the cerebrum, leading to a caudo-rostral or amygdala-based distribution of LP. A unique feature of the diseases is their peripheral manifestations, such as cardiac sympathetic denervation, seen as diminished tyrosine hydroxylase (TH) staining. The aim of this study is to quantify cardiac sympathetic denervation in Lewy body related diseases and to describe its relationship with the subtypes.
Methods: To quantify the effect of LP in the CNS on cardiac sympathetic innervation and its relationship to the proposed caudo-rostral and amygdala-based progression patterns, we have developed an AI algorithm that quantifies TH-positive staining in heart tissue and calculates its ratio to the analysed tissue area. Data from left ventricular samples of 76 subjects from Helsinki Biobank and interventricular septal samples of 135 subjects from the Vantaa 85+ -study were analysed.


Cardiac TH-positivity and DLB consortium stage in Helsinki Biobank subjects
NS.
**
NS.
***
**
NS.
0.004
0.003
0.002
0.001
0.000
TH-positivity
No LBD
Brainstem-predominant
Limbic
Diffuse neocortical
DLB consortium stage

Results:



In the Helsinki Biobank subjects, more diffuse LP as defined by DLB Consortium criteria was inversely correlated with TH-positivity. In the Vantaa 85+ subjects, TH-positivity was significantly lower in those with a caudo-rostral pattern compared to amygdala-based subjects and subjects with no LP, and this association held its statistical significance in multiple linear regression models containing different explanatory variables. **Conclusions:** These results concur with previous research demonstrating the degeneration of cardiac sympathetic innervation associated with the progression of LP in the CNS, describe for the first time the differences in cardiac pathologic manifestations between the proposed progression patterns and in this way provide novel evidence supporting multiple progression patterns of LP.

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SHIFT 01-057

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHERS
2-3 April 2025

ASSESSMENT OF THE NOVEL NEURONAL SYNUCLEIN DISEASE STAGING SYSTEM IN STRATIFYING DEMENTIA WITH LEWY BODIES PATIENTS

Maria Camila Gonzalez Velez[1], Silvia Morbelli[2], Patty Hoede[3], Charlotte Teunissen[3,4], Andrea Chincarini[5], Matteo Pardini[6], Afina Lemstra[7], Dag Aarsland[8]
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Aims: This study explores the applicability of the integrated Neuronal Synuclein Disease (NSD) staging system, initially developed for Parkinson's disease (PD), in patients clinically diagnosed with Dementia with Lewy Bodies (DLB). While both conditions are characterized by alpha-synuclein (αSyn) pathology, DLB exhibits unique clinical features. The NSD system anchors the diseases primarily on the presence of pathological αSyn (S), dopaminergic neurodegeneration shown by dopamine transporter (DAT) SPECT (D), and the degree of clinical signs and functional impairment. We hypothesize that most DLB patients will conform to the NSD staging system (S+/D+), although a significant subset (10-20%) may be S+/D-.
Methods: From the European DLB Consortium, we have selected 600 subjects with probable DLB, CSF and DAT-SPECT scans. CSF will be analyzed with αSyn Seed Amplification Assay (SAA) and robust AD biomarkers assays. DAT SPECT scans will be processed with DaTQuant software, incorporating additional metrics to improve the quantification of dopaminergic neurodegeneration. The study will compare DAT scan results with the Parkinson's Progression Markers Initiative dataset to establish z-scores and correlate these with clinical data and CSF markers. To test our hypothesis, we will conduct quantitative analyses to determine the proportion of DLB patients aligning with the NSD staging system and identify any deviations. Additionally, we will evaluate the correlation between AD pathology biomarkers and deviations from the NSD stages using statistical methods, such as regression analysis, to explore this inverse relationship. Furthermore, we will expand on the clinical considerations by not only assessing functional impairment but also addressing the key DLB core symptoms.
Results: We anticipate that a sample size of approximately 600 patients will yield robust results, with an margin of error of ±1.82%.
Conclusions: Preliminary results will be presented at ADPD.

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SHIFT 01-058

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHERS
2-3 April 2025

INVESTIGATING MICROBIOTA-IMMUNE INTERACTIONS IN THE 3KL MODEL OF PARKINSON'S DISEASE

Leah Beauchamp[1,2], Lily Palumbo[1], Danielle Leserve[1], Millicent Ekwudo[1], Shuqi Li[1,2], Silke Nuber[1,2], Howard Weiner[1,2], Laura Cox[1,2]
[1]Brigham and Women's Hospital, Ann Romney Center For Neurologic Diseases, Boston, United States of America, [2]Harvard Medical School, Boston, United States of America

Aims: The gut microbiome and inflammation contribute to Parkinson's disease (PD), but little is known about the role of specific microbes and the immunologic mechanisms.
Methods: To identify changes in the gut microbiota associated with disease progression in the 3KL model of PD, we utilized individual antibiotics to deplete specific bacterial populations. We administered metronidazole, neomycin, or penicillin to 3KL mice from 7-12 months of age, then tested motor function over time. We performed 16S rRNA sequencing on stool samples and characterized microglia responses by RNA sequencing. Based on findings from the antibiotic study, we cultured and administered *Alistipes muris* to mice from 6-8 months of age and performed flow cytometry on splenocytes and characterized microglia responses by RNA sequencing.
Results: Metronidazole slowed progression of motor phenotype in male 3KL mice. Using 16S sequencing, we identified *Alistipes muris* was selectively depleted by metronidazole. Using KEGG pathway analysis from microglial sequencing, we found that metronidazole altered disease-relevant processes such as PD and mitophagy, and immunologic processes including Th17 cell differentiation and IL-17 signaling. These data demonstrate that metronidazole slowed the progression of motor dysfunction, which we link to a reduction in *Alistipes*, a reduction in peripheral inflammatory T cell responses and a modulation of microglial PD- and inflammatory transcriptional profiles. Subsequently, we demonstrated that *Alistipes muris* worsened the motor phenotype of 3KL male mice and increased pro-inflammatory cytokine production in splenic T cells, including IFNγ from CD8+ T cells and IL-17 from γδ T cells.
Conclusions: These data suggest that *Alistipes*, a bacteria that is over abundant in PD, promotes PD pathogenesis by modulating microglia and peripheral immunity, and we identify IL-17 as a potential mechanistic pathway.

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SHIFT 01-059

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHERS
2-3 April 2025

PREDICTION OF FALLING IN PARKINSON' S DISEASE USING FILTER-BASED FEATURE SELECTION METHODS

Jong Sam Baik[1], Jin Whan Cho[2], Minkyung Kim[3], Myung Jin Chung[3], Hakje Yoo[4], Jinyoung Youn[2]
[1]Department of Neurology, Inje University Sanggye Paik Hospital, Seoul, Korea, Republic of, [2]Sungkunkwan University/samsung Seoul Hospital, Neurolgy, Seoul, Korea, Republic of, [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Radiology, Seoul, Korea, Republic of, [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Bio-mechatronic Engineering, Seoul, Korea, Republic of

Aims: Falling is a common and disabling symptom in patients with Parkinson's disease (PD). Various motor and non-motor parkinsonian symptoms, especially gait problems, can affect falling in PD. Therefore, we investigated the prediction model of falling in PD using figure selection methods.
Methods: We recruited PD patients at Samsung Medical Center from May 2022 to December 2023. All enrolled subjects performed objective gait analysis with GAITRite walkaway system (CIR Systems, Clifton, New Jersey, USA), and clinical falls and related symptoms were evaluated with Gait and Falls questionnaire (GFQ), timed up and go test, Tinetti gait and balance test, Korean Activities-Specific Balance Confidence Scale (K-ABC), hospital anxiety depression Scale, Korean version of Montreal Cognitive Assessment, Single-Question Screen for REM sleep behavior disorder, and Scale for Outcomes in Parkinson's disease for Autonomic Symptoms (SCOPA-AUT).
Results: We enrolled 273 PD patients in this study. An architecture was developed to predict the risk of falls in PD patients. This algorithm was designed to distinguish between healthy controls, Parkinson's disease patients who experienced falls, and Parkinson's disease patients who did not experience falls, by integrated analysis of clinical and gait data. Using machine learning techniques, an accuracy of 93% was ultimately achieved with Random Forest algorithm. Among various motor and non-motor parkinsonian symptoms, The scores fomr K-ABC, Tinneti test, SCOPA-Aut, velocity from GAITrite away were the most associated features with falling.
Conclusions: We suggested the prediction model of falling in PD patients using machine learning techniques and the associated features can give more understanding of patho-mechanism of falls in PD.

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SHIFT 01-061

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
2-3 April 2025

GRP78 INTERACTION MEDIATES THE NEUROPROTECTIVE EFFECTS OF CDNF AND HER-096

Aušra Domanska, Natalia Kulesskaya, Kira Holmström, Arnab Bhattacharjee, Henri Huttunen
Herantis Pharma, Espoo, Finland

Aims: CDNF and its C-terminal domain (C-CNDF) have been reported to display neuroprotective activity *in vitro* and *in vivo*. HER-096 is a brain-penetrating peptidomimetic derived from the active site of human CDNF protein and is developed as a disease-modifying treatment for Parkinson's disease. The aim of this study is to improve understanding of the multimodal mechanism of action of CDNF and HER-096.
Methods: We used small-angle X-ray scattering (SAXS), nuclear magnetic resonance (NMR), rat primary midbrain neuron model (MPP+), mutagenesis, and immunocytochemistry to elucidate the molecular mechanism of CDNF neuroprotection.
Results: CDNF binds to the nucleotide-binding domain (NDB) of GRP78 (a.k.a. BiP/HSPA5), a key ER chaperone and the master regulator of Unfolded Protein Response (UPR) pathway. Using SAXS and NMR methods, we solved the structure of C-CDNF in complex with GRP78-NBD and defined the key amino acid residues responsible for C-CDNF binding to GRP78-NBD by protein mutagenesis. In contrast to wildtype C-CDNF, C-CDNF mutants that do not bind GRP78-NBD show no neuroprotection in rat midbrain neuron model nor modulate UPR markers in response to stress. We show that GRP78 is exposed on the cell surface of cultured mesencephalic cells and thus potentially could serve as an entry receptor for CDNF. This structural information was used to support the design of HER-096, a blood-brain barrier penetrating CDNF mimicking peptidomimetic currently in Phase 1b clinical trials in Parkinson's disease.
Conclusions: UPR pathway is a key mediator of the neuroprotective activity of C-CDNF where interaction with GRP78 plays a central role. HER-096 is designed based on the GRP78-binding interface and mimics the cytoprotective effects of CDNF.

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SHIFT 01-063

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
2-3 April 2025

EARLY SYNAPTIC DYSFUNCTION INDUCED BY ALPHA-SYNUCLEIN AND AMYLOID-BETA TRIGGER NEURODEGENERATION IN PROTEINOPATHY; IN VITRO EVIDENCE

Catherine Botto, Laura Rouviere
Neuro-Sys, Gardanne, France

Aims: Misfolded proteins such as α-synuclein (αSyn) in Parkinson's disease (PD) and amyloid-beta (Aβ) in Alzheimer's disease (AD) are key drivers of synaptic dysfunction, triggering the neurodegenerative cascades characterizing these disorders. Aβ oligomers and αSyn protofibrils are identified as the most pathogenic species among their various conformations. The synaptic affinity of Aβ is well-characterized, with toxic Aβ oligomers accumulating directly in synaptic clefts and disrupting synaptic function. The synaptic interactions of αSyn, however, remain less understood, αSyn protofibrils being thought to be taken up by neurons and transported to synapses. This study aimed to investigate and to compare the differing mechanisms by which Aβ and αSyn induce early synaptic dysfunction.
Methods: We developed *in vitro* models using primary rat hippocampal or mesencephalic neuronal cultures which were exposed to $A\beta_{1-42}$ oligomers (0.2 µM, 24-96h) or αSyn protofibrils (250 nM, 48h-96h). Immunofluorescence staining assessed several pre- and post-synaptic markers over time, to observe protein-induced synaptic dysfunction, synaptic loss, and early pathological changes.
Results: Both Aβ and αSyn exposure resulted in significant synaptic loss in the different neuronal populations. Aβ treatment in neurons induced rapid synaptic death and increased Tau phosphorylation, while αSyn resulted in a progressive reduction in synaptic markers. Notably, synaptic impairment (associated with mitochondrial defects) preceded neuronal death in both models, suggesting that early synaptic dysfunction is a critical trigger for neurodegeneration in these proteinopathies.
Conclusions: The *in vitro* models developed in this study offer a reliable tool for investigating early synaptic toxicity associated with Aβ and αSyn pathology. Our results support that targeting synaptic preservation may offer promising therapeutic strategies to prevent the cascade of widespread neuronal damage initiated by toxic protein aggregates in AD and PD.

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SHIFT 01-064

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
2-3 April 2025

INVESTIGATING KEY NEURAL ACTIVITY METRICS UNDERLYING PATHOPHYSIOLOGY ASSOCIATED WITH IN-VITRO MODEL OF PARKINSON'S DISEASE (PD)

Amit Chouhan[1], Eddie Burns[1], Cyntha Van Der Berg[2], Berke Gurkan[2], Kimberly Lo[2], David Ketskemety[2], Mathew Hembury[2], Malika Bsibsi[2], Cindy Loomans[2], Dario Magnani[1], Mariangela Iovino[1]
[1]Charles River Laboratories, Saffron Walden, United Kingdom, [2]Charles River Laboratories, Leiden, Netherlands

Aims: Functional characterization of an in-vitro model of PD obtained using patient iPSC-derived Dopamine Neurons cultured on Multi-Electrode Array (MEA) Platform.
Methods: Commercially available iPSC-derived Dopamine Neurons with PD linked genetic mutations SNCA (A53T) & GBA (N370S) were used for this study. Human iPSC-derived Dopamine Neurons were co-cultured with healthy control iPSC-derived Astrocytes for up to 5 weeks using standard culture medium and sterile conditions. Neural activity using Multi-Electrode array platform was recorded twice a week starting at Days in-vitro (DIV)-7. Data were processed using the neural metric tool (Axion BioSystems) and GeneData software.
Results: All used human iPSC-derived dopaminergic neurons fire spontaneously and display good network activity and cell coverage over MEA electrodes. Human iPSC-derived dopaminergic neurons with PD linked mutations, SNCA (A53T) & GBA (N370S), show increase in functional activity (DIV-20). Human iPSC-derived dopaminergic neurons with PD linked mutations display enhanced synchronised network activity (DIV-8) and have more spikes/network burst (DIV-20).
Conclusions: We successfully demonstrate that in-vitro models of Parkinson's disease developed using human iPSC-derived dopaminergic neurons provide valuable insight to understand disease associated pathophysiology at neuronal and at neural network level. This model therefore serves as a valuable tool for advancing translational drug discovery efforts for Parkinson's disease.

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SHIFT 01-067

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
2-3 April 2025

LEVERAGING FEDERATE LEARNING TO ACCELERATE DRUG DEVELOPMENT FOR PARKINSON'S DISEASE

Laura Gaetano[1], Graham Jones[1], Jamie Adams[2], Chrystalina Antoniades[3], Bastiaan Bloem[4], Camille Carroll[5], Jesse Cedarbaum[6], Joshua Cosman[7], David Dexter[8], Marissa Dockendorf[9], Jeremy Edgerton[10], Erkuden Goikoetxea[11], Derek Hill[12], Fay Horak[13], Elena Izmailova[14], Tairmae Kangarloo[15], Dina Katabi[16], Catherine Kopil[17], Michael Lindemann[18], Jennifer Mammen[19], Ken Marek[20], Kevin Mcfarthing[21], Anat Mirelman[22], Martijn Muller[23], Gennaro Pagano[24], Judith Peterschmitt[25], Jie Ren[26], Lynn Rochester[5], Sakshi Sardar[23], Andrew Siderowf[27], Tanya Simuni[28], Christine Swanson-Fischer[29], John Wagner[30], Amit Khanna[31], Diane Stephenson[32]
[1]Novartis AG, Basel, Switzerland, [2]University of Rochester, Rochester, United States of America, [3]University of Oxford, Oxford, United Kingdom, [4]Radboud University Medical Center, Parkinson Center Nijmegen (ParC), Nijmegen, Netherlands, [5]Newcastle University, Newcastle-upon-Tyne, United Kingdom, [6]Coeruleus Clinical Sciences, Yale University department of Neurology, Woodbridge, United States of America, [7]AbbVie Pharmaceuticals, North Chicago, United States of America, [8]Parkinson's UK, London, United Kingdom, [9]Merck & Co., Inc, Kenilworth, United States of America, [10]Biogen Inc., Cambridge, United States of America, [11]UCB Pharmaceuticals, Leuven, Belgium, [12]University College London, London, United Kingdom, [13]Clario, Portland, United States of America, [14]Koneksa Health, New York, United States of America, [15]Takeda Pharmaceuticals, Cambridge, United States of America, [16]MIT, Cambridge, United States of America, [17]The Michael J. Fox Foundation for Parkinson's Research, New York City, United States of America, [18]Roche Information Solutions, Roche Diagnostics, F. Hoffmann-La Roche Ltd., Basel, CH, Basel, Switzerland, [19]University of Massachusetts Dartmouth, Dartmouth, United States of America, [20]Insitutute for Neurodegenerative Disorders, Neurology, New Haven, United States of America, [21]Parkinson's research advocate, Oxford, United Kingdom, [22]Tel-Aviv Medical Center, Neurology, Tel-Aviv, Israel, [23]Critical Path Institute, Tucson, United States of America, [24]Roche Ltd, Neuroscience And Rare Disease, Basel, Switzerland, [25]Sanofi, Cambridge, United States of America, [26]Merck & Co. Ink., Rahway, United States of America, [27]University of Pennsylvania, Philadelphia, PA, United States of America, [28]Northwestern University, Feinberg School Of Medicine, Chicago, United States of America, [29]National Institutes of Health, Bethesda, United States of America, [30]Koneksa Health, Medical Office, New York, United States of America, [31]Novartis Pharma AG, Basel, Switzerland, [32]Critical Path Institute, Critical Path For Parkinson's, Tucson, United States of America

Aims: To advocate for leveraging recent advances in the deployment of artificial intelligence models for federated data analysis and Federated Learning (FL) in deriving insights from multimodal data (including

digital data) to increase our understanding of disease pathology, etiology and symptom manifestation, and to ultimately accelerate drug development in Parkinson's Disease (PD).

Methods: Pros/cons of data sharing (i.e. distribution of the same data to multiple entities), federated data sharing networks (i.e. collaborating parties collectively access, analyze geographically distributed datasets via several decentralized, interconnected locations) and FL (i.e. decentralized raw data held by participants that is not shared or moved but, instead, subjected to artificial intelligence/ machine learning models deployed on the data where they are locally trained) approaches were outlined. Key considerations were identified and a roadmap for adoption in PD is proposed.

Results: Compared with data sharing and despite technical challenges, FL approaches are promising, since they can preserve sensitive data fidelity and privacy, while making pooled data analysis possible. When designing a prospective roadmap for FL adoption, key considerations include: (1) what should we measure, analyse and when?, (2) how should we measure, analyse it?, (3) how can we leverage existing data sources?. Multi-stakeholder efforts in the past, e.g. MELLODDY project, Effiris platform, have already demonstrated the potential benefit for the drug discovery arena.

Conclusions: New advances and new data available for FL can spearhead coordinated efforts to accelerate successful drug development in PD. Given the highly engaged PD community of academics, non-profit, people with Parkinson's and corporate leaders, these approaches could become a realistic near-term objective, benefiting all involved.

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SHIFT 01-069

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / DRUG DELIVERY SYSTEMS
2-3 April 2025

TALINEUREN IN PARKINSON'S DISEASE: PRELIMINARY RESULTS OF PHASE I TRIAL NEON

Vanessa Aires[1], Céline Kaufmann[1], Silvia Erni[1], Camille Peitsch[1], Michael Schüpbach[2], Stefan Halbherr[1]
[1]InnoMedica Schweiz AG, Bern, Switzerland, [2]Institute of Neurology, Konolfingen, Switzerland

Aims: Monosialotetrahexosylganglioside (GM1) is a promising molecule with neuroprotective and immunomodulating properties. Treatment with GM1 is documented to be effective in several neurological indications. In Parkinson's disease (PD), administration of GM1 has yielded encouraging results in preclinical models and a randomized placebo-controlled trial. However, therapeutic breakthrough has been hampered by limited delivery to the CNS and feasibility of chronic treatments. Talineuren, a liposomal formulation of GM1, was designed to improve GM1 biodistribution and reduce administration frequency. In the Phase I trial NEON, we assess the safety, tolerability, and preliminary efficacy of weekly Talineuren infusions in PD patients.
Methods: Since December 2021, a total of 22 PD patients have been enrolled in this ongoing single-center, single-arm, open-label Phase I clinical trial. After determining the maximum suitable dose by dose escalation, patients have been treated with weekly Talineuren infusions as add-on therapy. Primary objectives: Safety and tolerability. Secondary objective: Determination of maximum suitable dose and pharmacokinetic profile. Preliminary efficacy data based on clinical assessments (e.g. MDS-UPDRS).
Results: Valuable long-term data (>2 years) on chronic Talineuren treatment have been collected. The determined maximum suitable dose of 720mg has been generally well tolerated. In some patients, acute infusion reactions were observed, which could be reduced with diminishing infusion rate. Preliminary data suggests clinical benefits associated with Talineuren administration: 8 weeks after treatment start, MDS-UPDRS total "on" and "off" scores improved before stabilizing over hitherto >2 years treatment duration.
Conclusions: The consistent preliminary results on symptom amelioration and stabilization over up to >2 years treatment go in line with previous findings and highlight the potential of Talineuren for treating PD. Lastly, the hypothesized mode of action could go beyond PD therapy and might be relevant for other neurodegenerative disorders.

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SHIFT 01-070

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / ENZYME MODULATORS
2-3 April 2025

A PHASE 1 STUDY OF NEU-411, AN ORALLY AVAILABLE, POTENT, SELECTIVE, AND BRAIN-PENETRANT SMALL-MOLECULE INHIBITOR OF LRRK2

Sam Jackson[1], Suresh Dheerendra[1], Luc Desnoyers[1], Rob Rubens[1], Fatta Nahab[1], Carol Wong[1], Jim Zheng[1], Tam Dang[1], Scott Savage[1], Kathy Butler[1], Chris Wynne[2]
[1]Neuron23, South San Francisco, United States of America, [2]New Zealand Clinical Research, Christchurch, New Zealand

Aims: We conducted a Phase 1 study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of NEU-411, an orally available, potent, selective, and brain-penetrant small-molecule inhibitor of leucine-rich repeat kinase 2 (LRRK2) in healthy adults and elderly volunteers. Gain-of-function mutations in LRRK2 are known causes of familial Parkinson's disease (PD) and increased LRRK2 pathway activity is implicated as a driver of idiopathic PD.
Methods: This was a Phase 1 study conducted in five parts. Part A was a single ascending dose study including a food effects (FE) evaluation; Part B was a seven-day multiple ascending dose study; Part C was a 28-day dosing study testing three dose levels; Part D was a non-randomized, two-period open-label, single dose sequential design to determine if there was a drug-drug interaction (DDI) with itraconazole, a strong cytochrome P450 3A4 inhibitor; and Part E was a six-sequence, cross-over, randomized open-label study design to evaluate the relative bioavailability and FE of NEU-411 in a capsule formulation as compared to NEU-411 in a tablet formulation.
Results: NEU-411 was well tolerated in a total of 123 healthy adult and healthy elderly volunteers. There were no serious adverse events and all adverse events were either mild or moderate in severity. An analysis of phospho-LRRK2 and other biomarkers indicated robust, dose-dependent target engagement.
Conclusions: The risk-benefit and pharmacokinetic-pharmacodynamic (PK-PD) profile of NEU-411 warrant further study in patients with PD. Neuron23 is developing a proprietary companion diagnostic designed to identify patients with LRRK2-driven PD who may be more likely to benefit from treatment with NEU-411. The NEULARK Phase 2 proof-of-concept study, a placebo-controlled, randomized clinical trial of NEU-411 in diagnostically positive patients with LRRK2-driven disease will test this hypothesis.

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SHIFT 01-071

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / IMMUNOTHERAPY
2-3 April 2025

A PRECLINICAL EVALUATION OF UCB7853, AN ANTI ALPHA-SYNUCLEIN ANTIBODY IN CLINICAL DEVELOPMENT FOR PARKINSON'S DISEASE

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Aims: UCB7853 is a humanised immunoglobulin G4P antibody that targets the C-terminal region of alpha-synuclein. Comprehensive *in vitro* and *in vivo* studies were conducted to evaluate the potential of UCB7853 to prevent the development of pathological alpha-synuclein, as a treatment for people with Parkinson's disease (PD).
Methods: UCB7853 was tested against recombinant alpha-synuclein pre-formed fibrils in *in vitro* binding and cellular seeding assays, as well as in an *in vivo* mouse seeding model. To confirm the ability to bind pathological human alpha-synuclein, UCB7853 was assessed by immunohistochemistry and immunoprecipitation using samples from people with synucleinopathies. Pharmacokinetic studies were performed in cynomolgus monkeys.
Results: UCB7853 preferentially bound to fibrillar forms of alpha-synuclein and recognised pathological inclusions in people with PD, LBD and MSA. UCB7853 potently inhibited aggregation induced by fibrillar alpha-synuclein in both *in vitro* and *in vivo* models. Using real-time quaking-induced conversion, we demonstrated that UCB7853 bound to, and removed, seed-competent alpha-synuclein species from the CSF of people with PD and LBD. *In vivo* studies conducted in non-human primates showed that UCB7853 had excellent pharmacokinetic properties.
Conclusions: Collectively, these preclinical findings support the clinical development of UCB7853 as a treatment for people with PD.

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SHIFT 01-072

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / IMMUNOTHERAPY
2-3 April 2025

PHASE I STUDY RESULTS: UCB7853 SAFETY, TOLERABILITY AND PHARMACOKINETICS IN HEALTHY PARTICIPANTS (SINGLE-ASCENDING DOSE) AND PEOPLE WITH PD (MULTIPLE-ASCENDING DOSES)

Philip Kremer[1], Malcolm Boyce[2], Tasmin Arnould[3], Anne Benoit[4], Maria Burian[5], Laurent Detalle[5], Pepijn Eijsvogel[1], Rachna Kasliwal[6], Maria Key Prato[4], Walter Krauwinkel[5], Annelies Resink[4], Kathy Rice[7], Tim Buchanan[5]
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Aims: This first-in-human, Phase I, randomised, double-blind, placebo-controlled study assessed the safety, tolerability and pharmacokinetics (PK) of UCB7853, a recombinant humanised, full-length immunoglobulin G4P monoclonal antibody that preferentially targets oligomeric forms of alpha-synuclein, in single ascending doses (SAD; Part 1) in healthy participants, and multiple ascending doses (MAD; Part 2) in people with Parkinson's (PwP).
Methods: Participants included healthy males aged 18–55 years (SAD), and males or females aged 40–80 years, with a clinical diagnosis of Parkinson's disease (PD), bradykinesia and muscular rigidity and/or resting tremor and Hoehn and Yahr stage ≤3 (MAD). Participants were randomised 3:1 to receive UCB7853 or placebo. The primary endpoint was incidence of treatment-emergent adverse events (TEAEs). Laboratory parameters, vital signs, PK (in serum and cerebrospinal fluid [CSF]) and anti-drug antibodies (ADAs) in serum were also assessed.
Results: Forty healthy participants each received 1 dose of study drug (UCB7853, n=30; placebo, n=10); the incidence of TEAEs was similar between UCB7853 (n=22 [73%]) and placebo (n=7 [70%]). Study duration: 141 days. Seventeen PwP received ≥1 dose of study drug (UCB7853, n=13; placebo n=4); all participants had TEAEs. Study duration: 197 days. There were no serious TEAEs, discontinuations due to AEs or deaths reported. UCB7853 had a linear PK over the dose range evaluated, a low volume of distribution, slow clearance and long half-life; distribution to CSF was confirmed. No differences in PK were identified between healthy participants and PwP. There were no meaningful or dose-related trends observed in vital signs and laboratory parameters. ADAs were detected in one healthy participant receiving UCB7853.
Conclusions: UCB7853 was well tolerated with an acceptable safety profile in healthy participants and PwP. These results support further clinical development of UCB7853 in PD.

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SHIFT 01-073

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROTRANSMITTER-BASED AGONISTS AND MODULATORS, GLP-1 RECEPTOR AGONISTS
2-3 April 2025

DESIGNING A PATIENT-INFORMED TRIAL: ATLANTIS PHASE II STUDY OF THE D1 RECEPTOR PAM, UCB0022, IN ADVANCED PD

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Aims: UCB0022 is an orally available, selective, positive allosteric modulator of the D1 receptor (D1 PAM) that enhances D1 signalling only when and where dopamine is released. We describe ATLANTIS (NCT06055985), a Phase IIa study evaluating efficacy, safety, tolerability and pharmacokinetics (PK) of oral UCB0022 in people living with advanced Parkinson's disease (PD), including how people with Parkinson's (PwP) helped shape the study.
Methods: ATLANTIS is a multicentre, randomised, double-blind, parallel-group, placebo-controlled study. Participants (aged 35–85 years; ON state H&Y Stages 1–3; PD diagnosis for ≥5 years with daily motor fluctuations) are randomised (1:1:1) to receive low-dose UCB0022, high-dose UCB0022 or placebo for 10 weeks (followed by a 2-week safety follow-up). UCB0022 or placebo are administered as adjunctive treatment to standard-of-care, including at least levodopa therapy. Primary endpoint is change from Baseline to Day 70 in the average number of hours of OFF time (Hauser diary). Secondary endpoints include safety and PK. A Patient Council (comprising Patient Organisations, PwP, and care partners in the UK and USA) was established during study development to review and inform the protocol and co-create patient-facing materials (eg., informed consent forms and trial recruitment materials).
Results: ATLANTIS commenced in 2023 and will enrol 189 participants from sites across the USA. Through co-creation with the long-term Patient Council, direct and consistent engagement with PwP identified actionable insights and helped optimise study design and implementation, including: reducing duration of study visits, implementing a transportation service and ensuring patient-facing materials were understood/endorsed by PwP.
Conclusions: ATLANTIS is a proof-of-concept study, the design and implementation of which was shaped from the earliest stages by direct and consistent involvement of PwP. Findings from this study will inform future clinical development of UCB0022.

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SHIFT 01-075

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / DISEASE-CAUSING MUTATIONS
2-3 April 2025

RFC1 EXPANSIONS IN PARKINSONISM

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Aims: Cerebellar ataxia with neuropathy and vestibular areflexia syndrome (CANVAS) is a neurodegenerative disease caused by biallelic mutations in the *RFC1* gene, mostly $(AAGGG)_n$ expansions in intron 2 (Cortese., Nat Genet. 2019). Several studies reported null variants in patients (Benkirane., Brain. 2022 ; Weber., Brain. 2023) supporting the hypothesis of a loss-of-function mechanism. Our team revealed that 10% of CANVAS patients had parkinsonism, a rate 10-fold higher than matched population of similar age (Huin., Brain. 2022). Moreover, rare cases of *RFC1* biallelic expansions have been reported in patients with atypical parkinsonism. Our hypothesis is that parkinsonism is an entryway into *RFC1* pathology.
Methods: We screened for *RFC1* pathogenic expansions in four cohorts of patients with Parkinson's disease (PD) (n=744), inherited parkinsonism (n= 846), atypical PD with dysautonomia (n=368) and multiple system atrophy (MSA) (n=194). We used the methods of molecular diagnosis of CANVAS, with a duplex fluorescent PCR, three repeat-primed PCR and a long-range PCR with southern blot revelation.
Results: We uncovered 11/2152 (0.50%) biallelic $(AAGGG)_n$ *RFC1* expansions in our four cohorts with a higher frequency of homozygous carrier in MSA cohort (3/194 ; 1,55%). These patients' phenotypes consist in three atypical PD with dysautonomia, one atypical PD with cerebellar syndrome, two typical *RFC1*-related disorders and three probable MSA without sensory neuropathy. Two patients had a classical PD for 6,5 years and were treated by neurostimulation.
Conclusions: Our results favor an association between *RFC1* mutations and parkinsonism. Further phenotypic characterizations are needed to propose guidelines for the molecular screening, but some patients have a phenotype undistinguishable from a classical PD. We suggest that patients with unknown causes of inherited parkinsonism or MSA be screened for *RFC1* mutations.

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SHIFT 01-076

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / DISEASE-CAUSING MUTATIONS
2-3 April 2025

THE FREQUENCY, MUTATION SPECTRUM, AND BLOOD BIOMARKERS IN GBA1-ASSOCIATED PARKINSON'S DISEASE: A KOREAN COHORT STUDY

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Aims: Variants in the GBA1 gene are a significant genetic risk factor for Parkinson's disease (PD). Measuring glucocerebrosidase (GCase) activity and glucosylsphingosine (GluSph) levels is essential for understanding disease progression and developing targeted therapies for GBA1-associated PD (GBA-PD). This study aimed to investigate the frequency and mutation spectum in Korean patients with PD and assess blood GCase activity and GluSph levels to evaluate their diagnostic accuracy in distinguishing GBA-PD from non-GBA-PD patients.
Methods: We recruited 464 patients with PD and performed Sanger sequencing of the entire GBA1 gene. A subset of 25 GBA-PD and 27 non-GBA-PD patients were analyzed for GCase activity and plasma GluSph levels. GCase activity was quantified using the 4-methylumbelliferyl β-D-glucopyranoside leukocyte assay. The GCase activities of each patient and three healthy controls were measured simultaneously. The GCase patient/controls ratio (%) was also calculated for consistency (GCaseRatio). Plasma glucosylsphingosine (GluSph) levels were measured using LC-MS/MS. Diagnostic accuracy was evaluated using the area under the curve (AUC) values.
Results: Heterozygous GBA1 variants were detected in 30 patients (6.4%), with a higher frequency in early-onset PD than in late-onset PD. Most of these variants were classified as severe. No significant differences in demographics or disease characteristics were found between GBA-PD and non-GBA-PD patients. GCaseRatio was significantly lower in patients with GBA-PD ($p<0.01$). Plasma GluSph levels were higher in GBA-PD patients and were negatively correlated with the GCaseRatio ($r=-0.326$; $p<0.01$). The GCaseRatio demonstrated higher diagnostic accuracy (AUC = 0.93) than plasma GluSph levels (AUC = 0.77).
Conclusions: This study highlights that GCase activity and plasma GluSph levels are crucial biomarkers for distinguishing GBA1-PD from non-GBA-PD in a Korean population, where the majority of variants are classified as severe.

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SHIFT 01-078

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2-3 April 2025

GENETIC ARCHITECTURE OF PARKINSON'S DISEASE: INVESTIGATING THE RELATIONSHIPS BETWEEN POLYGENIC RISK SCORES AND NEUROANATOMICAL FEATURES

Houman Azizi[1,2,3], Alexandre Pastor-Bernier[2], Christina Tremblay[4], Nooshin Abbasi[1], Lang Liu[1,5], Konstantin Senkevich[1], Peter Savadjiev[1,6], Eric Yu[5], Jean-Baptiste Poline[1,6], Ziv Gan-Or[1], Yashar Zeighami[2,7], Alain Dagher[1,6]
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Aims: Parkinson's disease (PD) is associated with various genetic risk factors and brain structural alterations. However, how these genetic factors influence brain anatomy and potentially contribute to disease risk remains unclear. Here we aimed to characterize neuroanatomical correlates of PD genetic risk and identify genetically determined patterns of cortical organization that may relate to PD susceptibility.
Methods: Associations between polygenic risk scores of PD (PD-PRS) and structural and microstructural brain measures were examined using linear regression, and potentially causal relationships between brain structure and PD diagnosis were investigated through Mendelian randomization. Cortical regions were separated into factors based on the genetic similarity of their surface area (SA) using genomic structural equation modeling (GenomicSEM), and linear regression was used to investigate the association between each factor's SA and their anatomically connected white matter tract fractional anisotropy (FA).
Results: PD-PRS showed widespread positive associations with cortical SA, subcortical volumes, and white matter FA. Mendelian randomization revealed increased cortical SA and larger subcortical volumes to have a potentially causal effect on PD development. GenomicSEM identified six genetically distinct cortical SA factors which were in turn significantly associated with the FA of their anatomically connected white matter tracts.
Conclusions: Our findings reveal a link between PD genetic risk and brain structure, indicative of greater size of grey matter and higher white matter integrity potentially leading to increased risk of PD development. Additionally, our results suggest that cortical surface area and white matter microstructure may be influenced by shared genetic factors especially during early brain development. These results provide new insights into how genetic risk factors might shape brain structure and contribute to PD susceptibility, potentially through developmental mechanisms.

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SHIFT 01-079

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2-3 April 2025

COFFEE CONSUMPTION LINKED TO DELAYED AGE AT ONSET OF PARKINSON'S DISEASE

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Aims: To explore the genetic association and potential causal relationship between caffeine consumption and the age at onset (AAO), risk, and progression of Parkinson's disease (PD).
Methods: Methods: We employed Mendelian randomization (MR) and genetic correlation methods to assess the causal relationship between coffee consumption and PD. MR analysis was conducted with coffee consumption as the exposure and PD risk, AAO, and motor and cognitive progression as outcomes. We then analyzed common and rare variants in genes related to caffeine metabolism and receptors (*ADORA2A*, *AHR*, *CYP1A2*, *NAT2*, *UGT1A6*, and *XDH*). Common variants were extracted from the largest PD GWAS (Nalls et al., 2019 Lancet), while rare variant analysis (MAF<1%) was performed using SKAT-O in two independent cohorts: AMP-PD (N cases=1,963; N controls=3,093) and UKBB (N cases = 2,966; N controls = 64,936). We also applied pathway-specific polygenic risk score (PRS) of genes related to coffee consumption to assess PD risk.
Results: Results: After identifying and excluding several pleiotropic variants, a significant association was observed between coffee consumption and delayed PD AAO (IVW: OR, 1.91; 95% CI 1.53–2.38; P = 8.072e-09). No causal link was found between caffeine consumption and PD risk or progression. Additionally, no significant genetic correlation between coffee consumption and PD risk was observed. Common variant analysis and pathway PRS did not yield any significant associations. Rare variant analysis identified a nominal association between all *NAT2* rare variants and PD (P=0.01; Pfdr=0.50) and between *CYP1A2* variants with high CADD scores (>20) and PD (P=0.027; Pfdr=0.24).
Conclusions: Conclusions: Our study suggests a potential protective association between coffee consumption and delayed AAO in PD. However, neither common nor rare variant analysis provided strong evidence for coffee consumption's role in overall PD risk.

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SHIFT 01-082

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

EVALUATING THE ASSOCIATION BETWEEN DIAGNOSED SLEEP DISORDERS AND PARKINSON'S DISEASE IN THE ALL OF US RESEARCH PROGRAM COHORT

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Aims: Parkinson's disease (PD) is the second most common neurological disease and is expected to double in prevalence in the coming decades. This coincides with global advances toward a 24/7 culture and significant changes in sleep habits worldwide. The objective of this work is to: 1) leverage the All of Us Research Program (AoURP), a large USA-based cohort study, to evaluate the potential association between sleep phenotypes and the development of PD in populations that are commonly underrepresented in biomedical research; and 2) conduct a Mendelian randomization (MR) analysis to determine the potential causal role sleep may play in PD development.
Methods: A preliminary analysis was conducted on 206173 participants in the AoURP who provided long-read whole genome sequencing (WGS) data and historical access to their electronic health records (EHRs). 1422 participants had been diagnosed with PD (SNOMED: 49049000), while 26949 individuals were diagnosed with insomnia (SNOMED: 193462001) and 28881 were diagnosed with obstructive sleep apnea syndrome (OSAS; SNOMED: 78275009). Chi-square statistics and odds ratios (ORs) were calculated to evaluate the unadjusted association between sleep phenotypes and PD.
Results: Individuals with PD had 2.99 times the odds of having an insomnia diagnosis (OR=2.99, 95% CI: 2.67-3.36) compared to those without PD. Similarly, individuals with PD had 3.15 times the odds of having an OSAS diagnosis (OR=3.15, 95% CI: 2.82-3.53) compared to those without PD. Each association was statistically significant at alpha=0.05.
Conclusions: This preliminary analysis suggests a strong association between both insomnia and OSAS and prevalent PD. A future Mendelian randomization analysis will focus on determining the potential causal role of sleep in PD development in this population.

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SHIFT 01-083

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

PRESENCE AND EXTENT OF SLEEP ALTERATIONS IN PARKINSON'S DISEASE IS ASSOCIATED WITH WORSE NON-MOTOR, BUT NOT MOTOR CLINICAL SYMPTOMS.

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Aims: Sleep disorders are common in Parkinson's disease (PD), can appear before motor onset and increase in frequency throughout the disease course. This study attempts at clustering motor and non-motor clinical phenotypes in PD according to alterations to one or more clinical sleep scales.
Methods: 416 people with PD (PwP) underwent comprehensive clinical motor and non-motor assessment, and administration of the Parkinson's disease Sleep Scale (PDSS), Epworth Sleepiness Scale (ESS), Insomnia Severity Index (ISI) and Pittsburgh Sleep Quality Index (PSQI). Abnormality to each scale was assessed according to published cut-offs. Patients were clustered as having none, one, two, three, or four altered scales, and compared with regards to motor and non-motor symptoms. Non-parametric Mann-Whitney or Kruskal-Wallis tests for non-parametric measures was used, adjusting for age and disease duration.
Results: PwP scoring beyond the cut-off on each sleep scale showed significantly worse scores, compared to those with normal scores, on the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts one, two and four; Hoehn & Yahr (H&Y); anxiety (State-trait Anxiety Inventory); depression (Beck Depression Inventory-II); global non-motor symptoms (Non-Motor Symptoms Scale) and quality of life (Parkinson's Disease Questionnaire-39) (all $p<0.001$). After covariating for age and disease duration, patients scoring beyond the cut-off on two or more tests, displayed significant differences in severity, as opposed to those without any abnormalities, in all non-motor ($p<0.001$) and Hoehn & Yahr scale ($p=0.006$), but not the MDS-UPDRS 3 ($F=1.344$, $p=0.253$).
Conclusions: Sleep disturbance in PD is part of a widespread non-motor syndrome which severity is proportional to the extent of sleep disturbance, but seems to be disjointed with presence of PD motor symptoms as assessed with the MDS UPDRS 3 score.

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SHIFT 01-084

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

LIFESTYLE FACTORS AND DEMENTIA WITH LEWY BODIES IN THE NATIONAL ALZHEIMER'S DISEASE COORDINATING CENTER COHORT

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Aims: Cigarette smoking is associated with reduced risk of Parkinson's disease (PD). The association between alcohol consumption and PD is less clear but with some studies indicating an increased risk in heavy alcohol consumers. We examined the relationships of these lifestyle factors to a diagnosis of the related disease, dementia with Lewy bodies (DLB), in the National Alzheimer's Coordinating Center (NACC) cohort.
Methods: In this cross-sectional study, the exposures of past and current cigarette smoking and a history of alcohol use disorder were related to the outcome measure of a clinical diagnosis of DLB using logistic regression, adjusted for age and sex. Sensitivity and specificity of a diagnosis of DLB compared to autopsy findings in the NACC cohort were also determined.
Results: Odds of a diagnosis of DLB were reduced in both current (OR 0.640, 95% CI 0.419 - 0.947) and former (OR 0.871, 95% CI 0.761 - 0.997) smokers; odds of a diagnosis of DLB were increased in participants with a history of alcohol use disorder (OR 1.362, 95% CI 1.031 - 1.799). There was high specificity (98%) of a clinical diagnosis of DLB, supporting the quality of and use of this cohort for study of DLB.
Conclusions: Cigarette smoking is associated with lower odds of DLB, mirroring the well-established inverse association between smoking and PD, and alcohol use disorder is associated with increased odds of DLB in the NACC cohort, a cohort with high specificity for diagnosis of DLB. These preliminary findings may reflect effects of these exposures on the pathophysiology of DLB and warrant further study.

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SHIFT 01-085

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

EXPOSURE TO AIR POLLUTANTS AND PARKINSON'S DISEASE : A UK BIOBANK STUDY

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Aims: The primary aims of this research are: (1) to investigate the association between air pollution and Parkinson's disease (PD) using the extensive UK Biobank dataset, focusing on the impact of various air pollutants (PM2.5, PM10, NO2) on PD risk, and (2) to validate these findings through sensitivity analyses using incident COPD, a condition known to be linked with air pollution, as well as to explore the association between pesticide exposure and PD as a positive control.
Methods: This study used UK Biobank data to examine the association between air pollution (PM2.5, PM10, NO2) and Parkinson's disease (PD) in 2,593 PD cases and 1:5 matched controls. Logistic regression models assessed air pollutant exposure, with additional logistic regression used for sensitivity analyses, confirming associations between air pollution and COPD. Pesticide exposure was also evaluated as a positive control for PD risk.
Results: The results of the study found no association between exposure to air pollutants (PM2.5, PM10, NO2) and incident Parkinson's disease (PD). Sensitivity analyses, using the same air pollutants and incident COPD, confirmed a positive association with NO2 and PM2.5, validating the approach used for the negative findings with PD. Additionally, logistic regression with pesticide exposure showed a positive association with incident PD in males.
Conclusions: This study found no significant association between air pollution (PM2.5, PM10, NO2) and Parkinson's disease (PD). Sensitivity analyses validated the findings, showing a positive link between air pollution and COPD. A positive association between pesticide exposure and PD in males suggests environmental factors may influence PD risk, highlighting the need for further longitudinal research.

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SHIFT 01-086

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / WHOLE GENOME SEQUENCING
2-3 April 2025

PD GENERATION: EXPANDING GENETIC TESTING AND COUNSELING INTERNATIONALLY USING THE WHOLE GENOME SEQUENCING PLATFORM FOR PARKINSON'S DISEASE.

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Aims: Genetic testing and counseling in PD have been traditionally limited to very selective populations. PD GENEration (NCT04994015), sponsored by the Parkinson's Foundation in partnership with the Global Parkinson's Genetics Program (GP2), aims to make genetic testing and counseling accessible to a wide population of people with PD (PWP) and their clinicians.
Methods: PD GENEration offers genetic counseling and testing using a whole genome sequencing (WGS) platform to PWP. The study – already at 63 US and Canadian sites – recently expanded to 10 additional sites in the US that focus on racially and ethnically diverse populations, to 5 Latin American countries (Colombia, Mexico, Peru, Chile, Ecuador), and to Israel. We further developed genetic counseling materials in English and Spanish and are empowering healthcare providers worldwide to deliver genetic results as part of standard of care.
Results: PD GENEration enrolled 4,476 participants in 2024 (as of September), resulting in an overall cohort of more than 18,000 PWP with genomic characterization. The positivity rate of this cohort is 12.2%, where *GBA1* is 7.4%, *LRRK2* is 2.4%, *PRKN* is 2.4%. All clinical and genomic sequencing data will be made publicly available through the GP2 program.
Conclusions: By working individually with clinicians and by taking into consideration each country's infrastructure, cultural differences, and genetic counseling training needs, PD GENEration is able to engage with and garner significant interest from the Parkinson's community thereby achieving high rates of recruitment. As a result, PD GENEration can facilitate the execution of precision medicine trials in PD, help reduce disparities and improve overall participation in precision medicine trials.

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SHIFT 01-089

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
2-3 April 2025

COMPOUND MUSCLE ACTION POTENTIAL AS A TRANSLATIONAL BIOMARKER IN MOUSE MODELS OF PARKINSON´S DISEASE

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Aims: Electromyography (EMG) recently emerged as a valuable tool for early diagnosis and progression tracking in Parkinson's disease (PD). EMG evaluation is often an overlooked technique in mouse models of motor disorders since evaluation of voluntary movements is challenging in animals. However, compound muscle action potential (CMAP) could help bridging this gap. CMAP can reveal motor unit dysfunctions, such as impaired motor neuron recruitment and synaptic transmission that are linked to PD's neurodegenerative progression. The aim of the study was to establish EMG readouts for the analysis of muscle pathologies by exemplarily testing motor unit dysfunction in a PD mouse model.
Methods: Six-month-old hA53Ttg mice were anesthetized with isoflurane and a needle EMG system was utilized to stimulate the sciatic nerve and record resulting CMAP from gastrocnemius muscle. The following parameters were measured: the “initial activation” to assess the excitability of motor units, the “maximal CMAP amplitude” to measure the maximal strength of the muscle response, the “latency to onset” reflecting nerve conduction speed, the “latency to peak” giving insight into synchrony of muscle unit activation, and the “change in CMAP amplitude after repeated stimulation” as it can detect conditions such as neuromuscular fatigue or synaptic dysfunction.
Results: While analyses are still ongoing, our preliminary results show that CMAP measurements can be easily performed and are severely impaired in hA53Ttg mice.
Conclusions: By detecting abnormalities related to motor units and synaptic transmission, CMAP measurements represent an under-utilized technique that holds a considerable potential for the evaluation of treatment responses in rodent models of various motor disorders.

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
2-3 April 2025

GAIT INSTABILITY AND COGNITIVE FUNCTION OF PEOPLE WITH PARKINSON'S DISEASE

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Aims: Automatic movement and coordination are known to be related to cognitive function such as attention and executive function. This study aimed to analyze the association between cognition and gait instability at various speed in people with Parkinson's disease (PD).
Methods: The cognitive function was evaluated by Montreal Cognitive Assessment (MoCA). Using shoe-type embedded IMU sensors, the gait was evaluated on a 20 m overground walkway at three walking speeds. The slower and faster speeds were set at 80% and 120%, respectively, of the preferred walking speed (PWS). Univariable and multivariable regression analyses using stepwise regression were performed to identify 30 gait variables related to the MoCA score.
Results: The participants of this study were 48 people with PD aged ≥ 60 years. The participants' degrees of agreement at slower and faster speeds were 83.1% and 91.4%, respectively. As the MoCA score decreased, the coefficient of variance (CV) of stride length at the PWS increased.
Conclusions: Our result showed that the CV of stride length at the PWS is related to cognitive function, and its explanatory power is 24%. The variability is related to automatic movement and indicate gait instability. Thus, gait instability found in CV of stride length at the PWS can help identify cognitive decline of people with PD.

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
2-3 April 2025

SCORING DISCREPANCIES IN MDS-UPDRS PART III IN CLINICAL TRIALS OF PARKINSON'S DISEASE UNDERGOING INDEPENDENT REVIEW

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Aims: To evaluate frequency of MDS-UPDRS part III scoring discrepancies identified by independent reviewers in Parkison's disease (PD) clinical trials, identify items that are most prone to discrepancies, and assess whether the frequency of discrepant scores varies by disease severity measured by MDS-UPDRS part III total score.
Methods: Aggregated MDS-UPDRS part III data collected by site raters in 3 multi-national double-blind clinical trials of PD were evaluated to determine frequency of scoring errors. Part III assessments were Independently reviewed via video recording (N = 20,239) by a team of trained and tightly calibrated clinicians. Assessments were divided into quartiles according to severity of motor symptoms based on part III total score, and discrepancy rates were calculated for each severity group.
Results: Approximately 25% of assessments reviewed had at least one scoring discrepancy following independent review. Discrepancies were highest for Hoehn and Yahr (H&Y), finger tapping and hand movements, and lowest for rest tremor amplitude items, freezing of gait and speech. Assessments with lower Part III total score had the highest rate of discrepancies. Differences among severity quartiles were statistically significant with discrepancy rates decreasing with motor symptom score increase.
Conclusions: Despite the wide use of the MDS UPDRS part III total score as primary outcome measure in PD trials and robust training provided by MDS, motor assessments conducted by experienced raters are still prone to subjective interpretation and/or scoring errors, particularly the H&Y. Scoring discrepancies were highest in the group with lowest part III scores, suggesting raters find subjects with milder motor symptoms more difficult to rate.

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2-3 April 2025

EVALUATING ACCURACY OF GAIT OUTCOMES AT PREDICTING DIAGNOSIS OF MANIFEST A-SYNUCLEINOPATHIES IN MILD COGNITIVE IMPAIRMENT WITH PROBABLE REM SLEEP BEHAVIOR DISORDER

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Aims: To assess the accuracy of baseline gait outcomes at predicting diagnosis of a manifest α-synucleinopathy in individuals with mild cognitive impairment (MCI) with probable REM sleep behavior disorder (pRBD) after follow-up.
Methods: This study included 20 individuals with MCI and pRBD who were diagnosed with a manifest α-synucleinopathy (17 DLB, 3 PD) after follow-up, and 20 age-, sex- and education- matched individuals with MCI and pRBD who were diagnosed with prodromal α-synucleinopathy in the Mayo Clinic Study of Aging and Alzheimer's Disease Research Center. At baseline and follow-up visits, participants walked on an instrumented walkway at a normal place, beginning and terminating their walk 1 m before and after the walkway. Gait outcomes were compared using 2x2 (group x time) mixed ANOVAs, while adjusting for UPDRS-III, MMSE and follow-up duration. Significantly different outcomes were entered into a hierarchical logistic regression model to estimate their accuracy at predicting progression to α-synucleinopathy after follow-up compared to UPDRS-III and MMSE at baseline.
Results: Step time asymmetry was greater in non-converters than converters at baseline ($p < 0.001$) and follow-up ($p = 0.02$). There was a significant interaction effect for stride velocity variability ($p = 0.01$), which did not remain significant after covariate adjustment. Baseline UPDRS-III and MMSE predicted progression to DLB/PD with 70% accuracy, 72% sensitivity, and 68% specificity (AUC: 0.77). Adding step time asymmetry and stride velocity variability improved the model (80% accuracy, 72% sensitivity, 83% specificity, AUC: 0.81).
Conclusions: Step time asymmetry and stride velocity variability increased the accuracy and specificity of predicting the future diagnosis of a manifest α-synucleinopathy in MCI with pRBD compared to UPDRS-III and MMSE alone. This should be confirmed in MCI with polysomnography-confirmed RBD.

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / FUNCTIONAL MRI
2-3 April 2025

RESTING-STATE FUNCTIONAL MRI REGIONAL HOMOGENEITY CORRELATES WITH MOTOR SCORES IN PARKINSON'S DISEASE

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Aims: This study investigated the neural mechanisms underlying Parkinson's disease (PD) subtypes—tremor dominant (TD) and postural instability gait difficulty (PIGD)—by analyzing regional homogeneity (ReHo) values from resting-state functional magnetic resonance imaging (R-fMRI).

Methods: Fifty-nine PD patients (29 TD patients, 30 PIGD patients) and 30 healthy controls (HCs) were enrolled. ReHo values were analyzed via analysis of variance , with age and sex as covariates. Correlations between ReHo values and clinical motor symptoms were also examined.
Results: Distinct ReHo patterns were observed in patients with the PD subtypes and HCs. TD patients presented decreased ReHo in the frontal gyrus, temporal gyrus, and cerebellum, whereas PIGD patients presented lower ReHo in the caudate nucleus and supplementary motor area. TD patients had greater ReHo in the bilateral dorsolateral superior frontal gyrus and supplementary motor area but lower ReHo in the bilateral orbital part of the middle frontal gyrus and other regions than PIGD patients. Specific brain area ReHo values were correlated with tremor scores, PIGD scores, and rigidity scores.

Conclusions: Different motor subtypes of PD patients and HCs showed distinct ReHo patterns. ReHo correlation with clinical traits suggests its value as a biomarker for subtype-specific diagnostic and treatment strategies.

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SHIFT 01-098

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2-3 April 2025

DEVELOPING A BLOOD-BASED BIOMARKER TARGETING A-SYNUCLEIN FRAGMENTS FOR THE EARLY DIAGNOSIS OF PD

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Aims: Developing a sensitive immunoassay that detects α-synuclein fragments cleaved by calpain I in peripheral blood for the early diagnosis of PD. It has been previously established that these fragments contribute to the formation of aggregates, which are associated with the early onset of the disease.
Methods: An antibody was generated to specifically target α-synuclein fragments cleaved by calpain I. A competitive ELISA was developed to analyze serum samples from clinical PD cohorts with a mean age of 64.2 years. These cohorts exhibited hypokinesia, postural instability, muscle rigidity, and tremor, having been diagnosed for one and a half years. Additionally, the SH-SY5Y neuroblastoma cell model was used to bridge brain pathology to peripheral biomarkers and further validate the immunoassay.
Results: The developed antibody demonstrated specificity for α-synuclein fragments. A competitive ELISA was developed and validated for measurements in serum, it can significantly distinguish between healthy and PD serum samples. Moreover, α-synuclein fragments were detected in the supernatant of apoptotic SH-SY5Y cells.
Conclusions: α-Synuclein fragments cleaved by calpain I represent key early drivers of PD pathology. This blood-based biomarker holds promise for early diagnosis and may provide crucial insights into patient eligibility for targeted therapeutic interventions in PD.

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SHIFT 01-099

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2-3 April 2025

QUANTITATIVE LIGHT REFLEX PUPILLOMETRY IN DEMENTIA WITH LEWY BODIES – A CROSS-SECTIONAL STUDY

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Aims: Autonomic dysfunction, partly resulting from specific cholinergic deficiency, is present in patients with dementia with Lewy bodies (DLB). As the light reflex is governed by cholinergic nuclei of the midbrain, we hypothesized that it may be altered in DLB. Quantitative pupillometry, which can be performed bedside, is an easily applicable method for assessing the light reflex. We aimed to determine the differences in light reflex in DLB, and further study which clinical features (core features and dysautonomia) may be associated with changes in the light reflex.
Methods: Single-center cross-sectional study. Patients were diagnosed and recruited at a tertiary university memory clinic. Eight distinct characteristics of the light reflex, such as the constriction velocity, latency, and dilation velocity, were measured using a hand-held, research-grade, quantitative pupillometer (PLR-3000, NeurOptics) in ambient light conditions. Groups were compared using multiple linear regression concerning light reflex characteristics with adjustment for age, sex and baseline pupil diameter. One-way ANOVA with Tukey's post-hoc HSD was used to assess differences between disease stages in DLB patients.
Results: In total, 54 patients with DLB (mean age 76.2 years, 15 % female) and 50 aged healthy controls (71.4 years, 62 % female) (HCs) were included. We found a significantly decreased average and maximum constriction velocity (-.25 mm/secs, -0.1- -0.41, P=.001) and an increased latency (+4 %, 95 % CI: 1.6-6.3 %, P<.001) in the DLB group. No association between clinical features and the light reflex was identified. Changes in pupil parameters were significantly associated with increasing disease severity, most pronounced for mild cognitive impairment vs. mild dementia.
Conclusions: The light reflex is altered in DLB and quantitative pupillometry may serve as an adjunctive bedside stage biomarker.

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SHIFT 01-100

Poster on Board - Shift 01
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2-3 April 2025

UMSARS-MS: A PATIENT-CENTRIC MODIFIED SCORE BASED ON THE UMSARS SCALE

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Aims: The Unified Multiple System Atrophy Rating Scale (UMSARS) is an established scale to assess clinical disease severity in Multiple System Atrophy (MSA). However, its patient-centricity and its sensitivity to change have been questioned. We aimed to enhance the patient-centeredness and clinical sensitivity of the UMSARS while retaining its validated items.
Methods: MSA patients, MSA key opinion leaders (KOLs), and experienced MSA caregivers rated the relevance of each UMSARS-I and UMSARS-II item regarding patient-meaningful outcomes. Weighting factors for each item were generated based on its assigned global relevance, while rescaling factors for each individual item response were created based on whether the response reflects a meaningful milestone within MSA disease course. Using these weighting and rescaling factors, a modified analysis pattern of the original UMSARS, the UMSARS modified score (UMSARS-MS), was generated and tested in previous clinical trial data sets.
Results: All UMSARS-I and -II items were deemed strongly relevant by at least some MSA patients, so no item was discarded. Within these items, patients', KOLs', and MSA caregivers' input revealed gait-related items, speech, and bowel function as most relevant. Applying weighting factors based on patients' surveys and rescaling factors based on combined KOLs and caregivers' opinions provided a particularly robust UMSARS-MS score. This UMSARS-MS was positively correlated with the original UMSARS-total. Power simulations indicated increased sensitivity to change with UMSARS-MS. In MSA-C and MSA-P subtypes, UMSARS-MS showed similar disease progression patterns over 48 weeks as the original UMSARS.
Conclusions: UMSARS-MS retains all validated UMSARS items while improving patient-centeredness and sensitivity to clinical change. This approach could aid in reducing trial arms while improving assessment of patient-meaningful outcomes in future clinical trials, until a novel scale is developed and validated.

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SHIFT 01-104

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
2-3 April 2025

OCCIPITAL HYPOPERFUSION, MOTOR RESERVE, AND COGNITION IN PARKINSON'S DISEASE: AN EARLY-PHASE 18F-FP-CIT PET STUDY

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Aims: This study aimed to explore the alterations in regional cerebral perfusion associated with motor reserve in patients with newly Parkinson's disease (PD) using early-phase ^{18}F-FP-CIT PET images. Additionally, we investigated whether alterations in regional cerebral perfusion mediate the association between motor reserve and the risk of dementia conversion.
Methods: Individual motor reserve was estimated based on initial parkinsonian motor deficits and striatal dopamine transporter availability in 397 patients with PD who underwent dual-phase ^{18}F-FP-CIT PET. Patients were then classified into three groups according to motor reserve estimates: the highest quartile group (n=100), the intermediate group (n=197), and the lowest quartile group (n=100). We explored differences in regional uptake on early-phase ^{18}F-FP-CIT PET images between the three PD groups. Cox regression analysis was performed to compare the risk of developing dementia between the groups. Mediation analysis was conducted to evaluate whether regional cerebral perfusion mediated the association between the PD groups and the risk of dementia conversion.
Results: Patients with low motor reserve exhibited decreased uptake in the occipital region compared to those with high motor reserve. Cox regression analysis demonstrated that patients with high motor reserve had a lower risk of dementia conversion than the those with low motor reserve (hazard ratio, 0.432; 95% confidence interval, 0.201−0.931; p=0.032), whereas the effect of the PD groups according to motor reserve estimates on the risk of dementia conversion was not mediated by occipital hypoperfusion (p=0.392).
Conclusions: Patients with PD with low motor reserve exhibited decreased uptake in the occipital region on early-phase ^{18}F-FP-CIT PET images, which did not mediate the reduced risk of dementia conversion in these patients. These findings suggest the presence of complex neural correlates of motor reserve and cognitive decline in PD.

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SHIFT 01-105

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
2-3 April 2025

CLINICAL FEATURES OF PATIENTS WITH METABOLICALLY EARLY DLB: FDG-PET AS A TOOL FOR DIAGNOSTIC CLARITY

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Aims: Diagnosing early stages of dementia with Lewy bodies (DLB) remains difficult despite advances in clinical criteria. Neuroimaging via fluorodeoxyglucose-positron emission tomography (FDG-PET) detects metabolically early DLB with high sensitivity, yet its relationship with emerging symptoms of DLB and effect on clinician impressions are understudied. Objectives include characterizing early DLB symptoms and influence of FDG-PET on clinical diagnoses in a cohort with metabolically early DLB.
Methods: We identified 46 cases with FDG-PET findings of metabolically early DLB (i.e. occipital hypometabolism with relative sparing of posterior cingulate cortex), evaluated in Memory Clinic between November 2021 and August 2024. Data were extracted from clinic notes, neuroimaging, and neuropsychological tests. Clinicians' impressions were compared before and after FDG-PET.
Results: Frequently noted clinical symptoms of early DLB included visuospatial concerns (43%), autonomic dysfunction (33%), hallucinations (31%), inattention (67%), and executive dysfunction (52%). Other DLB symptomatology such as REM sleep behavior disorder or parkinsonism was observed in 33% of patients. Neuropsychological profiles revealed impairment in visuospatial and executive functioning, as well as delayed recall. Post FDG-PET, clinicians changed the primary diagnosis in 35 of the 46 patients (76%). DLB diagnoses increased from 0 to 13 (37%) post FDG-PET ($p<0.001$, McNemar test). Of the remaining changed diagnoses, 13 were categorized as Alzheimer's disease (37%) and 9 were other neurodegenerative diseases (28%), with DLB as possible co-pathology.
Conclusions: Clinicians incorporated DLB in their impressions post FDG-PET imaging in a significant number of cases. This applied even if patients had few supportive clinical features of DLB. If clinicians encounter a patient with possible early DLB, they could consider obtaining an FDG-PET scan for further diagnostic clarity.

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SHIFT 01-106

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLATELET AND PLATELET-POOR PLASMA PROFILES OF NEURODEGENERATION-RELATED PROTEIN DIFFER BETWEEN DEMENTIA WITH LEWY BODIES AND ALZHEIMER'S DISEASE

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Aims: Dementia with Lewy bodies (DLB) ranks second in worldwide incidence of dementia behind Alzheimer's disease (AD). Due to their overlapping features, clinical diagnosis of DLB is challenging and biomarkers are urgently needed. Since we have identified disease specific changes in DLB platelets, here we investigated levels of seven neurodegeneration-related proteins in platelets.
Methods: Levels of A-beta40, A-beta42, alpha-synuclein, total-Tau, neurogranin (NRGN), TDP-43 and kallikrein-6 (KLK6) were analyzed in lysed platelets (PLTs) and platelet-poor-plasma (PPP) by multiplex immunoassays using a Luminex platform. Samples were obtained from DLB and AD patients, and controls (n=13, each).
Results: Whereas the concentrations of NRGN, TDP-43, total-Tau, alpha-synuclein and A-beta40 presented higher concentrations in PLTs, KLK6 levels were higher in PPP. A-beta42 levels were similar in PLTs and PPP. In PLTs, A-beta40 and A-beta42 were increased in DLB and AD vs controls ($p=0.0220$ and $p=0.0104$, respectively for A-beta40; $p=0.0004$ and 0.0014, respectively, for A-beta42). A-beta42 was also increased in DLB-PPP vs AD- ($p=0.0033$) and control-PPP ($p=0.0009$). In PLTs, alpha-synuclein levels were higher in DLB vs AD ($p=0.0288$) and controls ($p=0.0013$) and TDP-43 was increased in DLB vs AD ($p=0.478$) and controls ($p=0.0365$), and in AD vs CTRLs ($p=0.0478$). KLK6 was elevated in DLB-PLTs vs controls ($p=0.0207$) and in DLB-PPP compared to AD ($p=0.0365$) and controls ($p=0.0151$). Finally, NRGN was increased in AD-PPP vs controls ($p=0.0202$) and total-Tau did not differ between the groups in PLTs or PPP.
Conclusions: Neurodegeneration-related proteins accumulate in PLTs of DLB patients compared to controls, but show also higher levels in DLB compared to AD. If the differences observed between alpha-synuclein and TDP43 levels in PLTs of DLB and AD patients, and those found for KLK6 in PPP might be useful biomarkers needs further investigation.

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SHIFT 01-107

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
2-3 April 2025

SLEEP QUALITY AND REM SLEEP BEHAVIOR DISORDER AND ITS ASSOCIATION WITH EARLY SIGNS OF PARKINSONISM

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Aims: The aims of this study are to investigate sleep disturbances and their associations with parkinsonian symptoms in neurologically healthy controls. Future work will analyze biomarkers related to sleep and early parkinsonism, highlighting the importance of early detection and management.
Methods: Neurologically healthy controls were examined for parkinsonian symptoms using UPDRS and for sleep disturbances using sleep questionnaires, including REM sleep behavior disorder (RBD) Screening Questionnaire (RBDSQ), Insomnia Severity Index (ISI), Circadian Type Inventory, and Pittsburgh Sleep Quality Index. Cerebrospinal fluid (CSF) and plasma were collected and analyzed.
Results: Among the initial 114 controls (mean age 68 ± 9.9, 52.4 % female), 8 exhibited scores indicative of RBD. The group displayed a range of sleep disturbances, from subthreshold insomnia (n=39) to moderate (n=7) and severe insomnia (n=2). We found significant association between insomnia score (ISI) and parkinsonism (total UPDRS) (β = 0.381, 95% confidence interval [CI] = [0.227, 0.536], *P* = 3.44e-06, adjusted R2 for the entire model = 0.183). There is a trend towards higher RBD score and parkinsonism, (β = 0.056, 95% confidence interval [CI] = [–0.005, 0.117], *P* = 0.073, adjusted R2 for the entire model = 0.026), not reaching significance.
Conclusions: Preliminary data show that insomnia severity is significantly associated with parkinsonian symptoms in neurologically healthy controls. These findings underscore the importance of assessing and addressing sleep disturbances in individuals at risk for or exhibiting early signs of parkinsonism.

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SHIFT 01-108

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
2-3 April 2025

AUTOPHAGIC SIGNATURES IN PERIPHERAL BLOOD MONONUCLEAR CELLS FROM PARKINSON'S DISEASE PATIENTS

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Aims: To investigate the potential of autophagy-lysosomal pathway (ALP)-associated proteins in peripheral blood mononuclear cells (PBMCs) as diagnostic biomarkers for early-stage Parkinson's disease (PD).
Methods: We analyzed PBMC samples from PD patients within three years of symptom onset and age-matched controls with essential tremor. Quantitative immunoblotting was used to measure levels of ALP-associated proteins. Autophagic flux and lysosomal pH were assessed using functional assays. Correlation analyses were performed to investigate relationships among ALP-associated proteins, functional readouts, and clinical features. A biomarker model was developed using logistic regression analysis.
Results: Quantitative analysis revealed a significant reduction in optineurin (OPTN) levels in PBMCs from PD patients compared to controls. Expression levels of various ALP-associated proteins were tightly correlated, suggesting coordinated dysregulation of the pathway. Correlation analyses revealed associations between ALP-associated features and clinical characteristics, such as age at onset and motor impairment assessed by UPDRS-III scores. Multiple positive correlations were identified among ALP-associated proteins and functional readouts, highlighting the interconnectivity within the pathway. A PBMC biomarker model incorporating lysosomal-associated membrane protein 1 (LAMP1) and OPTN exhibited high diagnostic accuracy in distinguishing PD patients from controls.
Conclusions: These findings highlight the potential of ALP-associated protein signatures in PBMCs, particularly OPTN and LAMP1, as novel diagnostic biomarkers for early detection of PD. This approach offers insights into the systemic manifestations of the disease and may facilitate timely intervention strategies.

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SHIFT 01-109

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
2-3 April 2025

EXPLORING IMMUNOASSAYS FOR DOPA DECARBOXYLASE IN CSF AND PLASMA

Megan De Pauw[1], Julie Goossens[1], Lucilla Parnetti[2], Lorenzo Gaetani[2], Giovanni Bellomo[2], Katharina Bolsewig[3], Charlotte Teunissen[3], Eugeen Vanmechelen[1]
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Aims: Recent studies have identified DOPA decarboxylase (DDC) as a potential biomarker to differentiate Alzheimer's dementia (AD) from Dementia with Lewy Bodies (DLB) in cerebrospinal fluid (CSF), complementing the synuclein amplification assay as a pathological fluid marker for dopaminergic deficits. Using highly specific and sensitive antibodies, low CSF levels of DDC were quantified by ELISA. While DOPA metabolism in serum is well-studied, the clinical value of the DDC protein in plasma is less explored. Explore the clinical relevance of DDC in paired CSF-plasma samples using a commercial antibody pair in immunoassays.
Methods: Analytical performance of the prototype ELISA was determined in CSF and plasma. A clinical cohort (n=152, mean age 70y (range 50-83y, 45% female)) including AD (n=76), PD/DLB (n=38) and controls (n=38) was assayed for DDC concentrations in CSF and plasma. The antibody pair was also transferred to the Lumipulse G platform to expand the measurement range.
Results: Prototype ELISA plasma DDC levels (572-15047 pg/mL, %CV=2,3%) were on average 120 times higher compared to CSF (4,1-96,3 pg/mL, %CV=4,5%). Spike recovery experiments in CSF and plasma demonstrated suboptimal recovery. CSF DDC levels were significantly higher in PD versus controls and AD ($p<0,0001$). Plasma DDC levels were increased in PD compared to AD ($p<0,0001$) and controls ($p=0,014$), further evaluation of dopaminergic treatment is ongoing. Preliminary results on the Lumipulse platform detected low DDC levels in CSF and the measurement range could be expanded up to 10000 pg/mL.
Conclusions: The DDC CSF ELISA assay shows promise for diagnosing DLB. Optimization of the immunoassay format on the Lumipulse may further allow studies in larger cohorts to improve our understanding of the clinical value of DDC in multiple fluid matrices.

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SHIFT 01-110

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
2-3 April 2025

IDENTIFICATION OF BIOMARKERS OF THE GBA1 PATHWAY IN DEMENTIA WITH LEWY BODIES

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Aims: Dementia with Lewy bodies (DLB) is an α-synucleinopathy, recognized as one of the most prevalent causes of dementia worldwide. Despite the significant number of affected patients, this disease remains highly underdiagnosed due to a lack of validated biomarkers. Heterozygous mutations in the *GBA1* gene are the most important genetic risk factor for DLB. The contribution of heterozygous *GBA1* mutations to the pathophysiological mechanisms of DLB remains poorly understood. The *GBA1* gene encodes for a lysosomal enzyme, glucocerebrosidase, responsible for the catabolism of glycosphingolipids. Several biomarkers of GBA1 pathway are detectable in the cerebrospinal fluid (CSF) and plasma, such as CCL18, GPNMB, or Sema 7A. The aim of our project was to determine whether these biomarkers are altered in CSF or plasma of DLB patients.
Methods: In this order, we used serum and CSF from patients with DLB and neurological controls followed at the Clinical Neurology Center (Fernand Widal Hospital - APHP). Three different biomarkers were analyzed using ELISA tests, CCL18, GPNMB, or Sema 7A.
Results: We observed an increase in plasma Sema7A, which may play a role in the abnormal neuroinflammation characteristic of Lewy body disease. Additional correlations were noted, such as between plasma Sema7A and plasma GPNMB, as well as between plasma and CSF levels of CCL18. In contrast, we found no significant changes in the other markers, CCL18 and GPNMB, in the plasma or CSF of DLB patients compared with control subjects.
Conclusions: Our preliminary results show that Sema 7A is modulated in DLB patients, independently of a background of GBA1 mutations. Our resuts highlight the significance of the GBA1 pathway, and prompting further investigation into its pathophysiological consequences in DLB.

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SHIFT 01-111

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
2-3 April 2025

A STUDY INTO THE STABILITY OF PROTEIN AGGREGATES IN PLASMA SAMPLES FOR STORAGE AT -80 DEGREES FOR USE AS DIAGNOSTIC BIOMARKERS.

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Aims: The search for a stable and clinically significant blood based biomarker for neurodegenerative disease is a global research goal. Variations in concentrations of specific protein aggregates in plasma samples is widely explored and provides promising biomarker targets to distinguish the early onset neurodegenerative disease patients from healthy controls. In the development stage of these biomarkers and for clinical screening, samples are routinely frozen on collection and thawed at a later date for analysis. The handling conditions and duration of storage may be a source of variation and inaccurate analysis, slowing and potentially misleading this critical field of study.
In this study, we have performed a time series analysis on the stability and robustness of the protein aggregates in plasma to storage at -80 degrees.
Methods: Plasma samples were tested using both single molecule pull down imaging (SiMPULL) and SIMOA (Quanterix) to quantify the alpha synuclein, amyloid beta and tau content at specific time points over a three month storage. Changes in concentration and aggregate size were quantified.
Results: The results of this experiment give confidence that changes to these protein aggregate concentrations is within an order of magnitude. Additionally, the protein aggregates tested demonstrate robustness to changes in storage duration and sample handling.
Conclusions: This study demonstrates the theoretical viability of blood based protein aggregate detection as a clinical screening tool with the samples stable for short term storage and testing. Additionally, in the development stage of the biomarkers, the biomarker combinations providing diagnostic significance are relatively unaffected by the handling and storage of the samples.

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SHIFT 01-112

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
2-3 April 2025

DOPA DECARBOLXYLASE AS AN EARLY PARKINSON'S DISEASE BIOMARKER

Ellen Appleton[1], Shervin Khosousi[1], Michael Ta[2], Michael Nalls[2], Andrew Singleton[3], Andrea Sturchio[1], Ioanna Markaki[1], Wojciech Paslawski[1], Hirotaka Iwaki[2], Per Svenningsson[1]
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Aims: DOPA Decarboxylase (DDC) in CSF has recently shown up as a promising biomarker candidate for parkinsonian disorders. The aim of this study was to validate those findings, compare CSF and plasma DDC levels, and investigate the influence of dopaminergic medication on DDC.
Methods: We measured CSF and plasma levels of DDC in prodromal, de novo, and treated Parkinson's Disease (PD) patients and controls using proximity extension assay (PEA) in three independent cohorts, namely Biopark, the Parkinson's Progression Markers Initiative (PPMI), and Parkinson's Disease Biomarkers Program (PDBP). All three cohorts had matched plasma and CSF. 91 proteins were quantified in Biopark whereas1463 proteins were measured in the PPMI and PDBP cohorts. Biopark and PPMI cohorts had untreated de novo PD cases, and the PPMI cohort included additional prodromal PD cases.
Results: The most changed CSF protein in all three cohorts was DDC, with a similar fold change increase in all cohorts. Similar levels of increased DDC were found in prodromal and de novo PD patients, with even higher DDC levels in levodopa treated patients. A positive correlation between levodopa treatment and DDC levels was found. An increase in DDC was also found in plasma, but only in levodopa treated patients. No change in plasma DDC was found in de novo or prodromal PD.
Conclusions: CSF DDC is a promising biomarker for PD that appears to be increased in early and even prodromal stages of PD.

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SHIFT 01-119

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SPECT
2-3 April 2025

SUB-REGIONAL STRIATAL BINDING RATIOS IN EARLY PARKINSON'S DISEASE: ASSOCIATIONS WITH SYNUCLEIN PATHOLOGY AND CLINICAL PHENOTYPES

Amgad Droby[1], Lenoy Sahar[2], Danielle Sharon[2], Daniel Atias[1], May Eshel[1], Roni Asulin[2], Nir Giladi[3], Anat Mirelman[1,4], Avner Thaler[1]
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Aims: ***Background:*** Parkinson's disease (PD) is characterized by a dorso-posterior to ventro-anterior gradient of striatal dopamine depletion. Dopamine transporter imaging (DaTscan) is widely used for PD diagnosis and risk estimation, playing a crucial role in likelihood ratio (LR) scores during the preclinical stages. ***Objectives:*** Here, we investigated the overtime dynamics of striatal sub-regional binding ratios (SBRs) based on synuclein seeding assay (SAA) status and disease severity in early-stage PD patients.
Methods: ***Methods:*** 42 PD patients (13 idiopathic, 14 GBA1, 15 LRRK2) [mean age ±SD = 63.16 ± 9.5 yrs; F/M: 13/29]. All participants underwent comprehensive neurological and cognitive assessments, lumbar puncture for CSF collection; as well as DAT-SPECT and MRI scans at baseline and after 2 years. Sub-regional SBRs were calculated using convolutional neural network segmentation of T1-weighted images applied to the acquired DaTscans.
Results: ***Results:*** 33 out of 42 were found to be SAA+ based. These demonstrated higher SBRs in left anterior and right posterior caudate versus SAA- ($p<0.05$). Longitudinally, SAA- showed a significant overtime increase of right caudate SBRs, while SAA+ showed a left ventral striatum (VSt) SBR decrease ($p<0.05$). In the SAA+ group, VSt SBR correlated negatively with UPDRS-III scores ($r=-0.5$, $p=0.012$).
Conclusions: ***Conclusion:*** In early PD, measured sub-regional SBR values showed potential to characterize striatal dopaminergic integrity based on SAA status. The differential SBR patterns between SAA+ and SAA- groups suggest distinct striatal dopaminergic pathophysiological processes regardless of genetic status. Further research is needed to validate these findings and determine their clinical utility.

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SHIFT 01-121

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2-3 April 2025

MULTI-SCALE IMAGING OF A-SYNUCLEIN AND MICROSTRUCTURAL CHANGES IN A MOUSE MODEL OF PARKINSON'S DISEASE

Benjamin Combes[1], Alicia Rosenau[2], Sheng-Fu Huang[3], Yi Chen[4], Hikari Yoshihara[4], Annika Keller[3], Marco Reisert[5], Dominik Von Elverfeldt[5], Fanni Geibl[2], Martin Henrich[2], Roger Nitsch[1], Daniel Razansky[4], Wolfgang Oertel[2], Christoph Hock[1], Ruiqing Ni[1]
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Aims: The goal of this project is to map the spatial-temporal association between α-synuclein inclusions and white matter microstructural changes in a mouse model of α-synucleinopathy.
Methods: We injected the substantia nigra pars compacta (SNc) of wild-type mice unilaterally with preformed-fibrils (PFFs) or monomeric α-synuclein and performed at 12 and 20 weeks post-injection (wpi) the *ex vivo* diffusion tensor imaging (DTI) magnetic resonance imaging (MRI) at 9.4T to study white matter structural connectivity, and light-sheet microscopy (LSM) to map the distribution of α-synuclein aggregates. Voxel-based analysis (VBA) and atlas-based analysis (ABA) of DTI mouse brain data were performed and validated by immunostaining.
Results: Injection of PFFs led to a dense α-synuclein pathology at 12 and 20 weeks wpi in the dopaminergic neurons of the SNc, which was associated with neuronal cell death. This model also showed that the pathogenic α-syn exhibited prion-like seeding activity by converting the physiological form of α-syn to pathogenic aggregates and spread to other brain regions, mainly in the striatum. The loss of dopaminergic cells in the SNc was accompanied by dopaminergic denervation of the striatum. Preliminary VBA showed a decrease in fractional anisotropy in the corpus callosum and external capsule of PFFs- compared to monomers-injected mice. These data indicates that dopaminergic neurodegeneration is associated with structural connectivity changes by DTI MRI.
Conclusions: The PFFs-injected model displayed abundant α-syn pathology, white matter impairment, and dopaminergic neuronal cell death, especially in the nigrostriatal pathway as seen in Parkinson's disease patients. The *ex vivo* MRI-LSM platform is an ideal tool for understanding the spreading of pathologies at the circuit and whole brain levels.

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SHIFT 01-122

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2-3 April 2025

PREDICTING POST-TREATMENT CLINICAL EVALUATIONS FROM NEUROIMAGING DATA IN PARKINSON'S DISEASE AND MOVEMENT-RELATED DISORDERS WITH NEUROMEDICALCP-BOX

Felix Carbonell[1], Jose Pineda-Pardo[2], Rafael Rodriguez-Rojas[2], Yasser Iturria-Medina[1]
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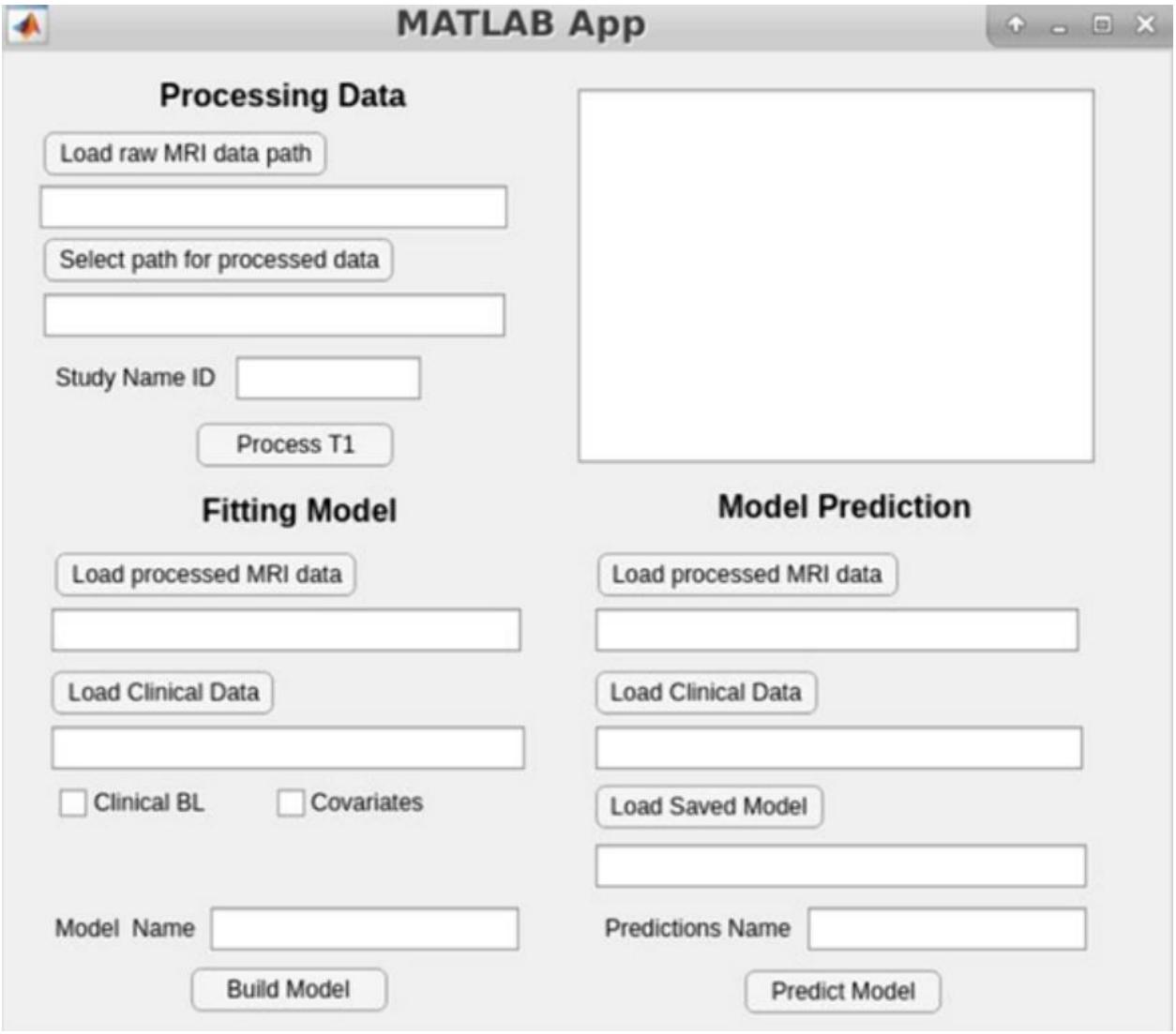
Aims: The here proposed and openly shared NeuroMedicalCP toolbox aims to facilitate the analysis and interpretation of the predictive relationship between brain structural biomarkers at baseline (i.e., T1 imaging-derived) and post-treatment clinical evaluations after magnetic resonance-guided focused ultrasound (MRgFUS) in Parkinson's disease and Essential Tremor.
Methods: The toolbox, developed in Matlab and compiled for major operational systems, consists of four main components: i) Imaging Pre-processing, ii) Model fitting, iii) Model prediction, and iv) Display console, as shown in Figure



1. Figure 1.

Notably, the toolbox includes multiple pre-constructed and validated models (from two concluded clinical trials), while allows constructing customized models based on the user's own data. The model fitting component is based on a Partial Least Squares (PLS) regression model that includes the Follow-up – Baseline change (e.g., 1-year change) in clinical score values (e.g., CRST scores) as response of interest and the MRI measurements (e.g., GM density and volumes) at baseline as predictors.

Results: The evaluated datasets are associated with different studies performed at the Centro Integral de Neurociencias HM CINAC (Madrid, Spain). These employed MRgFUS that allows ultrasound waves to be delivered directly into the subthalamic nucleus (STN) and ventralis intermediate nucleus (VIM), respectively. Each of these two pre-loaded training datasets has 4 fitted models associated, corresponding to the inclusion or not of covariates and baseline clinical scores in the model. Each of the 8 pre-fitted models produced more than 90 percent of variance explained in the response variable.

Conclusions: The NeuroMedicalCP toolbox aims to assist physicians to predict future clinical outcomes from pre-intervention data collected at baseline.

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SHIFT 01-123

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2-3 April 2025

ENLARGED PERIVASCULAR SPACES IN THE TEMPORAL LOBE AS A PREDICTOR FOR INCIDENT DEMENTIA IN PARKINSON'S DISEASE

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Aims: Although the potential role of enlarged perivascular spaces (EPVS) in Parkinson's disease (PD) is increasingly recognized, whether EPVS located in different anatomical regions exert differential effects on clinical manifestation remains uncertain. We investigated the regional EPVS burden and its association with cognition and neuropsychiatric symptoms (NPS) in newly diagnosed PD population.
Methods: In this retrospective, cross-sectional study, EPVS in the temporal lobe (T-EPVS), centrum semiovale (CS-EPVS), and basal ganglia (BG-EPVS) were visually rated in drug-naïve PD patients who underwent magnetic resonance imaging, dopamine transporter (DAT) scans, neuropsychological assessments, and Neuropsychiatric Inventory Questionnaire at baseline. Cognitive performance, NPS burden, vascular risk factors, small vessel disease (SVD) imaging markers, and DAT availability were compared across groups dichotomized by their regional EPVS burden (cut-off for high- versus low-degree: > 10 for T-EPVS/BG-EPVS and > 20 for CS-EPVS).
Results: The proportion of high-degree T-EPVS and BG-EPVS exhibited an increasing trend across the cognitive spectrum, corresponding to worsening cognition. Compared to low-degree group, high-degree BG-EPVS group showed higher SVD burden (moderate-to-severe white matter hyperintensity, lacune, and cerebral microbleeds, greater atrophy in cortical gray matter of intracranial volume, and lower cognitive performance (in language and visual memory domains. High-degree T-EPVS group presented with greater NPS burden in terms of decreased motivation (0.61±1.78 vs. 1.35±2.36, P = 0.007), affective dysregulation (0.88±2.13 vs.2.36±3.53, P < 0.001), and impulse dyscontrol (0.43±1.67 vs. 1.74±4.29, P < 0.001), compared to the low-degree T-EPVS group. Meanwhile, the burden of CS-EPVS did not reveal any differences in cognition or NPS.
Conclusions: BG-EPVS and T-EPVS appear to exert differential effects on cognition and NPS in patients with PD. Investigating the EPVS profile in distinct anatomical regions may be useful in disentangling the heterogeneity within PD.

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SHIFT 01-125

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-INFLAMMATORY, ANTI-OXIDANT
2-3 April 2025

BHV-8000, A SELECTIVE BRAIN-PENETRANT TYK2/JAK1 INHIBITOR FOR NEUROINFLAMMATORY AND NEURODEGENERATIVE DISEASES, DEMONSTRATES FAVORABLE PK/PD AND SAFETY IN PHASE 1 STUDIES

Peter Ackerman[1], Nick Kozauer[1], Raj Bhardwaj[2], Andrea Ivans[1], Bavani Shankar[1], Bharat Asware[1], Randall Killingsworth[1], Eric Ashbrenner[1], Jo Ann Malatesta[2], Emily Thompson[1], Dustin Walters[1], Alyssa Cheng[1], Lindsey Lair[1], Richard Bertz[1], Bruce Car[1], Irfan Qureshi[1], Vlad Coric[1]
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Aims: Central and peripheral inflammation play an important role in the pathogenesis of neurodegenerative diseases including Alzheimer's disease (AD) and Parkinson's disease (PD). BHV-8000 is a novel, brain-penetrant, investigational oral small molecule highly selective against the TYK2 and JAK1 enzymes within the JAK-STAT pathway; avoiding the safety liabilities of JAK2 and JAK3. TYK2 and JAK1 signaling is essential to the pathological immune responses present in AD and PD.
Methods: BHV8000-101 and BHV8000-102 are Phase 1 double-blind, placebo-controlled studies. BHV8000-101 is a combined SAD/MAD study that evaluated doses between 6 and 30mg. BHV8000-102 included one multiple-dose cohort (20 mg). Eight participants were randomized 3:1 to receive BHV-8000 or placebo. Multiple-dose cohorts received study drug once-daily for 7 (-102 study) and 14 (-101 study) consecutive days. The primary objectives for each study were safety, tolerability, and pharmacokinetics (PK).
Results: The median T_{max} ranged from 4-6 hours. The geometric mean $t_{1/2}$ for BHV-8000 ranged from 11-14 hours. The accumulation ratio at steady state for AUC and C_{max} was ~1.7-fold. The mean (CV%) CSF-to-plasma ratio at 6- and 24-hours post-dose was 0.43 (10.1) and 0.50 (13.3), respectively. Across the two Phase 1 studies, there were comparable rates of adverse events (AEs) between BHV-8000 (~25%) and PBO (~33%). All AEs were mild in intensity except one moderate headache. There were no severe or serious AEs. In the -101 MAD phase, reductions from baseline in inflammatory biomarkers (IP-10, hsCRP, and IFN-ß) were numerically greater for BHV-8000 treated participants vs. placebo.
Conclusions: Phase 1 data demonstrate BHV-8000 is a brain-penetrant oral small molecule with a favorable safety profile and the potential to provide disease-modifying effects in neuroinflammatory and neurodegenerative conditions including AD and PD.

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SHIFT 01-126

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ASO AND RNAI
2-3 April 2025

GPNMB AS A TARGET FOR DISEASE-MODIFYING TREATMENT FOR PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a globally prevalent neurodegenerative disorder with no current disease-modifying drugs. Most clinical trials fail due to uncertain validity and poor translability of targets selected from observational data. Computational methods, such as Mendelian Randomization, now enable target identification based on genetic data, pinpointing causal genes. One such target is GPNMB, a transmembrane glycoprotein. Higher levels of GPNMB are linked to increased PD risk (Haglund et al., 2024), with glial cells mediating this causal effect. This suggests that downregulating GPNMB could slow PD development or progression. Nucleic-acid therapies are gaining traction for neurological diseases due to easy delivery, rapid development, and long-term retention in the central nervous system. Our study aims to knock down GPNMB with siRNA and observe its effects on glial cell models (astrocytes and microglia). Our objective is twofold: to uncover the mechanism through which GPNMB affects Parkinson's disease risk, and to evaluate GPNMB's potential as a therapeutic target, assessing both its safety and efficacy.
Methods: The project is employing super-resolution imaging, RNA-seq, proximity-ligation assay, protein aggregation assays, and other molecular biology techniques to study how GPNMB knockdown affects patient-derived alpha-synuclein pathology, inflammatory responses, and endolysosomal function in iPSC-derived glial cells.
Results: While still in early stages, inhibition of GPNMB mRNA has been achieved using siRNA, with further experiments underway.
Conclusions: This project could validate in vitro assessment of nucleic acid therapies for disease modification in glial cultures as a scalable drug discovery platform.

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SHIFT 01-128

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / A-SYNUCLEIN
2-3 April 2025

EMRUSOLMIN A NOVEL A-SYNUCLEIN TARGETING DRUG, IS EFFICACIOUS IN IN VITRO MODELS OF MULTIPLE SYSTEMS ATROPHY

Yael Almog, Noa Barak Broner, Eran Schmukler, Ianai Fishbein
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Aims: Multiple system atrophy (MSA) is an α-synucleinopathy characterized by severe motor dysfunction and autonomic system failures. Distinctive from Parkinson's disease, MSA is caused mainly by the formation of α-synuclein (α-syn) aggregates in oligodendrocytes rather than neurons. Emrusolmin is a novel drug candidate designated for the treatment of MSA. It was previously shown to improve motor symptoms and decrease α-syn pathology in a mouse model of MSA at high doses. In this study we evaluated emrusolmin's potency in ascending concentrations which are at the clinically relevant range, using cell systems that are indicative of MSA.
Methods: To evaluate the efficacy of emrusolmin, we established two *in vitro* models of MSA: (1) human glial cell line U373 transfected with α-syn; (2) primary mouse oligodendrocytes treated with α-syn monomers and pre-formed fibrils (PFF). In these models, α-syn pathology was examined using immunocytochemistry and western blot analysis, showing increased intracellular aggregation and phosphorylation. We assessed the efficacy of emrusolmin in reducing intracellular α-syn pathology in these models.
Results: Treatment with emrusolmin reduced α-syn pathology in a dose-dependent fashion, demonstrating efficacy in MSA-relevant *in vitro* models.
Conclusions: These results demonstrate that emrusolmin inhibits α-syn aggregation in MSA *in vitro* models and that it does so in clinically relevant concentrations. Thus, these findings provide a foundation for further testing of emrusolmin's potential as a disease modifying agent in MSA patients.

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SHIFT 01-129

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / A-SYNUCLEIN
2-3 April 2025

DEVELOPMENT OF A VECTORIZED ANTIBODY TREATMENT OF PARKINSON'S DISEASE TARGETING AGGREGATED SPECIES OF ALPHASYNUCLEIN

Guus Scheefhals[1], Bas Blits[2], Bernard Schneider[3]
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Aims: For Parkinson's disease (PD) only symptomatic treatments are available today. Syngle Tx aims to develop a disease-modifying treatment using vectorized antibody therapy. With funding by The Michael J Fox Foundation we have generated 26F1, a novel high affinity antibody that specifically binds alphasynuclein (asyn) aggregates. These aggregated asyn species are considered to play a key role in the pathology. With a once-only administration of our vectorized antibody we aim to achieve a long term reduction of these toxic protein aggregates by having the antibody expressed and secreted in the brain. This treatment would have the potential to slowdown or halt progression of PD.
Methods: In an acute rat model of PD with induced overexpression of asyn developed and performed at EPFL in Switzerland, vectorized 26F1 antibody treatment was evaluated in a first experiment by unilateral concomitant administration in the substantia nigra (SN) of AAV6-asyn and AAV5-26F1. In a second therapeutic study overexpression of asyn was first administered in the SN and three weeks later followed by treatment with AAV5-26F1 in the striatum. AAV5 injected in the striatum transduces cells locally and nigral neurons retrogradely. Read-out has been TH-positive cell count in SN and TH-positive staining measured by optical density in the striatum and motor symptoms using the cylinder test.
Results: Both studies of vectorized 26F1 antibody treatment in the induced asyn overexpression rodent model demonstrated a neuroprotective effect on dopaminergic neurons and reduced motor symptoms, two hallmarks of PD.
Conclusions: In the acute PD rodent model, vectorized 26F1 treatment reduced neurodegeneration (both prophylactically and therapeutically) and resulted in less severe motor symptoms. Vectorized 26F1 thus shows potential for disease-modifying treatment of PD.

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SHIFT 01-133

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
2-3 April 2025

DEVELOPMENT OF SPK-10005, A NOVEL AAV-MEDIATED GENE THERAPY FOR SYNUCLEINOPATHIES EXPRESSING A MICRO-RNA TARGETING HUMAN ALPHA -SYNUCLEIN

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Aims: Synucleinopathies are a group of neurodegenerative disorders characterized by accumulation of misfolded and insoluble α-synuclein (α-syn). Although molecular pathogenesis remains to be fully elucidated, α-syn oligomerization has been shown to cause neuronal toxicity in preclinical models. Reduction of α-syn using RNA interference (RNAi) has been widely explored as a potential neuroprotective strategy to limit aggregate formation and spread. Here, we report the development of a proprietary Adeno-Associated Viral vector (AAV) expressing an artificial miRNA targeting human α-syn mRNA, SPK-10005.
Methods: Preliminary efficacy of SPK-10005 was evaluated using a viral vector (AAV1/2-A53T-α-syn) model of synucleinopathy. In this model, distribution of SPK-10005 and expression of α-syn mRNA were evaluated by qPCR, α-syn-protein by ELISA and striatal dopamine by HPLC. Additionally, targeting, pharmacology, and preliminary safety of SPK-10005 was evaluated in Substantia Nigra (SN) of *Chlorocebus sabaeus* (African green monkey, AGM, n=2/group, 3 doses). Specific qPCR-based assays quantified vector genomes, miRNA expression, α-syn mRNA, while cytoplasmic α-syn protein in dopaminergic neurons was measured by immunohistochemistry. H&E staining was performed to assess histopathology.
Results: Intraparenchymal delivery of SPK-10005 induced dose-dependent reduction of human α-syn mRNA and protein in the mouse model expressing human A53T-α-syn. Mice treated with an optimal dose of SPK-10005 had significantly improved maintenance of body weight, protection from loss of striatal dopamine and dopaminergic fibers vs. animals receiving a control vector. Neurosurgical pilot study in AGM injected with SPK-10005 had dose-dependent distribution of vector genomes that led to α-syn mRNA and

protein reduction with no adverse histopathological changes observed at any dose tested. The neurosurgical procedure was well tolerated with no adverse events during the 2-month in-life phase of the study.
Conclusions: Data supports development of SPK-10005 as a potential RNAi-based therapeutic for synucleinopathies.

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SHIFT 01-134

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
2-3 April 2025

BMP5/7 EXERT NEUROPROTECTIVE EFFECTS AGAINST ALPHA-SYNUCLEIN NEUROTOXICITY IN IPSC-DERIVED DOPAMINERGIC NEURONS AND A PREFORMED FIBRIL-BASED PARKINSON'S DISEASE MOUSE MODEL

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Aims: Neurotrophic factors, particularly GDNF, have been explored in clinical trials for Parkinson's disease (PD) but failed to demonstrate therapeutic efficacy, possibly due to their inability to protect dopaminergic (DA) neurons against α-synuclein toxicity. We previously showed that bone morphogenetic protein 5/7 (BMP5/7) promotes neurogenesis of DA neurons *in vivo* and in human stem cells. Based on these results, we aimed to test the potential of BMP5/7 to protect DA neurons against alpha-synuclein toxicity.
Methods: We used a PD mouse model based on striatal stereotactic injections of alpha-synuclein preformed fibrils (PFFs). Human DA neurons were generated from induced pluripotent stem cells (iPSCs) derived from PD patients carrying the A53T alpha-synuclein mutation. BMP receptor blockade in mice was achieved pharmacologically via intraperitoneal (i.p.) injections of the BMP receptor antagonist LDN212854.
Results: Mice treated with BMP5/7 delivered by viral vectors *after* the onset of motor symptoms caused by striatal PFF injections showed reduced pS129 alpha-synuclein aggregates in TH-positive cells, increased striatal DA projections, and improved motor behavior compared to mice treated with PFFs only. In iPSC-derived DA neurons from A53T alpha-synuclein mutation carriers, BMP5/7 reduced neuropathological changes, including protein aggregates. To elucidate the mechanism of action of BMPs, we blocked BMP signaling *in vivo*. LDN212854 treatment resulted in a significant 35% reduction in the immunostaining intensity of striatal TH-projections, a significant increase in the number of TH-positive neurons co-expressing pS129-α-synuclein, and an elevation of the pan-microglial marker IBA1 in the substantia nigra. We are currently directly comparing the therapeutic effects of BMP5/7 to GDNF.
Conclusions: Collectively, our findings provide evidence for BMPs as promising drug candidates for PD, with a mechanism of action that may involve a regulatory effect on alpha-synuclein homeostasis.

SHIFT 01-136

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

TREGS PROTECT DOPAMINERGIC NEURONS AGAINST MPP+ NEUROTOXICITY VIA CD47-SIRPA INTERACTION

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Aims: Regulatory T cells (Tregs) have been associated with neuroprotection in animal models of Parkinson's disease. Herein, we show that Tregs directly protect dopaminergic neurons against MPP^+ neurotoxicity via an interaction between the two transmembrane proteins CD47 and SIRPA.
Methods: Primary ventral mesencephalic (VM) cells or VM neurons were pretreated with Tregs before MPP^+ treatment. Live cell imaging system detected a dynamic contact of Tregs with VM neurons that were stained with CD47 and SIRPA, respectively. Dopaminergic neuronal loss was examined after silencing CD47 in Tregs or silencing SIRPA in VM neurons.
Results: Tregs prevented MPP^+-induced dopaminergic neuronal loss and glial inflammatory responses. CD47-labeled Tregs dynamically contacted with SIRPA-labeled VM neurons. Silencing CD47 gene in Tregs impaired the ability of Tregs to protect dopaminergic neurons against MPP^+ toxicity. Similarly, SIRPA knockdown in VM neurons reduced the ability of Treg neuroprotection. Rac1/Akt signaling pathway in VM neurons was activated by CD47-SIRPA interaction between Tregs and the neurons. Inhibiting Rac1/Akt signaling in VM neurons compromised Treg neuroprotection.
Conclusions: Tregs protect dopaminergic neurons against MPP^+ neurotoxicity by a cell-to-cell contact mechanism underlying CD47-SIRPA interaction and Rac1/Akt activation.

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SHIFT 01-137

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

THERAPEUTIC POTENTIAL OF PAINLESS NERVE GROWTH FACTOR IN A 6-OHDA MODEL OF PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder primarily marked by motor impairments, progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNpc), and chronic neuroinflammation. Additionally, PD patients exhibit reduced levels of nerve growth factor (NGF) in both plasma and SNpc, which may contribute to the disease's pathology. We hypothesize that NGF may serve as a therapeutic agent for PD by (1) counteracting neuroinflammation through its immunomodulatory effects and (2) regulating acetylcholine (ACh) levels via its target: the cholinergic system. Since DA neurons respond to ACh variations, this mechanism could help prevent their degeneration. The aim of this study is to test a mutated and painless form of NGF (hNGFp) as a therapeutic molecule, using an intranasal route of administration.
Methods: PD mice were generated by unilateral injection of 2 µl of 6-OHDA toxin (6 µg/µL) into the striatum. Following the lesion, mice were treated intranasally with hNGFp for 4 weeks. Motor impairment and recovery were evaluated weekly using the Schallert cylinder test. Lesion severity was determined by quantifying DA neurons and fibers in the SNpc and striatum while neuroinflammatory responses were examined by analyzing microglial density, morphology, and phagocytic activity in both hemispheres.
Results: The lesion induced significant motor impairment in the PD model. Notably, hNGFp treatment reduced motor deficits, promoting functional recovery. Neither the lesion nor the treatment affected brain weight or microglial density. However, the lesion and treatment affected microglial morphology and phagocytic activity.
Conclusions: This hNGFp treatment appears highly promising, both at the cellular and phenotypic levels, showing potential to modulate key disease mechanisms. Additionally, its non-invasive intranasal delivery method offers a significant advantage for therapeutic applications.

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SHIFT 01-138

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

MORPHOLOGICAL ANALYSIS OF NEUROINFLAMMATION IN THE AAV ALPHA-SYNUCLEIN MOUSE MODEL OF PARKINSON'S DISEASE

Joseph Flores, Laurent Potvin-Trottier, Lionel Breuillaud, Barry Bedell
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Aims: Misfolded α-synuclein is considered a key contributor to the pathogenesis of Parkinson's disease (PD). The objective of this work was to validate specific behavioral measures and analyze the morphology of microglia and astrocytes in a viral vector-induced α-synuclein mouse model of PD.
Methods: Adult C57BL/6 mice were unilaterally injected with AAV1/2-A53T-human-α-synuclein (AAV-A53T) or AAV1/2-empty vector (AAV-null) into the substantia nigra pars compacta (SNc). Asymmetric locomotor behavior was assessed at Week 5 and Week 10 post-injection. Tissue sections stained for phosphorylated α-synuclein, tyrosine hydroxylase (TH), Iba-1, and GFAP using multiplex immunofluorescence (IF) were quantitatively analyzed in neuroanatomical region-of-interests to measure α-synuclein levels, neurodegeneration, and neuroinflammation. In addition, cellular analysis of neuroinflammation was performed using a novel, high-throughput, fully automated platform based on computer vision and machine-learning (ML) algorithms.
Results: Unilateral expression of AAV-A53T induced significant motor coordination dysfunction and forelimb asymmetry. The α-synuclein expression was found in the ipsilateral SNc and midbrain, but did not spread into the striatum or contralateral (non-injected) hemisphere. TH-positive SNc neurons and striatal TH expression were significantly reduced. Compared to AAV-null mice, AAV-A53T-injected mice showed a high level of neuroinflammation, including increased microglial and astroglial IF density and activation in the ipsilateral SN and striatum. Using our automated cell analysis platform, we assessed the extent and degree of neuroinflammation by identifying and localizing microglia and astrocytes, quantifying their morphological phenotypes, and measuring their spatial relationship to the α-synuclein aggregates.
Conclusions: The combination of validated behavioral measures and the development of sensitive, cell-based metrics for assessing neuroinflammation in the AAV-A53T human α-synuclein mouse model makes this translational model well suited for the preclinical assessment of disease-modifying therapeutics in Parkinson's disease.

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SHIFT 01-139

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

IMPROVEMENT OF PARKINSON'S DISEASE MOTOR SYMPTOMS AND ALPHA-SYNUCLEIN PATHOLOGY VIA CJRB-302: A LIVE BIOTHERAPEUTIC PRODUCT FROM A HEALTHY HUMAN GUT MICROBIOTA

Yoon-Seong Kim
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Aims: Recent evidence highlights the microbiota-gut-brain axis as a key player in Parkinson's disease (PD) pathogenesis. PD patients often show microbial imbalances, including an increased Bifidobacterium, Lactobacillus, and Akkermansia, alongside reduced Prevotella, Roseburia, Blautia, and Faecalibacterium. These changes may contribute to neuroinflammation and PD progression by impacting gut permeability and immune responses. Clinical studies using fecal microbiota transplantation (FMT) have demonstrated motor symptom improvements in PD, with a 5 to 13-point increase in UPDRS motor scores, underscoring the therapeutic potential of targeting gut microbiota. However, FMT has limitations, including risks of pathogen transfer and inconsistent treatment outcomes. This highlights the need for safer, reproducible microbiome-based therapies. In this study, we evaluated CJRB-302, a live biotherapeutic derived from healthy human gut microbiota, to assess its ability to improve PD motor symptoms and pathology. CJRB-302 represents a controlled alternative with the potential to harness microbiome modulation for PD treatment.
Methods: CJRB-302 was evaluated in differentiated SH-SY5Y cells and ReNCell to assess its impact on alpha-synuclein-induced inflammation and MPP+-induced cytotoxicity. CJRB-302l was also tested in PD mouse models generated through systemic MPTP injection or alpha-synuclein overexpression in the substantial nigra.
Results: CJRB-302 reduced alpha-synuclein-induced inflammation in SH-SY5Y cells. Also, CJRB-302 protected neuronal cell viability from MPP+-induced toxicity, which effect was nullified by autophagy inhibitor, 3-methyladenine. In alpha-synuclein-injected mice, oral administration of lyophilized CJRB-302 significantly improved motor deficit and prevented dopaminergic neuronal cell death and phosphorylated-alpha-synuclein in the substantial nigra without critical safety issues including liver toxic signals. In MPTP-injected mice, orally administered lyophilized CJRB-302 dose-dependently reduced motor deficit and neuronal cell death, strongly correlated with microbiota composition changes.
Conclusions: CJRB-302 shows significant dopaminergic neuroprotection with improved motor behavior and changes in gut microbiota in preclinical PD models.

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SHIFT 01-141

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
2-3 April 2025

TARGETING ALPHA-SYNUCLEIN NEUROTOXICITY THROUGH PHARMACOLOGICAL MODULATORS OF BETA-GLUCOCEREBROSIDASE ACTIVITY

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Aims: The aggregation of α-Synuclein (αSyn) protein into amyloid fibrils is associated with Parkinson's disease (PD). Small oligomeric species forming during the aggregation process or released from fibrils play a crucial role in neurodegeneration. Recently, defective activity or mutations in GBA1, the gene encoding the lysosomal enzyme β-Glucocerebrosidase (GCase), have been associated with the increased risk of developing PD. Growing evidence suggests that increasing GCase stability and activity in the lysosome may represent a new therapeutic approach against αSyn accumulation. In this study we evaluated whether enhancing the activity of GCase through pharmacological chaperones can prevent αSyn neurotoxicity in neuronal PD models.
Methods: Human SH-SY5Y cells overexpressing WT or L444PG Case were exposed to different αSyn species following or not a pre-treatment with GCase enhancers. After evaluating the enzyme activity, we monitored αSyn accumulation and the resulting toxicities by using super resolution STED microscopy, confocal microscopy and the MTT reduction assay.
Results: SH-SY5Y cells overexpressing WT or L444P GCase were found to differently counteract against αSyn toxicity and the pre-treatment with GCase enhancers significantly increased GCase activity attenuating αSyn-induced neuronal dysfunction.
Conclusions: These results suggest that the employment of pharmacological GCase modulators could represent a valuable therapeutic strategy against the pathological accumulation of insoluble αSyn aggregates in the brain of PD patients. This research was supported by University of Florence (RICTD2024-2025, project VANGUARD to R.C, C.M. and A.M.); Work was also supported by #NEXTGENERATIONEU (NGEU) and funded by the Italian MUR, National Recovery and Resilience Plan (NRRP), project MNESYS (PE0000006) - A Multiscale integrated approach to the study of the nervous system in health and disease (D.R. 1553 11.10.2022; to R.C., F.Clemente, F.Cardona, C.C. and A. M).

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SHIFT 01-142

Poster on Board - Shift 01
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
2-3 April 2025

EFFICACY OF AMBROXOL IN A MOUSE MODEL OF PARKINSON'S DISEASE

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Aims: Sporadic Parkinson's disease (PD) is associated with glucocerebrosidase (GBA1) dysfunction, leading to glucosylceramide (GlcCer) accumulation and disrupted autophagolysosomal processes, which promote alpha-synuclein (SNCA) aggregation. Ambroxol, a mucolytic drug, improves the folding of mutated GBA1 and enhances its activity in vitro. Currently, it is being tested as add-on treatment for PD in clinical trials. We examined its efficacy in a PD mouse model with knockout of PTEN induced kinase plus human mutant SNCA expression (Pink1$^{-/-}$SNCA^{A53T}).
Methods: Pink1$^{-/-}$SNCA^{A53T} mice were treated with ambroxol in drinking water (cohort 1, n=10, ~150 mg/kg/d) or food pellets (cohorts 2-3, n=11-12, 75-100 mg/kg/d) for six months. Motor, sensory, and cognitive functions were assessed using IntelliCages, Thermal Gradient Ring, Hotplate, and Rotarod tests. Protein, lipidomic, and metabolomic analyses were performed on tissue samples. Data were analyzed using t tests, ANOVA, and multivariable tests ($p < 0.05$).
Results: Ambroxol was well tolerated but had minimal effects on behavior and lipids. Lipidomic analysis revealed ceramide accumulation in Pink1$^{-/-}$SNCA^{A53T} mice, with mildly reduced GlcCer levels only in the high-dose cohort. Ambroxol reduced SNCA and phosphorylated SNCA in the brain but not in the spinal cord. IntelliCage data showed increased activity and explorative behavior in ambroxol-treated mice during adaption phases, but no differences in learning tasks. Ambroxol-treated mice showed weaker cold avoidance in the Thermal Gradient Ring, likely due to local anesthetic effects. No effects were observed in Hotplate or Rotarod tests.
Conclusions: Ambroxol mildly reduced brain SNCA and GlcCer levels, the latter only in the high-dose cohort, suggesting that very high doses were required. Despite moderate effects on lipids, ambroxol showed limited impact on sensory or motor functions. IntelliCage behavior suggested a potential improvement in PD-associated encephalopathy that manifests in mice as slowness.

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SHIFT 01-143

Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / NON-MAMALIAN MODELS, OTHER
2-3 April 2025

INVESTIGATING TRANSTHYRETIN'S NEUROPROTECTIVE ROLE VIA GENE SILENCING IN A STREPTOZOTOCIN-INDUCED MURINE MODEL OF SPORADIC ALZHEIMER'S DISEASE

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Aims: Leptomeningeal amyloidosis, a subtype of familial transthyretin (TTR) amyloidosis, characterized by amyloid deposition in cranial and spinal leptomeninges presenting with cognitive impairment and CNS disorders, shares several similarities with sporadic Alzheimer's disease (sAD). To assess the extent of TTR involvement in sAD, we investigated the effect of TTR silencing in an intracerebroventricular (icv) streptozotocin (STZ)-induced model of sAD using adeno-associated virus (AAV) vectors with TTR gene knockdown shRNA.
Methods: Twenty-eight C57BL/6 male mice (Charles River Laboratories) aged 3 months were given icv either STZ (6 mg/kg, divided in 2 doses, 1 µl per ventricle) or citric buffer (pH 4), and AAV8-TTR-shRNA i.p. (1x10ˆ12 VG/ml) and icv (1,26x10ˆ11 VG/ml) or AAV8-scrambled-shRNA i.p. and icv (1 µl per ventricle) (SignaGen Laboratories). Behavioral tests were performed a month later, prior to sacrification and tissue collection.
Results: Open field revealed TTR silencing decreased the total distance covered in the apparatus while simultaneously increasing the time spent in the center in both control and STZ groups, indicating reduced mobility with increased disinhibition and/or diminished anxiety. There were no significant differences among groups in the T-maze spontaneous alteration test or the passive avoidance tests, suggesting spatial and aversive memory were not affected. Hippocampal tissue analysis by Western blot showed a decrease of Akt phosphorylation in both controls and STZ, whereas only STZ mice showed increases of total Tau levels. ELISA of hippocampal and striatal tissue homogenates showed tendencies of incremented amyloid beta load in STZ groups with abolished TTR expression.
Conclusions: Taken together, the obtained data point towards a confirmation of the postulated neuroprotective role of TTR in neurodegeneration and sAD. Research funded through the TransADamis project (73521469) within the „Junior Investigator Global ATTR Amyloidosis Research ASPIRE“, Pfizer Inc.

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SHIFT 01-146

Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS
2-3 April 2025

A REPRODUCIBLE HUMAN BRAIN TISSUE MODEL TO STUDY MICROGLIA STATES IN HEALTH AND DISEASE

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Aims: Human iPSC-based *in vitro* models have great potential for mechanistic and translational studies as they enable investigation of physiological and pathological processes in human brain cells. However, current iPSC 3D models show low reproducibility and cell type diversity, especially long-term incorporation of mature microglia, or show only earliest disease phenotypes, e.g. of Alzheimer's disease (AD). Therefore, we aimed to develop a more reproducible and controllable 3D model that combines multiple brain cell types, including mature microglia, and enables analysis of AD pathomechanisms in a human cortical tissue-like environment.
Methods: We optimized protocols to differentiate iPSCs into cortical neurons, astrocytes, and microglia. We combined these differentiated cells into 3D co-cultures and characterized them using transcriptomics, proteomics, stainings, and functional assays. Using CRISPR/Cas9 and seeding approaches, we initiated and studied AD pathology over time.
Results: By 3D co-culturing all cell types we established modular, human cortical tissue models that display dense networks of neuritic processes that are stable for >6 months without necrotic core formation.

Added microglia migrate into and tile the cultures, surveil the environment, react to tissue damage, and adopt an unprecedentedly ramified morphology and mature transcriptomic profile. We further confirmed maturation of the cultures, e.g., by synapse formation, astrocyte maturation, and deposition of a brain-like extracellular matrix, strongly increasing similarity to human brain tissue over time. AD cultures showed typical phenotypes such as increased Aβ secretion and age-dependent deposition of extracellular and insoluble Aβ, increased levels of phospho-tau and microglial activation towards an AD-relevant signature. Upon addition of exogenous Aβ42, we found aggregation into plaque-like structures with surrounding axonal dystrophies.

Conclusions: We developed a reproducible and controllable, human cortical tissue model to study cell states, crosstalk, and functionality in health and disease.

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SHIFT 01-150

Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
2-3 April 2025

DIFFERENTIAL EXPRESSION ANALYSIS IN THE CORTEX OF A HUMANIZED APOB TRANSGENIC MOUSE MODEL

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Aims: Apolipoprotein B (*APOB*) has been identified as an Alzheimer's disease (AD) biomarker linked to phospho-tau metabolism in the cerebrospinal fluid of asymptomatic subjects with a parental history of AD (Picard et al., 2022). Cognitive impairment and AD pathological hallmarks have been observed in a human *APOB* expressing transgenic mouse model (Bereczki et al., 2008). We used the model to conduct RNA sequencing and analyze expression patterns caused by APOB overexpression in transgenic and non-transgenic mice at various life stages.
Methods: 120 mice were ordered from Taconic biosciences (60 wild-types (C57BL/6) and 60 human *APOB* transgenic (C57BL/6Tg) mice). Animals were sacrificed at 6 months (n=60) and 1 year (n=60) of age. Brains were collected and dissected to collect frontal cortices. RNA extraction was performed using Qiagen kit catalog# 74804, following the manufacturer's instructions. RNA sequencing was performed at McGill genome Center using Illumina's technology. Quants were measured using Salmon software and analyses were made using R.
Results: Interferon regulatory factor 7 (*Irf7*) was the most differentially expressed gene in both young *APOB* vs young wild-type mice (log2 fold change=2.2 $p=1.04E^{-57}$) and in 12-month old *APOB* vs 12 month-old wild-type mice (log2 fold change=2.02 $p=5.68E^{-48}$) analyses. The "response to virus" genomic pathway was highly enriched in young 6 month-old APOB compared to young wild-type mice ($p=2.41E^{-30}$), while the "response to interferon-beta" pathway was enriched in 12 month-old APOB compared to old wild-type mice ($p=1.87E^{-22}$).
Conclusions: In closing, the RNA sequencing analysis of frontal cortices in APOB overexpressing mice indicates a heightened immune response within the brain associated with a significant oxidative stress response typically associated with AD pathology. Further molecular exploration of this transgenic mouse model, namely proteomics, is ongoing.

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SHIFT 01-151

Poster on Board - Shift 01
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
2-3 April 2025

NATURALIZATION OF ALZHEIMER'S DISEASE TRANSGENIC MICE

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Aims: Alzheimer's disease (AD) arises from intricate gene-environment interactions that disrupt neural homeostasis. However, conventional AD mouse models are raised in sterile, pathogen-free (SPF) conditions, limiting exposure to environmental factors such as microbes and toxins, which are key modulators of immune function. This study aimed to characterize AD-related pathologies in transgenic AD mice exposed to a naturalistic, farm-like setting.
Methods: Six-month-old female 3xTg-AD mice and wildtype (WT) controls were transferred to a non-SPF vivarium containing ecologically relevant elements (e.g., soil, grass, hay, manure, wood, and insects) designed to mimic a natural farm environment. We hypothesized that this "rewilding" would promote immune maturation and induce physiological responses absent in SPF-raised mice. Control cohorts remained in SPF conditions. After three months, mice were sacrificed and subjected to comprehensive phenotypic analyses, including flow cytometry, single-nucleus RNA sequencing (snRNA-Seq), qRT-PCR, immunohistochemistry, and Western blotting.
Results: Cytometric and snRNA-Seq analyses of brain, blood, and spleen revealed substantial immune reprogramming in rewilded mice compared to SPF controls. In rewilded 3xTg-AD mice, we observed increased T cells, B cells, and neutrophils, along with a shift toward an anti-inflammatory M2 microglia phenotype in the brain, despite no changes in total microglial numbers. Notably, at 9 months of age, the 3xTg-AD mice had not yet developed amyloid plaques or tangles but exhibited reduced levels of human Aβ and phosphorylated Tau. qRT-PCR analyses also showed elevated expression of anti-inflammatory cytokines, such as TGF-β, in rewilded 3xTg-AD mice. Additional findings from ongoing experiments with 5xFAD mice will also be discussed.
Conclusions: Our early findings suggest that a natural setting may mitigate AD-related pathologies in presymptomatic mice. Studies are ongoing with advanced disease stages and other AD mouse models, potentially increasing the translational relevance of rewilding.

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SHIFT 01-153

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
2-3 April 2025

MASTEROID MODEL OF ALZHEIMER'S DISEASE: EXAMINING APOE ISOFORMS IN TAU AGGREGATION AND LIPID METABOLISM

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Aims: Apolipoprotein E (APOE) is a key genetic factor in Alzheimer's disease (AD), with the APOE2 variant linked to a reduced risk. However, how different APOE genotypes affect AD pathology is still unclear. Studies suggest that APOE influences brain lipid metabolism, amyloid-beta deposition, and tau pathology in both neurons and glial cells. This study aims to elucidate the role of APOE2 in mediating lipid and protein interactions that drive tau pathology.
Methods: We hypothesize that ApoE-mediated lipid metabolism regulates the rate of tau aggregation and propagation between neurons and glial cells in AD pathogenesis. To test this, we use our innovative 3D neuron-glial brain assembloid model (Masteroids), derived from AD patient iPSCs representing ApoE2 and its isogenic ApoE3 genotypes. In brief, ApoE2 and ApoE3 iPSCs were differentiated in 2D cultures into neuronal, astrocytic, and microglial-like progenitor cells. Neuronal cells were then seeded with tau oligomers to simulate a pathological environment. The Masteroids, formed by combining these cell types, were examined for tau aggregation in neurons using Western blotting and immunocytochemistry. The underlying molecular mechanisms and pathways are further investigated by proteomic analysis via mass spectrometry.
Results: This advanced Masteroid model of AD replicates the complex cellular interactions of the human brain and reveals isoform-specific differences in tau aggregation and neuroinflammation between ApoE variants. ApoE3 neurons exhibit larger tau aggregates with potential cytotoxic effects, whereas ApoE2 neurons display smaller, more diffusely distributed aggregates, which may influence disease progression.
Conclusions: Our findings suggest that ApoE isoforms differentially impact lipid metabolism and tau pathology. By investigating neuroinflammatory and lipid metabolism pathways, our Masteroid model could pave the way for precision medicine approaches, offering new opportunities to target AD's underlying mechanisms.

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SHIFT 01-154

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
2-3 April 2025

3D IMMUNE-NEUROGLIAL-VASCULAR HUMAN BRAIN MODEL

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Aims: This research focuses on developing a powerful model system to explore the rare and genetically intricate elements of Alzheimer's disease (AD). By co-culturing all major brain cell types derived from patient-specific iPSCs, the goal is to establish a comprehensive Immune-Neuroglial-Vascular brain model. This model replicates critical in vivo-like characteristics such as neural activity, barrier integrity, immune responses, complex cellular interactions, and transcriptional profiles. Specifically, the focus is on amyloid aggregation and tau phosphorylation in sporadic AD models, targeting the key mechanisms that drive disease onset and progression, with the ultimate aim of identifying therapeutic targets.
Methods: To unravel the molecular and regulatory dysfunctions in AD, we will use a cutting-edge combination of brain assembloids and advanced imaging technologies. These models closely mimic the human brain, providing a powerful platform for studying AD mechanisms. Additionally, single-cell RNA sequencing will assess gene expression, deepening our understanding of cellular responses in AD models.
Results: This research centers on the creation of a model system designed to function as a "Disease Avatar," allowing for personalized therapeutic approaches based on the specific genetic and molecular signatures of patient-derived brain assembloids. One limitation encountered was the absence of functional blood circulation, which restricted the evaluation of drug delivery across the human blood-brain barrier (BBB)—a recognized challenge in in vitro models. This emphasizes the need for future studies incorporating human-mouse chimera models to simulate capillary blood flow. Despite these limitations, the study offers groundbreaking insights into the interactions between human neuronal and non-neuronal cells under conditions closely replicating those in vivo.
Conclusions: This work provides a deep and meaningful understanding of AD mechanisms through the development of a 3D Immune-Neuroglial-Vascular brain model that captures critical in vivo-like features of AD.

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SHIFT 01-155

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
2-3 April 2025

AAV-CRE MEDIATED TRIPLE KNOCKOUT OF THE AMYLOID PRECURSOR PROTEIN (APP) FAMILY: INSIGHTS INTO THE ROLE OF APP FOR CELL SURFACE AND SYNAPTIC PROTEIN EXPRESSION

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Aims: Alzheimer's disease (AD) is strongly associated with the amyloid precursor protein (APP). Yet, the physiological functions of APP and the related APLPs remain largely poorly understood due to functional redundancy. To overcome this challenge, we developed primary mouse neurons lacking APP, APLP1, and APLP2, allowing us to investigate their specific roles in synaptogenesis, neuronal morphology, and synaptic function. This project aims to comprehensively characterize these triple knockout (TKO) neurons by examining the cell surface proteome, neuronal structure, and synaptic transmission, providing new insights into the APP family's involvement in neural network formation and maintenance
Methods: Primary cortical and hippocampal neurons from $APP^{flx/flx}$, $APLP1^{-/-}$, $APLP2^{flx/flx}$ mice were transduced with AAV-Cre to generate triple KO (TKO) neurons. Western blotting was used to assess the expression of synaptic and structural proteins throughout synaptogenesis (DIV7-21). We will further characterize the TKO neurons by proteomics using "surface-spanning protein enrichment with click sugars" (SUSPECS) and "high-performance secretome protein enrichment with click sugars" (hiSPECS) to analyze alterations in the cell surface proteome and secretome.
Results: Western blot analysis revealed that the loss of all APP family members altered the expression of critical synaptic proteins, including NMDAR subunits and structural proteins like Homer1, during synaptogenesis. These findings suggest that APP, APLP1, and APLP2 are crucial for synapse formation and function. Ongoing SUSPECS and hiSPECS analysis will allow further insights into how the lack of the APP family affects the cell surface proteome and secretome.
Conclusions: In summary, TKO neurons offer a novel approach for studying the essential functions of APP independently from the functional redundancy within the APP family, enabling deeper insights into how APP influences synaptic protein expression, trafficking, and the formation and maintenance of neural networks.

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SHIFT 01-156

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
2-3 April 2025

UNRAVELING THE MOLECULAR BASIS OF PHENOTYPIC HETEROGENEITY IN FAMILIAL ALZHEIMER'S DISEASE: FOCUS ON AB43 AND SPASTIC PARAPARESIS

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Aims: More than 300 mutations in the Presenilin 1 (*PSEN1*) gene cause early onset autosomal dominant Alzheimer's disease (ADAD). While AD typically presents with memory loss and progressive cognitive decline, ADAD-linked *PSEN1* mutations show varied clinical presentations, with many associated with spastic paraparesis (SP). The molecular basis for this phenotypic heterogeneity remains unknown. This study investigated the relationship between Aβ profiles generated by *PSEN1* variants and SP.
Methods: PSEN1 is the catalytic subunit of the γ-secretase complex involved in the generation of Aβ peptides. ADAD-linked *PSEN1* variants consistently impair γ-secretase processivity, thereby leading to enhanced generation of longer Aβ peptides. To investigate the connection between Aβ profiles and SP, Aβ profiles reported for 160 ADAD-linked PSEN1 variants were analysed in the context of the SP phenotype. The analysis integrated univariate, principal component analyses, and machine learning approaches.
Results: Analysis of Aβ profiles generated by PSEN1 variants associated with AD or AD+SP revealed a strong correlation between high Aβ43 levels and the SP phenotype. Notably, overall γ-secretase activity showed no significant differences between the AD and AD+SP groups.
Conclusions: The analysis suggests that relative increases in Aβ43 levels may contribute to SP development in carriers of *PSEN1* variants. These findings warrant further investigations into a possible causative role of Aβ43 in the SP development.

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SHIFT 01-157

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
2-3 April 2025

METHOD DEVELOPMENT OF KINETIC MEASUREMENTS OF AETA FRAGMENTS IN HUMAN CEREBROSPINAL FLUID

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Aims: Amyloid Precursor Protein (APP) may be cleaved by η-secretase, and subsequently cleaved either by β-secretase or α-secretase, resulting in the release of soluble Aη-β and Aη-α fragments, respectively. Collectively, these are known as AETAs and have important physiological functions. Upon BACE1 inhibition, AETA is increased. Given the history of failed BACE1 inhibitor trials due to side effects and subsequent attempts to revitalize BACE1 inhibitors in low-dose forms, it is vitally important to understand the physiological and pathological processing of APP by η-secretase. **To date, no one has measured AETA turnover in humans. Our aim is to develop a method to quantify AETA kinetics in CSF as surrogates of η-secretase, β-secretase, and α-secretase cleavage of APP in humans who have undergone stable isotope labeling kinetics (SILK).**
Methods: 7PA2 cell culture media were depleted of abundant sAPPs using a mid-domain APP antibody. Subsequently, Mrk61 and W0-2 antibodies were used to immunoprecipitate (IP) remaining C-terminal sAPPs. After proteolytic digestion, a peptide specific to AETA was monitored by LC/MS-MS. Peptides from Mrk61 and W0-2 IPs represent Aη-β and Aη-α, respectively. After in vitro validation of methods, we assessed this IP in human specimens. Subjects underwent [U-$^{13}C_6$]-leucine labeling and hourly CSF collection over 36h. CSF from these subjects underwent similar IP methods.
Results: We will showcase the ongoing developments from in vitro and in vivo studies designed to identify and measure soluble AETA fragments by SILK-IP-LC-MS/MS.
Conclusions: Our study is in the nascent stage of our greater goal of determining the physiological turnover of these proteins, while also taking into account turnover of sAPPβ, sAPPα, and Aβ. This will enable us to develop a comprehensive picture of physiological APP processing in healthy aging and in AD.

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SHIFT 01-158

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
2-3 April 2025

IMPROVED LC-MS/MS ANALYTICAL MEASUREMENTS FOR B-AMYLOID DISEASE AND RELATED NEURODEGENERATIVE DISORDERS

Mariette Heins, Chris Williams
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Aims: Biomarkers for β-amyloid disease risk and onset predictions, together with other neurodegenerative disorders, have markedly improved over the past years. These steps result from large scale population screening studies and the use of increasingly sensitive platforms. One of the challenges for development of new treatments is the lack of cross-species reactivity and therefore the lack of translational markers throughout the drug discovery process.
Methods: As quantitation of relevant and translational biomarkers is an important part of preclinical research, we have used LC-MS/MS to develop relevant analytical methods for β-amyloid disease and related neurodegenerative disorders.
Results: Methods developed allow for amyloid quantitation of several species in the same run and is applicable in various tissues. These methods allow for comparison of the ratio of different β-amyloid forms within the same sample as well as for comparison of ratio for these β-amyloid forms between species as drug development progresses. In addition, we show further possibilities by analysis of multiple neurotransmitters with high sensitivity from the same samples.
Conclusions: The presented results demonstrate that LC-MS/MS can be applied for quantitative multiplexing analysis of translationally relevant biomarkers. These can be neurotransmitters, peptides such as β-amyloids or even proteins. Together with pharmacokinetic analysis of the test compound, this type of analytical method improvements will allow for PK/PD measurement from each sample and thus improved predictive compound and efficacy modelling.

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SHIFT 01-159

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
2-3 April 2025

PHENOTYPING OF APP KNOCKIN MICE LACKING THE ALPHA- AND BETA-SECRETASE SITES

Lara Kilian[1], Marija Banicevic[1], Jennifer Just[2], Christos Galanis[3], Michaela Back[4], Irmgard Amrein[5], Jakob Von Engelhardt[4], David Wolfer[5], Stefan Kins[6], Andreas Vlachos[3], Martin Korte[2], Ulrike Muller[1]
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Aims: Amyloid precursor protein (APP) is pivotal in the pathogenesis of Alzheimer's Disease, although the precise physiological roles of APP and its proteolytic fragments remain incompletely understood. APP and its homologs are crucial for synaptic adhesion, supporting synaptic stabilization, while proteolytic cleavage releases APPsalpha, which mediates structural and functional synaptic plasticity. To elucidate the interdependence of these synaptic processes in vivo, novel APP knockin mice were generated expressing a secretion-deficient APP variant through a targeted genomic deletion (APPdeltaS622) encompassing the alpha- and beta-secretase cleavage sites. Due to the absence of APPsalpha and Abeta, this mouse line provides a unique opportunity to investigate the mechanisms by which secreted APP fragments mediate Hebbian and homeostatic synaptic plasticity.
Methods: Brain lysates of APPdeltaS622 mice, were assessed for the expression of postsynaptic proteins involved in synapse formation and synaptic plasticity. Changes in the cell surface proteome and secretome of primary hippocampal neurons are currently analyzed using advanced proteomics.
Results: Analysis of APP processing in brain lysates from APPdeltaS622 mice revealed an accumulation of uncleaved APP at the cell surface, accompanied by a marked reduction in secreted APP fragments. Notably, expression levels of synaptic proteins, including Homer1 and Arc, were significantly altered. Additionally, electrophysiological recordings from the hippocampus of adult APPdeltaS622 mice demonstrated a pronounced deficit in the induction and maintenance of hippocampal LTP. Ongoing studies are aimed to investigate potential differences in neuronal morphology, spine density and morphology associated with deficits in LTP.
Conclusions: APPdeltaS622 mice represent a novel mouse line to explore the role of APP as a soluble ligand. Collectively, our findings suggest that soluble APPs plays a critical role in modulating the dynamic processes underlying synaptic plasticity.

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SHIFT 01-160

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
2-3 April 2025

TWO PHOTON CALCIUM IMAGING REVEALS INCREASED LOCAL PROPAGATING CALCIUM WAVES IN CEREBRAL ORGANOIDS WITH APP MUTATION

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Aims: Cerebral organoids are widely used to model aspects of human brain development, function and disease. However, little is known about the longitudinal neuronal network dynamics present in organoids, or how these dynamics are affected in Alzheimer's disease (AD). Here, we aimed to characterise these dynamics during the development of organoids, by recording neuronal activity at the single-cell level using two-photon Ca^{2+} imaging.
Methods: We cultured organoids from induced pluripotent stem cells from a reference line (KOLF2.1J) and an isogenic AD line with the same genetic background and the addition of a homozygous amyloid precursor protein (APP) V717I mutation. We then undertook two-photon recordings across the spherical organoid structure, labelled with the Ca^{2+} indicator Cal520-AM, between 80-300 days *in vitro*.
Results: We identified three distinct modes of spontaneous activity observed in both the control and AD lines: unsynchronous activity, synchronous activity and local propagating waves. These waves consisted of a propagating radius of Ca^{2+} transient events across multiple cells, which initiate from a central cell. Pharmacological experiments revealed that the waves are primarily initiated by calcium release from intracellular stores, and propagate via glutamatergic synaptic connections. In the AD organoid line, we observed significantly more spontaneous propagating waves compared to the control line, suggesting that the APP mutation in human cells may have an impact on this network activity.
Conclusions: By employing two photon Ca^{2+} imaging, we reveal that organoids develop functionally interconnected networks of neurons which display multiple types of spontaneous activity, including local propagating waves. To the best of our knowledge, these waves have not been described previously and may be significant in the early development of human neuronal networks, and be significantly affected by an APP mutation.

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SHIFT 01-161

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
2-3 April 2025

GENOME-WIDE EQTM MAPPING IN HUMAN BRAIN SAMPLES TO CHARACTERIZE KNOWN EWAS SIGNALS IN ALZHEIMER'S DISEASE

Marit Junge[1], M. Muaaz Aslam[1], Valerija Dobricic[1], Laura Parkkinen[2], Lars Bertram[1]
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Aims: DNA methylation (DNAm) is an epigenetic mark involved in the regulation of gene expression. Since the advent of microarray-based high-throughput DNAm genotyping technologies, DNAm at specific cytosine-guanine dinucleotides (CpGs) has been studied in the context of numerous epigenome-wide association studies (EWAS), several focusing on Alzheimer's disease (AD) risk. However, little is known whether and which of these DNAm-based associations also relate to changes in gene expression in the brain.
Methods: This study is part of a larger effort to perform genome-wide mapping of expression quantitative trait methylation (eQTM) loci in human brain samples, i.e. snap-frozen post-mortem entorhinal cortex (EC) slices of 183 individuals (AD(n)=91, controls(n)=92). DNAm profiling was performed using the "Infinium MethylationEPIC" array (Illumina, Inc.) while transcriptome profiles were generated via short-read (2x100 bp) RNA sequencing of TruSeq Stranded Total RNA libraries (Illumina, Inc.). For genome-wide eQTM mapping we used Torch-eCpG (Kober et al. 2024).
Results: At the time of writing, the eQTM mapping analyses are still ongoing. For this presentation, we will focus on highlighting CpGs previously implicated in AD brain-based EWAS, i.e. the studies by Smith et al, 2021, Sommerer et al, 2023, and Piras et al, 2023. Of note, while the latter study also generated DNAm and mRNA data in n=135 overlapping samples, the DNAm data was based on a lower-resolution microarray (i.e. Illumina's 450K array), potentially missing a significant fraction of relevant eQTM signals.
Conclusions: To the best of our knowledge, this is one of the largest eQTM studies conducted in human brain samples and the first to use EC. The results of our analyses will help guide the interpretation of existing and future brain EWAS results in AD and related traits.

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SHIFT 01-164

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
2-3 April 2025

IDENTIFICATION OF LONG NON-CODING RNAS DIFFERENTIALLY EXPRESSED IN ALZHEIMER'S DISEASE BRAINS USING RNA SEQUENCING

M. Muaaz Aslam[1], Marcel Schilling[2], Valerija Dobricic[1], Janina Fuß[3], Sören Franzenburg[3], Christina Lill[4], Laura Parkkinen[5], Lars Bertram[1]
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Aims: Long non-coding RNAs (lncRNAs) are non-coding transcripts of over 200 nucleotides in length that regulate gene expression, splicing, and translation. In Alzheimer's disease (AD), lncRNAs have previously been reported to show differential expression as compared to controls, albeit with inconsistent results. Only a few studies have explored lncRNA expression in human brain samples.
Methods: Post-mortem brain tissue was sampled from the entorhinal cortex (EC) of 177 individuals [AD(n)=95, controls(n)=82] and subjected to RNA sequencing followed by differential gene expression (DGE) analysis. LncRNAs identified to be differentially expressed were further assessed in an independent dataset from 277 ROSMAP participants [dorsolateral frontal cortex; AD cases (n) = 156, controls (n) = 121]. Post-DGE assessments included lncRNA-mRNA co-expression and gene ontology (GO) enrichment analyses to elucidate potential mechanisms.
Results: Transcriptome-wide DGE analyses resulted in a total of 307 differentially expressed lncRNAs [downregulated(n)=180, upregulated(n)=127] in AD vs. control brains. Besides replicating several lncRNAs previously reported to show differential expression in AD (e.g., *NEAT1*, *MALAT1*, *MIAT*, and *XIST*) we also identified several dozen lncRNAs not previously linked to AD. Among the top novel loci were *ITPKB-AS1*, *B3GALT5-AS1*, *MIR9-1HG*, *LINC02987*, and *CEDORA*. N=109 of the identified lncRNAs independently replicated in ROSMAP data. GO annotation revealed several biological processes of potential relevance for AD, e.g., vesicle-mediated transport in the synapse, signal release from the synapse, and neurotransmitter secretion.
Conclusions: To our knowledge, our study comprises the largest DGE analysis on lncRNAs using RNA sequencing in the human brain and the first to utilize EC samples. We identified and independently replicated several novel AD-associated lncRNAs. The results of our work underline the importance of lncRNA dysregulation in AD and provide a reference for future work on this topic.

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SHIFT 01-165

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
2-3 April 2025

SEX-SPECIFIC TRANSCRIPTOMIC PROFILING REVEALS KEY PLAYERS IN BONE LOSS ASSOCIATED WITH ALZHEIMER'S DISEASE

Mohini Gharpure, Sagar Vyavahare, Roger Zhong, Diana Asante, Marion Cooley, Carlos Isales, Sadanand Fulzele
Augusta University, auguata, United States of America

Aims: Alzheimer's disease (AD), a progressive neurodegenerative disorder, is frequently associated with musculoskeletal complications, including sarcopenia and osteoporosis, which substantially impair patient quality of life. Despite these clinical observations, the molecular mechanisms linking AD to bone loss remain insufficiently explored. In this study, we examined the femoral bone microarchitecture and transcriptomic profiles of APP/PS1 transgenic mouse models of AD to elucidate the disease's impact on bone pathology and identify potential gene candidates associated with bone deterioration.
Methods: We performed micro-computed tomography (microCT) and RNA transcriptome analysis on femoral bone of male and female APP/PS1 mice compared to their wild-type counterparts.
Results: We observed a significant reduction in bone microstructure in both male and female APP/PS1 mice compared to their wild-type counterparts. Transcriptomic analysis of femoral bone tissue revealed substantial differential gene expression between AD mice and controls. Specifically, APP/PS1 mice exhibited differential expression in 289 protein-coding genes across both sexes. Notably, in female APP/PS1 mice, 664 genes were differentially expressed, with key genes such as Shh, Efemp1, Arg1, EphA2, Irx1, and PORCN potentially implicated in bone loss. In male APP/PS1 mice, 787 genes were differentially expressed, with Sel1l, Ffar4, Hspa1a, AMH, WFS1, and CLIC1 emerging as notable candidates in the context of bone deterioration. Gene Ontology (GO) enrichment analysis further revealed distinct sex-specific gene pathways between male and female APP/PS1 mice, underscoring the differential molecular underpinnings of bone pathology in AD.
Conclusions: This study identifies novel sex-specific genes in the APP/PS1 mouse model and proposes potential therapeutic targets to mitigate bone loss in AD patients.

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SHIFT 01-166

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
2-3 April 2025

A NOVEL IN VITRO MODEL REPRESENTING NEURON DEGENERATION AND SYNAPTIC DISORDER USING CULTURED HUMAN IPSC-DERIVED NEURONS IN A MICROPHYSIOLOGICAL SYSTEM

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Aims: To address the need for streamlining within the novel drug development for neurological disorders such as Alzheimer's disease and Parkinson's disease, more physiologically relevant models are needed to screen potential candidate compounds in nascent testing stages. In the present study, a microphysiological system (MPS) device was developed for structured culture of human iPSC-derived neurons. Then, drug-induced neuron degeneration and inter-cellular signal conduction were analyzed to show its application for drug testing.
Methods: This MPS device could separate the cell body and neurites, so that elongated neurites morphology can be analyzed alone. COP (Cyclo olefin polymer), which has excellent observability and low drug adsorption, is used as the resin material. After combined the MPS device with microelectrodes arrays (MEA) using a directly photobonding method, the electrophysiological activities could be measured between different types of neurons.
Results: Successful culture of human iPSC-derived cortical neurons with separating neurites growth were achieved in the MPS for longer than 8 weeks. After administration of different types of Amyloid β, the toxic effects were evaluated by training two AI models on axonal and PSD-95 images. And the combined results indicated that Amyloid β1-42 and 1-40, but not 1-28, induced neuron degeneration, which is close to clinical reports. Using MPS-MEA device, a time delay was measured between network bursts of different types of neurons, indicating the formation of synaptic networks. After administration of Linopordine, a drug used to treat AD, to only one type of neuron, the responses in spontaneous activity could also be detected in another type of neuron through the synaptic signal conduction.
Conclusions: Taken together, it suggests that the present MPS combined with MEA is a useful platform for in vitro assessment of drug-induced neuron dysfunctions.

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SHIFT 01-168

Poster on Board - Shift 01
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / SECRETASES
2-3 April 2025

CHARACTERIZATION OF UNCULTURED METHANOGENIC ARCHAEON (UMA) AS GAMMA-SECRETASE

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Aims: Gamma-secretase (GS) is a protease involved in both Alzheimer's disease (AD) and cancer. Presenilin, the catalytic component of the complex, is responsible for the cleavage of transmembrane proteins, including amyloid precursor protein (APP) and Notch. APP is cleaved by GS to produce amyloid beta in different lengths. These peptides can aggerate to form harmful plaques and ultimately contribute to AD. GS in mammalian cells has been well characterized. The discovery of archaeal presenilin-like intramembrane proteases has raised questions of their activity against GS substrates, such as APP and Notch. We aim to characterize the archaeal presenilin homolog Uncultured Methanogenic Archaeon (UMA).
Methods: The structure of UMA was predicted and compared to the structure of presenilin. We have expressed and purified recombinant UMA in bacteria. We have analyzed UMA's ability to cleave APP and Notch substrates *in vitro* and its sensitivity to GS inhibitors and modulators.
Results: Alphafold structural prediction found UMA to have nine transmembrane domains with a similarity score to presenilin of TM=0.7885. We have found that recombinant UMA is able to cleave APP to AB40 and AB42 as well as Notch in biochemical assays. When incubated with a panel of GS inhibitors, only L458, a transition state inhibitor, was able to inhibit UMA's cleavage of APP. Allosteric site-based inhibitors of presenilin had no effect on UMA's cleavage in these studies. Similarly, UMA was successfully photolabeled by a GS active site directed inhibitor.
Conclusions: These studies establish UMA as an archaeal protease with striking similarities to presenilin in its cleavage of GS substrates APP and Notch. UMA is unique due to its lack of inhibition from allosteric GS inhibitors as well as functionality without the use of cofactors.

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SHIFT 01-173

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

ADVANCING ALZHEIMER'S DISEASE MODELS FOR PRECLINICAL DRUG TESTING

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Aims: Though Alzheimer's disease (AD) is the most common cause of dementia, complete disease-modifying treatments are yet to be fully attained. The development and commercialization of new drugs is a lengthy and very expensive process and current approaches targeting the too-late stages of AD have had no consistent clinical benefit. For this reason, development of predictive and robust preclinical models, recapitulating early neuropathological features of AD are of urgent need. Here, we report the progress in our development of high throughput in vitro models that captures AD characteristics using physiopathologically relevant culture conditions.
Methods: Assessment of cellular phenotypic changes (neurons or glial cells from rodent or human induced pluripotent stem cells (iPSCs) induced after an exposure of human amyloid oligomers (AβO and TauO) were performed using 2D-cultures, brain-on-chip (BoC) models, and a high content imaging system. These oligomeric preparations were prepared in-house from human $A\beta_{1-42}$ and Tau (2N4R) monomers and were well-characterized by various methods (SDS-page, dot-blot, 8-Anilino-1-NaphthaleneSulfonic acid (ANS) and Sedimentation Velocity Analytical Ultracentrifugation (SV-AUC) assays).
Results: Our data showed that increasing concentrations of oligomers have been associated with significantly loss of synaptic markers, reduction of neurite outgrowth and ultimately neuron death. They also triggered neuroinflammatory processes *via* activation of astrocytes. Induced neurodegeneration and neuroinflammation were successfully attenuated by pharmacologic compounds, including monoclonal antibodies, which have produced encouraging therapeutic results in clinical trials.
Conclusions: In conclusion, we characterized many experimental situations to better understand the mechanisms underlying AD, and targeting oligomers or their harmful effects, should give rise to new therapeutic interventions. Complexifying of in vitro models, combining neuron and glia, using BoC devices and targeting both amyloid and tau for development next generation AD prevention could be of great interest.

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SHIFT 01-174

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

ROLE OF NITRATION IN AMYLOID-BETA FIBRILLATION AND MICROGLIAL ACTIVATION

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Aims: Amyloid-beta pathology has several morphologies with distinct Amyloid-beta peptide profiles and neuroinflammatory patterns. However, the consequences of nitration at Amyloid-beta peptide tyrosine-10 on oligomerization processes, neurotoxicity and microglial activation are still unclear.
Methods: The parietal cortex of five Alzheimer's Disease cases, was (immuno)histochemically stained for Thioflavin-S, N-terminal Amyloid-beta (IC-16) and nitrated tyrosine. We assessed 80 Amyloid-beta deposits, including diffuse, classic cored, coarse-grained plaques and Cerebral Amyloid Angiopathy (CAA) deposits, for occurrence of nitration within fibrillar and non-fibrillar Amyloid-beta. We conducted the *in vitro* nitration of monomeric Amyloid-beta(1-42) peptide exploiting a light-inducible peroxynitrate-releasing probe, and confirmed the nitration at tyrosine-10 through High-Resolution Mass Spectrometry. The nitrated Amyloid-beta was analyzed for aggregation through western blot and Thioflavin-T fluorescence. It was tested for its biological activity on differentiated SH-SY5Y neuroblastoma cells, and microglial C57BL/6 BV2 cells.
Results: Nitration was differently located in the diverse Amyloid-beta deposits (figure 1). In diffuse plaques we observed no nitration, in classic cored plaques it was confined to the core, in coarse-grained plaques it was dispersed throughout the plaque, while CAA vessels show almost complete nitration. The nitration overlaps with Thioflavin-S, indicating the colocalization with fibrillary Amyloid-beta. The *in vitro* nitration of the monomer resulted into amorphous (i.e., not fibrillary) Amyloid-beta aggregates. The nitration of Amyloid-beta did not affect the viability of neuronal-like cells after 48 hours post-treatment. However, nitration did increase the number of ameboid microglial cells, measured after 24 and 72

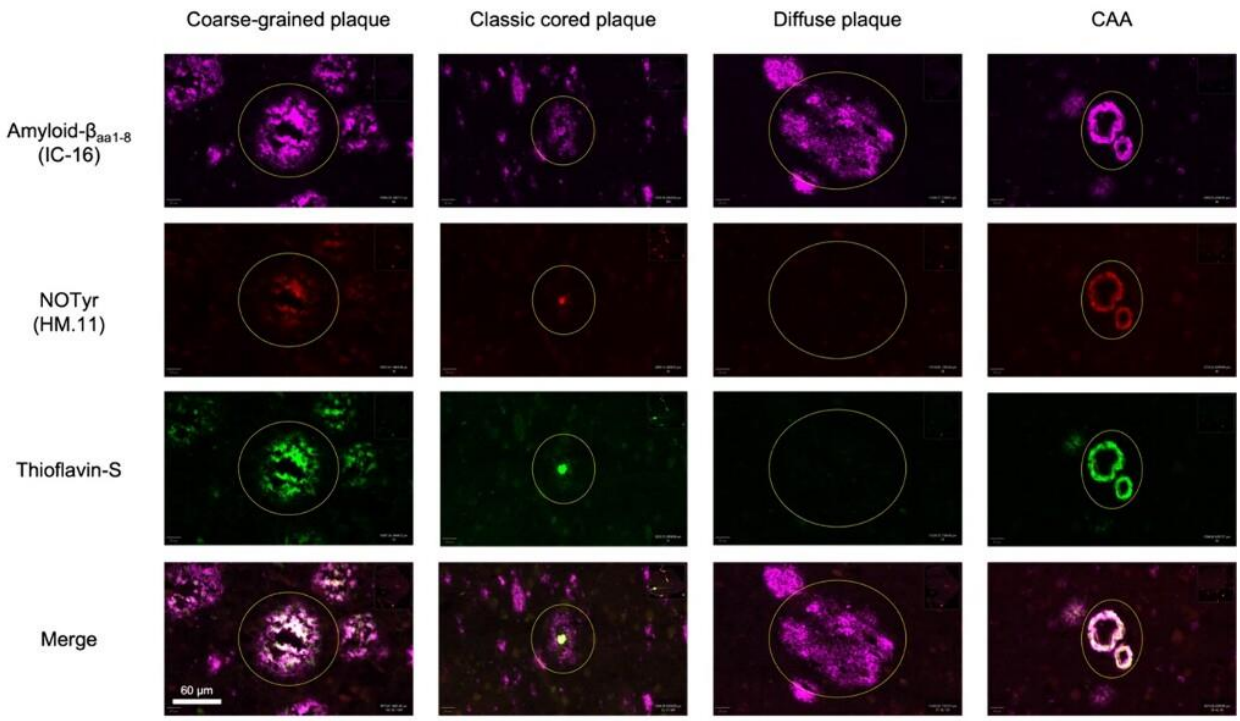

Figure 1. Immunofluorescence triple staining to assess nitration localization within the different Amyloid-beta deposits. Scale bar applies to all images.

hours.

Conclusions: Overall, our data show that nitration is dispensable for Amyloid-beta fibrillation. Since fibrillar Amyloid-beta in tissue is nitrated, these findings suggest that nitration appears as a subsequent event after fibril formation. Moreover, nitrated Amyloid-beta is not neurotoxic but modulates microglial activation.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

CHARACTERISATION OF IN VITRO NEURONAL AND MICROGLIAL DISEASE MODELS TO SUPPORT DRUG DISCOVERY EFFORTS FOR NEURODEGENERATIVE DISEASES

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InnoSer, Diepenbeek, Belgium

Aims: Alzheimer's disease (AD) and Parkinson's disease (PD) preclinical research is held back due to the lack of reproducible in vitro models that can be used to screen and select disease-modifying therapeutics in a relatively inexpensive, efficient, and fast fashion. The present study aimed to validate in vitro neuronal and microglial neurodegenerative disease models to enable screening of disease-modifying compounds.
Methods: The pathophysiology of AD and PD was modeled in vitro by treating microglial (HMC3) and differentiated neuronal-like cells (SH-SY5Y) with pre-formed amyloid beta (Aβ) or alpha-synuclein (αSyn) fibrils. The most common hallmarks of neurodegeneration were evaluated by performing aggregation, neurotoxicity, ROS production, and phagocytosis assays. The HMC3 cells' phagocytic capacity was investigated by treatment with pHrodo labeled pre-formed fibrils and detected by an IncuCyte S3 Live-Cell Analysis System, while HMC3 and SH-SY5Y cell's viability was assessed using the MTT assay.
Results: Incubation (24 hours) of Aβ–fibrils with the reporter Thioflavin-T (20 µM) lead to significant increases in fibril aggregation, confirming the fibrils' suitability in subsequent assays. Following Aβ or αSyn fibril treatment, the phagocytic capacity of HMC3 cells was significantly increased indicating the internalization of the fibrils. Simultaneous treatment with Aβ and Aducanumab significantly increased the phagocytic capacity of the HMC3 cells compared to fibril treatment alone. Treatment with Aβ–42 and α-synuclein fibrils induced neurotoxicity in SH-SY5Y and HMC3 cells compared to the control condition. Similarly, Aβ fibrils induced a significant increase in ROS production in SH-SY5Y, which was rescued by co-treatment with the ROS scavenger Edaravone.
Conclusions: Cellular neurodegenerative disease models focusing on fibril-induced cell toxicity, ROS production, and phagocytosis can serve as a highly efficient tool to screen neurodegenerative disease-modifying drugs before screening in vivo.

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SHIFT 01-176

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

INTERACTION BETWEEN AMYLOID-BETA 42 AND THE PRION PROTEIN DEPENDS ON PHASE SEPARATION AND ASSEMBLY STATE OF BOTH PROTEINS

Laszlo Hosszu, Mark Batchelor, Jan Bieschke
UCL Institute of Prion Diseases, London, United Kingdom

Aims: The cellular prion protein (PrP^C) is known to play a role in the neurotoxicity pathway of multiple misfolded proteins, such as the 42 aa Amyloid-beta peptide (Abeta42), tau protein and alpha-synuclein. PrP is thought to act as a membrane receptor that binds oligomeric misfolded protein species. Two putative binding regions for Abeta42 in the unfolded N-terminus of PrP have been identified. Our study test how the aggregation state of both polypeptide affects their interaction, amyloid formation and toxicity.
Methods: We analyzed the interaction between Abeta42 and PrP in vitro in kinetic aggregation assays, fluorescence super-resolution imaging and flow-induced dispersion analysis (FIDA). We then systematically probed the co-aggregation reaction space for the presence of neurotoxic species in primary neurons by measuring neurite retraction and fragmentation.
Results: To our surprise, full-length PrP was a potent inhibitor of Abeta42 self-assembly, while its truncated mutants PrP 90-231 and PrP 119-231 had little to no effect. Interaction and inhibition depended on the self-assembly of PrP in the pre-fibrillar phase and was blocked by inhibitors of phase separation, suggesting that PrP assemblies, rather than monomers, confer amyloid-related neurotoxicity.
Conclusions: Amyloid formation and toxicity is governed by co-assembly of amyloid intermediates with PrP assemblies. This observation could yield a new paradigm for therapeutic intervention in AD and other amyloid diseases by targeting the assembly state of PrP^C to prevent neurodegeneration.

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SHIFT 01-177

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

PROTOCOL FOR THE PREPARATION OF STABLE MONOMERIC AMYLOID BETA

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Aims: Soluble amyloid beta oligomers (AβOs) are early, persistent drivers of Alzheimer's disease (AD) pathogenesis. Since Aβ monomers are ≥1,000-fold more abundant than AβOs in AD CSF, understanding selectivity of Aβ assays is crucial. However, rapid *in vitro* aggregation of canonical Aβ peptides, including $Aβ_{1-42}$ and $Aβ_{1-40}$, make this challenging. Well-defined methods for preventing aggregation during analysis times are needed. We compared published methods for production of pure, stable monomers and applied resultant preparations to assays utilizing the AβO-selective antibody sabirnetug (ACU193), which is currently being tested in the phase 2 study ALTITUDE-AD.
Methods: Aβ peptides (1-28, 1-38, 1-40) were HFIP-treated, solubilized in NaOH or DMSO, diluted in F12 media, and in some cases filtered at 10 kDa. The monomeric state and stability of the preparations was characterized by western immunoblotting. Immunoreactivity of the preparations to an antibody with established AβO selectivity (sabirnetug) was tested by biolayer interferometry (BLI) and a modification of the target engagement (TE) assay used for sabirnetug in the phase 1 study INTERCEPT-AD.
Results: All solubilization methods applied to $Aβ_{1-40}$ resulted in oligomerization. NaOH solubilization resulted in a distinct low molecular weight (MW) oligomer band on western immunoblots while DMSO promoted formation of additional higher MW (75-150kDa) distribution. $Aβ_{1-40}$ oligomers were immunoreactive with AβO-selective antibodies in BLI and TE assays. $Aβ_{1-28}$ and $Aβ_{1-38}$ also formed low MW AβOs; $Aβ_{1-38}$ oligomers were weakly detected by the TE assay. However, 10kDa filtration of $Aβ_{1-40}$ produced a purely monomeric preparation that remained stable for ≥8 hours at 4 °C and was not detected by AβO-selective antibodies by BLI or the TE assay.
Conclusions: 10kDa filtration of $Aβ_{1-40}$ enables production of pure monomeric Aβ solutions essential to assess selectivity of assays during development.

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SHIFT 01-178

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

SINGLE NUCLEI TRANSCRIPTOME AND HISTONE MODIFICATIONS PROFILING IDENTIFIES DIFFERENTIAL GENE EXPRESSION AND CHROMATIN STATE OF OLIGODENDROCYTES IN WHITE AND GRAY MATTER DURING ALZHEIMER'S DISEASE PROGRESSION

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Aims: This study seeks to elucidate the region-specific roles of oligodendrocytes in gray and white matter of the human brain during Alzheimer's disease progression. Utilizing single-nuclei RNA sequencing (snRNA-seq) and single nuclei multiome(Paired-Tag) analysis, we seek to identify transcriptional changes and epigenetic regulatory mechanisms in ODC populations of gray and white matter during AD progression and apply high-dimensional Weighted Gene Co-expression Network Analysis (hdWGCNA) to reveal cell-type specific gene modules associated with disease progression. This study aims to uncover ODC-specific gene networks linked to AD, challenging traditional neuron-centric views
Methods: We performed single-nuclei transcriptomic profiling on approximately 300 human postmortem brain samples from gray and white matter in the prefrontal and temporal cortex of control, early-path, and late-path AD cases. Using hdWGCNA, we constructed co-expression networks within ODCs to identify gene modules associated with AD progression. Next, we performed joint profiling of histone modifications and transcriptome, using Paired-Tag, and produced oligodendrocyte specific maps of chromatin state and transcriptome from different brain regions.
Results: Our application of hdWGCNA revealed distinct gene co-expression modules specific to ODCs in both gray and white matter, with several modules showing strong associations with AD progression. Notably, we identified modules enriched for amyloidogenic pathway genes, supporting the role of ODCs in Aβ production. These co-expression networks also exhibited significant region- and sex-specific variations, reflecting the heterogeneity of ODC function in AD. In addition, integrated analysis of Paired-Tag revealed the functional states of cCREs and provided mechanistic insights of regulatory programs of oligodendrocytes from heterogeneous cellular environments.
Conclusions: This study sheds new light on the molecular mechanisms underlying ODC involvement in AD, identifying novel therapeutic targets for intervention strategies aimed at mitigating ODC-related disease pathology.

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SHIFT 01-179

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

SPECIFIC DIMERIC CONFORMATIONS IN THE AMYLOID PATHOLOGY OF ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease is a neurodegenerative disorder characterized by an accumulation of amyloid plaques (Aβ) within the brain. This buildup of Aβ peptides – particularly Aβ42, produced by the cleavage of its precursor C99 by a γ-secretase – sets off a pathological cascade of events that eventually leads to amyloid deposition, an early AD feature. Recent studies suggested that soluble Aβ oligomers, from dimers to dodecamers, rather than amyloid plaques, are the primary drivers of cellular toxicity. However, their molecular structure and their link to the development of the disease remain poorly understood. We previously evidenced that C99 amyloidogenic fragments can associate into dimers, whose specific dimeric conformations influence its downstream processing. This study aims at determining if a precise dimeric conformation of C99 would trigger particular assemblies that initiate the formation of toxic Aβ oligomers.
Methods: Asparagine mutations were introduced at seven consecutive positions within C99 or Aβ42 transmembrane domains to generate diverse dimeric conformations. These HA-tagged constructs were expressed into SH-SY5Y cells and primary neurons to assess their impact on the formation of pathogenic Aβ42 assemblies.
Results: Two specific conformations, harboring the A30N and V36N mutations, significantly influenced the production of pathological assemblies. A30N promoted Aβ assembly formation, while V36N inhibited oligomerization, indicating their roles in modulating disease-relevant processes. Thioflavin T assay (seeding experiment), immunostainings, survival assays, are conducted to further validate these findings and explore their potential for therapeutic intervention.
Conclusions: With the identification of mutations driving C99 or Aβ42 dimerization in a specific interface, we aim to explore potential connections between these specific conformations, their subcellular localization, and associated γ-secretases. By characterizing these dimeric conformations, we hope to gain insights into the mechanisms underlying the aggregation process in amyloid pathology.

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SHIFT 01-180

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

CIRCADIAN CONTROL OF ALZHEIMER'S DISEASE IN DROSOPHILA MELANOGASTER

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Aims: Circadian rhythms are intrinsic time-keeping mechanisms crucial for neurological health. Disruptions in these rhythms are linked to neurodegenerative diseases, including Alzheimer's disease (AD), which is marked by cognitive decline and amyloid-beta plaque buildup. This study utilizes *Drosophila melanogaster* as a model to investigate how circadian dysregulation influences Alzheimer's pathology, aiming to uncover molecular mechanisms that connect disrupted rhythms to neurodegeneration and identify potential therapeutic targets.
Methods: Our investigation centres on disrupting the circadian rhythm by manipulating the light exposure on these flies, maintaining them in predominantly dark conditions with minimal light exposure to disrupt circadian rhythms, while flies in a normal light-dark cycle served as controls.
Results: Under normal light/dark conditions, flies showed strong rhythmic activity and rest cycles, confirming normal circadian rhythm. However, flies exposed to altering light lose rhythmicity, indicating circadian rhythm disturbance. AD flies expressing amyloid beta showed a substantial decrease in climbing activity when exposed to minimal light affecting circadian rhythms. Interestingly, disturbed circadian models activity reduces as they age. This contrasted with Alzheimer model flies kept under typical light-dark circumstances, which showed reduced climbing activity modification throughout age. These findings demonstrate how circadian rhythm abnormalities impair motor performance in an AD model. We also examined AD model strains with cycle genes (cyc^{01}) and found that climbing ability declined significantly with age, suggesting that the mutation worsens age-dependent motor impairments. This indicates a combined impact of impaired circadian function and Aβ toxicity on the decline of motor performance over time.

Conclusions: Disruption of circadian rhythms significantly worsens motor decline in Alzheimer's disease model *Drosophila melanogaster* and interacts synergistically with amyloid-beta toxicity. These findings suggest that targeting circadian function could be an effective strategy to mitigate neurodegenerative symptoms in Alzheimer's disease.

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SHIFT 01-181

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

A LACK OF ADAMTS4 AMELIORATES MOTOR DEFICITS AND ABETA4-X PATHOLOGY IN THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is characterized by the formation of extracellular senile plaques, primarily composed of amyloid-beta (Abeta) peptides. These peptides form a heterogeneous group regarding the length of their N- and C-termini. We recently identified ADAMTS4, an oligodendrocyte-specific protease, to be involved in the generation of the highly abundant and N-terminally truncated isoform Abeta4-x in vitro and in vivo. To address the role of ADAMTS4 in vivo, a knockout (KO) of this protein in the 5XFAD mouse model was generated.
Methods: 5XFAD mice on an ADAMTS4 knock-out background were characterized with a variety of motor as well as learning and memory tasks at different time points. In addition, markers of neuroinflammation and Abeta peptide levels were assessed with immunohistochemistry, quantitative RT-PCR and immunoassay approaches. The integrity of myelinated axons in various white matter tracts was assessed by electron microscopy.
Results: At 9 months of age, motor deficits in 5XFAD/ADAMTS4-KO mice were ameliorated compared to 5XFAD mice while other behavioral tasks were largely unaffected. In the cortex, Abeta4-x peptide levels and markers of neuroinflammation were reduced. Interestingly, thread-like Abeta4-x-immunoreactive structures were detected in white matter tracts of aged 5XFAD mice but not in 5XFAD/ADAMTS4-KO mice. Axonal myelination, as indicated by the g-ratio, remained unaffected.
Conclusions: Our findings suggest that ADAMTS4 contributes to AD etiology, possibly due to its involvement in Abeta4-x peptide generation. Motor deficits and markers of neuroinflammation were reduced in 5XFAD/ADAMTS4-KO mice, despite only minor effects on overall Abeta levels. In summary, our study suggests an important role of this protease in AD pathology.

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SHIFT 01-182

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

CRYO-EM STRUCTURES OF AMYLOID-BETA FIBRILS FROM HUMAN AND MURINE BRAINS CARRYING THE UPPSALA A-BETA UPP1-42Δ19-24 MUTATION

Lothar Gremer[1,2], Fernanda Salome Peralta Reyes[2], Mara Zielinski[1], Martin Ingelsson[3,4,5], Dag Sehlin[5], Stina Syvänen[5], Dieter Willbold[1,2], Gunnar Schröder[1,6]
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Aims: Today, 13 pathogenic intra-amyloid-β (Aβ) amyloid precursor protein (APP) gene mutations are known to cause familial Alzheimer's disease. Most of them are point mutations causing an increased production or a change in the conformation of Aβ. The Uppsala APP mutation (Δ690- 695) is the first known multi-codon deletion causing autosomal dominant Alzheimer's disease. Here we aimed to determine the fibril structures of Aβ and tau underlying the pathology from a human patient brain as well as from AβUpp$_{Δ19-24}$ derived from tg-UppSwe mouse brains.
Methods: We applied cryo-electron microscopy (cryo-EM) to investigate the 3D structures of Aβ fibrils with the Uppsala deletion mutation from tg-UppSwe mouse brain tissue, of Aβ fibrils from the temporal cortex of a patient with the Uppsala mutation and of AβUpp1-42$_{Δ19-24}$ fibrils formed *in vitro*.
Results: Murine AβUpp1-42$_{Δ19-24}$ are made of two identical S-shaped protofilaments with an ordered fibril core of S8 - A42. The murine Uppsala fold is almost identical to previously described human type II filaments, although the aa sequences differ considerably. In contrast, the cryo-EM structure of Aβ fibrils from the temporal cortex of a patient with the Uppsala mutation shows high similarity to previously described type I filaments, but at medium-resolution it remains elusive whether the fibrils are made of wild-type or mutant Uppsala Aβ, or are composed of both. The structures of tau paired-helical filaments and tau straight filaments from the human sample are identical to those found in sporadic AD. Finally, we present the 3D cryo-EM structures of four dominant AβUpp1-42$_{Δ19-24}$ fibril polymorphs, formed *in vitro*. All four polymorphs differ from the observed folds of Uppsala Aβ in murine and Aβ in human brain tissue.
Conclusions: The 3D-fibril structures underlying the pathology are solved.

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SHIFT 01-183

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

STRUCTURAL IMPACT OF N-TERMINAL PYROGLUTAMATE IN AN AMYLOID-BETA(3-42) FIBRIL PROBED BY SOLID-STATE NMR SPECTROSCOPY

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Aims: Extracellular amyloid-β (Aβ) plaques, primarily formed by Aβ(1-40) and Aβ(1-42) fibrils, are a hallmark of Alzheimer's disease. The Aβ peptide can undergo a high variety of different post-translational modifications including formation of a pyroglutamate (pGlu, pE) at N-terminal Glu3 or Glu11 of truncated Aβ(3-x) or Aβ(11-x), respectively. Here we aimed to determine structural similarities and differences at atomic level between pEAβ(3-42) and LS-shaped Aβ(1-42) fibrils obtained under identical conditions.
Methods: Solid-state NMR spectroscopy, along with AFM and far-UV CD spectroscopy was applied for in-depth structural analysis of recombinant, pyroglutamylated [U-^{13}C,^{15}N]-pEAβ(3-42) fibrils. Results were compared to well characterized LS-shaped Aβ(1-42) fibrils (Gremer et al. Science 2017, doi:10.1126/science.aao2825, Becker et al. JACS 2023, doi:10.1021/jacs.2c09231) obtained under acidic conditions (pH 2).
Results: We report on solid-state NMR characterization of a pEAβ(3-42) fibril morph at pH 2 and, after pH-adjustment, at pH 6.5. Comparison with LS-shaped Aβ(1-42) fibrils reveals remarkable structural similarities and indicates a conserved central region spanning residues L17 to I32, around the turn at V24 in both fibrils. The missing N-terminal residues D1-A2 along with pE3 formation in pEAβ(3-42) preclude the formation of a salt bridge between K28-D1' present in Aβ(1-42) fibrils. Obviously, this salt bridge is not needed for a rigid N-terminus in this fibril morph. G37 and G38 act as highly sensitive sensors for the modified N-terminus as seen by their shift perturbations. Notably, pEAβ(3-42) fibrils harbor β-strand positions highly similar to those in LS-shaped Aβ(1-42) fibrils including the rigid N-terminal region.
Conclusions: Compared to Aβ(1-42), pEAβ(3-42) shows higher toxicity in mouse models, a faster aggregation rate, and it cross seeds and accelerates the aggregation of Aβ(1-42). The observed structural similarity between fibrillar pEAβ(3-42) and Aβ(1-42) might explain their cross seeding activity.

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SHIFT 01-184

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
2-3 April 2025

SORL1 VARIANTS IN ALZHEIMER DISEASE INCREASE INTRACELLULAR AB-SEEDING COMPETENT SPECIES.

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Aims: Mounting evidence supports a role of intracellular Aβ (iAβ) accumulation as an early trigger in Alzheimer Disease (AD) pathophysiology. Precise regulation of iAβ levels may thus represent a crucial step in preventing the development of Aβ pathology. The *SORL1* is a major AD risk factor. The SORL1/SorLA protein play a key role in the control of Aβ levels by preventing APP targeting to late endosomes where it is cleaved into Aβ, and directing Aβ to lysosomal degradation. Numerous *SORL1* rare variants have been identified in AD patients, but their functional impact on Aβ peptide levels, particularly iAβ, remains largely unknown. Here, we aimed to determine the functional consequences of rare *SORL1* missense variants on iAβ levels and Aβ seeding activity.
Methods: By overexpressing AD-associated rare SorLA missense variants in HEK293 cells, we first categorized 29 variants located in the VPS10p domain of the protein based on their impact on SorLA trafficking or their ability to disrupt Aβ interaction. Then, we assessed the functional impact of both types of variants by introducing patient-specific variants by CRISPR/Cas9 in hiPSCs, followed by neuronal differentiation.
Results: The initial screen identified 6 new trafficking-defective variants, and 2 novel Aβ interaction-defective variants. When expressed endogenously in hiPSCs and iPSC-derived neurons, both categories of variants led to significantly higher iAβ levels. Importantly, this increase in iAβ levels positively correlates with Aβ seeding activity of cellular lysates. Conversely, there was no correlation between iAβ levels and Aβ secretion.
Conclusions: Our results highlight the potential role of *SORL1* missense variants in the initial stages of Aβ pathology and further reinforce the idea that iAβ accumulation is a very early sign of AD pathophysiology and a causative event in disease development.

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SHIFT 01-188

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
2-3 April 2025

ALZHEIMER'S DISEASE: AGING AND AMYLOID-BETA NEUROTOXICITY

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Aims: Aging is the primary risk factor for Alzheimer's disease (AD), and the aging brain shares many characteristics with the early stages of AD. We developed an AD-like *in vivo* model, using the stereotactic injection of amyloid-beta $(Aß)_{1-42}$ oligomers into the hippocampi of aged mice. Here we show, in comparison to younger adult mice, that the aging brain environment increases the susceptibility, allowing the acute Aß toxicity to spark a progressive injury, recreating key features of AD pathology. We investigate how the aging brain, with its impaired cellular clearance, increasing synaptic dysfunction and inflammation, creates fertile soil for the progression of neurodegenerative diseases.
Methods: $Aβ_{1-42}$ oligomers were stereotactically injected into the hippocampi of aged (16–18 month) and young adult (3 month) mice. Cognitive impairments were assessed using a Y maze. Immunohistochemical and protein analyses were conducted to evaluate neuronal survival, synaptic function and number, levels of Tau hyperphosphorylation, microglial activation, autophagy, and mitochondrial function.
Results: In aged mice, Aβ toxicity led to progressive cognitive impairments, neuronal and synaptic loss, and spreading of hyperphosphorylated Tau (AT100) beyond the initial lesion. Lysosomal and mitochondrial dysfunction, along with sustained microglial activation, were observed. In contrast, young mice exhibited only acute effects without long-term progression of pathology.
Conclusions: Combining aging-related dysfunctions in autophagy, mitochondria, and immune response with an acute Aß injury promote a progressive AD-like pathology, whereas younger brains are able to overcome this injury. The processes of aging should be considered as an integral factor in the development of the disease. Targeting aging mechanisms may provide new strategies for AD prevention and treatment, as well as for other neurodegenerative diseases.

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SHIFT 01-189

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
2-3 April 2025

LONGITUDINAL EVIDENCE OF SLOWER BRAIN AGING IN SUPERAGERS

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Aims: Superagers, older adults maintaining exceptional cognitive abilities, exhibit preserved brain structure compared to typical older adults. As brain structural changes during aging serve as the indicator of biological brain age, we aimed to investigate whether superagers have biologically younger brains based on their structural integrity.
Methods: An older adult cohort (*n* = 153, aged 61-93 years) was recruited, with 63 categorized as superagers based on their superior episodic memory, and 90 as typical older adults. Of these, follow-up occurred two years later for 64 participants. A deep neural network model for brain age prediction, trained on a broad age range adult cohort (*n* = 899, aged 31-93 years) from publicly accessible datasets, was adapted to the older adult cohort through transfer learning. Brain age gap (BAG), the deviation of predicted brain age from chronological age, was measured as the index of brain aging status, and its annual rate of change was calculated to measure brain aging speed. The association between BAG and cognitive performance was assessed, and BAG and its annual rate of change were compared among subgroups.
Results: Lower BAGs correlated with more favorable cognitive status in memory and general cognitive function. Superagers exhibited a lower BAG than typical older adults at both baseline and follow-up. Individuals who maintained or attained superager status at follow-up showed a slower annual rate of change in BAG compared to those who remained or became typical older adults.
Conclusions: Superaging brains manifested maintained neurobiological youthfulness in terms of a more youthful brain aging status and a reduced speed of brain aging. These findings suggest that cognitive resilience, and potentially broader functional resilience, exhibited by superagers during the aging process may be attributable to their younger brains.

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SHIFT 01-191

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2-3 April 2025

THE DISTRIBUTION OF AQUAPORIN-4 IN ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES

Maja Brataas[1,2], Angelica Scaramuzza[3,4], Wilma Van De Berg[4,5], Mathias Toft[1,2], Kaja Nordengen[1,2]
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Aims: Proteinopathies are neurodegenerative diseases characterized by abnormal protein accumulation, among which amyloid beta, p-tau and alpha-synuclein. The recently discovered glymphatic system is believed to clear misfolded proteins from the brain via the influx of cerebrospinal fluid (CSF) through the periarterial space and efflux through the perivenous space. Astrocytic endfeet expressing aquaporin-4 (AQP4) surround these spaces, aiding the removal of proteins and metabolites from the brain. This study aims to investigate changes in AQP4 distribution in AD and DLB-patients to understand the role of glymphatic clearance in proteinopathies.
Methods: Postmortem brain tissue was collected from 42 individuals, comprising 13 cognitively healthy (mean age 82.2±6.7, 61.7% females), 15 AD patients (mean age 78.1±12.9, 46.7% females) and 14 had DLB patients (mean age 75.8±6.6, 42.7% females). Tissue samples from the cingulate gyrus was analyzed by multiplex immunofluorescence and confocal microscopy. The amount of AQP4 was quantified by measuring the signal intensity from the stained brain sections using FIJI software. The amount of AQP4 around arteries, veins, and capillaries, and compared it to the levels in the neuropil were quantified.
Results: Statistical analysis showed no distinct differences in AQP4 distribution across arteries, veins, capillaries, and neuropil among AD, DLB, and cognitively healthy controls by diagnostic category. However, increased perivascular AQP4 in different vessel types was significantly correlated with protein aggregates according to Thal phase and BraakNFT.
Conclusions: The increased levels of both parenchymal and perivascular AQP4 with rising protein aggregation suggest alterations in the glymphatic system in AD and DLB.

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SHIFT 01-192

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2-3 April 2025

CROSSTALK BETWEEN APOE4 GENOTYPE, PPARΓ AND ASTROCYTE REACTIVITY IN ALZHEIMER'S DISEASE PROGRESSION

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Aims: Peroxisome proliferator-activated receptor γ (PPARγ) is an interesting target for therapeutic intervention in patients with Alzheimer's disease (AD), given its anti-inflammatory and neuroprotective properties. PPARγ agonists have shown to be effective in AD preclinical models, but a lower effectiveness has been observed in individuals carrying the ε4 allele of the Apolipoprotein E (ApoE4) gene, the strongest genetic risk factor for sporadic AD. ApoE is the main lipoprotein involved in cholesterol transport and primarily produced by brain astrocytes. The aim of the Project is to investigate whether the ApoE ε4 genotype promotes the acquisition of a reactive phenotype in astrocytes, through PPARγ downregulation.
Methods: *In vitro*: i) Immortalized mouse astrocytes, obtained from ApoE-target replacement (ApoE-TR) mouse primary astrocytes, expressing the human ApoE3 or ApoE4; ii) human induced Pluripotent Stem Cells (hiPSCs)-derived ApoE3 or ApoE4 astrocytes, treated or not with a pro-inflammatory cytokine mixture. *Ex vivo*: human autopsy samples (temporal cortices) from ApoE3 or ApoE4 AD subjects, provided by the Neurological Institute Carlo Besta (Milan).
Results: Western blotting and qRT-PCR revealed a striking decrease of PPARγ gene expression and protein levels in both types of ApoE4 astrocytes. PPARγ gene expression levels were also significantly lower in the human brain samples from ApoE4 AD subjects, compared to the ApoE3 specimens. Moreover, the secretion in the astrocyte conditioned media of interleukin6 (IL-6) and serpinA3, two astrocyte reactivity markers, was clearly increased in ApoE4 hiPSCs-derived astrocytes treated with the cytokine mixture, compared to cytokine-treated ApoE3 astrocytes and ApoE4 untreated ones.
Conclusions: The outstanding downregulation of PPARγ in ApoE4 astrocytes and in ApoE4 human brain samples highlights the possibility of PPARγ to play a pivotal role in astrocyte reactivity, as confirmed by the increased IL-6 and SerpinA3 secretion.

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SHIFT 01-193

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2-3 April 2025

THE ROLE OF NORADRENERGIC SIGNALING IN ASTROCYTE PHYSIOLOGY AND RESPONSES TO ALZHEIMER'S AND PARKINSON'S DEMENTIA.

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Aims: The early alteration of the locus coeruleus in Alzheimer's disease (AD), Parkinson's disease (PD) and dementia with Lewy body (DLB) leads to a progressive imbalance of the noradrenaline (NA) levels in targeted brain areas associated with memory processes. NA is a potent modulator of neuronal activity, but also of astrocytes, a glial cell involved in many homeostatic processes. NA progressive depletion in AD and PD could therefore alter astrocyte physiology and promote disease progression. Our translational study aims to (1) characterise the association between noradrenergic receptors and astrocytes in NA-targeted brain regions, (2) define NA modulatory effect on astrocyte physiology, and (3) profile NA-associated gene expression in hippocampal astrocytes in AD and PD.
Methods: To assess the relationship between astrocytes and noradrenergic receptors and specific signatures in human *post-mortem* samples (age-matched CTLs, AD, PD with dementia and DLB), we used multiplex chromogenic, in situ hybridization or immunohistochemistry, confocal microscopy and digital pathology image analysis. In parallel, we analysed RNAseq data of primary mouse and human astrocytes exposed to NA.
Results: We found a differential distribution and expression of ADRA1a and ADRA2c across specific subtypes of astrocytes, both receptor subtypes being significantly affected in AD patients compared to CTLs. The RNAseq data highlighted the strong influence of NA on astrocyte core functions, such as the regulation of the cerebral blood flow (*Ptgs2, Ace*), their protective properties (*Cbs, Sod3*) or the astrocyte-neuron crosstalk (*EphB2, Dag1*). Protective markers such as CBS are significantly altered in AD patients compared to CTLs.
Conclusions: Our results suggest that the phenotypic control exerted by NA may be drastically impacted in disease: NA deprivation might lead to altered astrocyte roles and impaired neuroprotection, thus exacerbating pathology progression.

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SHIFT 01-194

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2-3 April 2025

DEVELOPMENT OF IPSC-DERIVED ASTROCYTE AND NEURONAL CO-CULTURE MODELS TO STUDY NEURONAL FUNCTIONALITY USING MULTIELECTRODE ARRAYS

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Aims: Astrocytes have an important role in maintaining homeostatic conditions in the brain. Astrocytes are involved in many processes such as clearing excess neurotransmitters, stabilizing and regulating the blood-brain barrier, and regulating axonal growth and support. The important role of glia cells in neurodegenerative diseases like Alzheimer's disease is increasingly recognized. Thus, there is a high need for neuronal co-culture models which incorporate glial cells, such as astrocytes for improved modelling of neurogenerative diseases. Here, we report on the use of an efficient protocol to generate human induced pluripotent stem cell (hiPSC)-derived astrocytes and how they can be implemented in neuronal co-culture systems to improve the study of functional cell responses.
Methods: Human iPSCs (BIONi010-C) containing an inducible NGN2 transcription factor are differentiated either directly to glutamatergic neurons by doxycycline induction or further to sensory neurons via addition of small molecule patterning factors. Human iPSC (BIONi010-C) are differentiated into astrocytes following a previously published protocol (Dittlau et al., Bio Protoc. 2024). Neurons and astrocytes are hereafter grown in co-cultures and are accordingly evaluated for expression of relevant markers by immunocytochemistry. Astrocyte functionality is evaluated for glutamate uptake and inflammatory responses and neuronal functionality is evaluated using multi-electrode arrays.
Results: We report on the use of a method to grow astrocytes in co-culture with different neuronal subtypes and how astrocytes affect the neuronal functional response.
Conclusions: Neuronal co-cultures with astrocytes are important to fully mature neurons to study neuronal functionality for improved response and modelling of relevance for CNS disease.

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SHIFT 01-195

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
2-3 April 2025

SECOND MESSENGERS AND THE ORPHAN GPR27 RECEPTOR ACTIVATION IN 3T3 CELLS AND ASTROCYTES

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Aims: Astrocytes are an abundant and heterogeneous type of glial cells, mediating various homeostatic functions, including brain energy metabolism, in which L-lactate (LL) is produced in aerobic glycolysis (AG). LL, a fuel and a signal, can exit astrocytes to support the high metabolic demands of neurons. It has been shown that AG in astrocytes can be potently activated through certain G protein-coupled receptors (GPCR) with agonists including noradrenaline (NA) and LL. We are studying the function of orphan receptor GPR27, a member of the family of super conserved receptors expressed in the brain. We have shown previously that GPR27 stimulation enhances AG and LL production in 3T3 cells and astrocytes. Here we investigated whether the activation of the GPR27 receptor affects second messengers, including Ca^{2+} and cAMP.
Methods: We used a Förster resonance energy transfer (FRET)-based cAMP nanosensor to monitor cytosolic cAMP with high temporal resolution in single cells. Intracellular Ca^{2+} concentration was measured with Ca^{2+} indicator Calbryte 520AM in real time. Cells were stimulated with L-lactate (2 mM, 5 mM) or GPR27 surrogate agonist (1 μM).
Results: Our preliminary results indicate that stimulation of 3T3 cells with LL increases $[cAMP]_i$ compared to controls, and appears it does not involve GPR27 activation. Stimulation of GPR27 with surrogate agonist increases $[Ca^{2+}]_i$ in 3T3 WT cells, but not cAMP. In astrocytes, GPR27 surrogate agonist also caused an increase in $[Ca^{2+}]_i$.
Conclusions: Further studies are needed to elucidate the second messenger dynamics following GPR27 activation and to understand its function in the brain. The GPR27 surrogate agonists used have a stimulatory effect on AG, that is similar to NA, making them promising candidates for novel medications to treat cognitive decline due to neurodegeneration.

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SHIFT 01-196

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, APOPTOSIS, CELL DEATH
2-3 April 2025

BAG3 IN ALZHEIMER'S DISEASE AND ITS IMPACT ON ASTROCYTE FUNCTION AND DISEASE PROGRESSION

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Aims: This study elucidates the role of BAG3 in Alzheimer's disease (AD) by examining its expression patterns and functional implications within the human brain and iPSC-derived astrocytes.
Methods: We assessed BAG3 expression in brain tissue from individuals with AD and those with no clinical/neuropathological diagnosis of AD using tandem mass tag-mass spectrometry (TMT-MS) and Western blot. snRNA-seq was performed on astrocytes from dorsolateral prefrontal cortex to analyze BAG3 expression across astrocyte subpopulations. Additionally, we generated BAG3 knockout iPSC lines and differentiated them into neurons and astrocytes. Protein and RNA-level changes due to BAG3 knockout were evaluated using TMT-MS and RNAseq, and endo-lysosomal function, protein degradation, and phagocytosis were assessed.
Results: BAG3 was markedly upregulated in AD brains, and expression correlated with disease severity. snRNA-seq revealed predominant expression of BAG3 in a subtype of astrocytes whose frequency is associated with progression to AD. Proteomic analysis of iPSCs showed BAG3 knockout had a more pronounced effect on astrocyte proteomes compared to neurons, disrupting protein transport and vesicular trafficking pathways. BAG3 knockout in astrocytes led to reduced lysosomal function and autophagic flux, as well as proteasome activity and phagocytosis. In co-cultures with APP/PSEN1 mutant neurons, BAG3 KO astrocytes exhibited impaired amyloid-beta clearance and altered levels of phosphorylated tau. Additionally, at the transcriptomic level, BAG3 shows a reduction in reactive astrocyte signatures and a reduction in secreted C3.
Conclusions: BAG3 is essential for lysosomal function, maintaining autophagy, phagocytosis, and astrocyte reactivity, which in turn affects the ability of astrocytes to clear extracellular amyloid-beta. Given the crucial role of BAG3 in managing protein aggregates within the brain, its mechanistic insights could be pivotal for developing future therapeutic approaches, such as protein degraders and AUTACs, aimed at treating neurodegenerative diseases.

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SHIFT 01-197

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, APOPTOSIS, CELL DEATH
2-3 April 2025

IDENTIFICATION OF NEURONAL SUBTYPES SELECTIVELY VULNERABLE TO DEPLETION IN ALZHEIMER'S DISEASE USING IMAGING MASS CYTOMETRY

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Aims: Alzheimer's disease pathology (AD) shows regional progression over time, with different regions showing distinct patterns of selective neuronal degeneration. Multiple mechanisms have been suggested to be implicated in selective neuronal vulnerability, with intrinsic properties of neurons likely to play an important role. Here, we describe neuronal subtype-specific vulnerability in the human lateral entorhinal cortex.
Methods: We employed highly multiplexed imaging mass cytometry and a robust, scalable workflow for reproducible single neuronal subtype analysis to establish which neurons are lost in AD. Cells were segmented and neuronal subtypes were defined based on the presence of markers within each cell.
Results: We observed a relative reduction (80±9.4%, N=12) in the density of neurons expressing RORb with AD. Selective loss of Reelin-positive neurons, as indicated through single nuclear RNA sequencing (Mathys et al., 2024), was tested for, but we found no evidence of a reduction in cells expressing Reelin protein.
Conclusions: We are now applying single nuclear RNA sequencing in paired samples to test this discrepancy further and to explore the potential mechanisms that distinguish individual subtypes of neurons to make them either more vulnerable or resilient to AD with the aim of identifying novel therapeutic targets to limit the loss of vulnerable neurons.

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SHIFT 01-198

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, APOPTOSIS, CELL DEATH
2-3 April 2025

NATIVE PLGA NANOPARTICLES PROTECT NEURONS AGAINST BETA-AMYLOID TOXICITY BY INFLUENCING ENDO-LYSOSOMAL SYSTEM

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Aims: Alzheimer's disease is characterized neuropathologically by the presence of tau-positive neurofibrillary tangles, β-amyloid (Aβ)-containing neuritic plaques and the loss of neurons in defined brain regions. At present, the cause of selected neuronal vulnerability in AD brains remains unclear. Altered activity of the endo-lysosomal system has long been suggested to enhance the level/aggregation of Aβ peptide which can trigger loss of neurons *via* increased release/activation of lysosomal enzymes including cathepsins D (CatD) into the cytosol. In this study we reveal how native poly (D,L-lactide-co-glycolide)(PLGA) nanoparticles, which constitute a family of FDA-approved biodegradable polymers, by regulating activity of the endo-lysosomal system can protect mouse cortical cultured neurons against Aβ-mediated toxicity.
Methods: Mouse cortical cultured neurons were first treated with Aβ1-42 to establish toxicity. Subsequently, neurons were treated with Aβ1-42 in the presence and absence of native PLGA and evaluated using western blotting and immunoctytochemistry to measure altered levels/expression of various endo-lysosomal markers. In parralles, control and treated cultured neurons were processed to measure lysosomal leakage, deacidification and CatD activity using various assays.
Results: Our results show that Aβ-mediated toxicity is associated with i) an increased levels of endosomal (Rab5, Rab7), autophagic (LC3II, beclin1) and lysosomal (LAMP1, CatD, TFEB) markers, ii) enhanced deacidification and leakage of lysosomes along with an increased activity of CatD. Treatment with native PLGA is found to protect neurons against Aβ-mediated toxicity by reversing altered levels of endo-lysosomal markers, attenuating lysosomal leakage/deacidification and decreasing the CatD activity.
Conclusions: Native PLGA nanoparticles are found to protect neurons against Aβ-mediated toxicity by regulating endo-lysosomal activity. These results, together with our earlier evidence that PLGA can Aβ levels/aggregation, highlight therapeutic potential of native PLGA in the treatment of AD pathology.

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SHIFT 01-199

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, APOPTOSIS, CELL DEATH
2-3 April 2025

UPSTREAM SENESCENCE ACCELERATES THE PROGRESSION OF AD LESIONS

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Aims: Population ageing is the main driver of the alarming growth of age-related neurodegenerative diseases such as Alzheimer's disease (AD). The precise mechanisms that translate ageing into neurodegenerative conditions remain elusive. However, senescence appears to be a key process in this context. The age-related accumulation of senescent cells in neurodegeneration is well-documented, and the clearance of senescent cells has beneficial outcomes on disease-related features. Several cellular and molecular hallmarks of senescence have been described in ageing brains, including genomic instability, telomere attrition, chronic inflammation due to the senescence-associated secretory phenotype (SASP). One critical question is to understand whether senescence acts as an upstream driver of pathology or appears as a consequence of disease progression. We elaborated on our very recent results indicating that neuronal senescence enhances intracellular Aβ accumulation to unravel the relationship between brain senescence and the onset and progression of AD-related tau pathology.
Methods: We crossed a mouse model of telomere shortening and accelerated senescence ($Terc^{-/-}$) with the tauopathy mouse model Tau P301S (PS19). We employed an array of biochemical and molecular techniques to investigate the features of senescence and the expression of tau-related neuropathological biomarkers.
Results: Brain tissue from $Terc^{-/-}$ mice displayed chronic cellular senescence, marked by increased secretion of pro-inflammatory SASP molecules, among other features including dysregulation of the cell-cycle gene module. Telomere-induced senescence exacerbates tau phosphorylation at specific residues in the hippocampal region. This senescence context amplifies an inflammatory phenotype associated with astrocyte activation in tau pathology, which correlates with neuronal loss.
Conclusions: Our results indicate that accelerated senescence may act as an upstream regulator of tau pathology, aggravating it and driving tau-related neurodegeneration. Full elucidation of this process could reveal potential therapeutic targets for early AD intervention.

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SHIFT 01-202

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / BLOOD-BRAIN BARRIER
2-3 April 2025

APOE GENOTYPE, BLOOD-BRAIN BARRIER PERMEABILITY AND DISEASE BURDEN IN ALZHEIMER'S DISEASE CONTINUUM: A SINGLE COHORT STUDY

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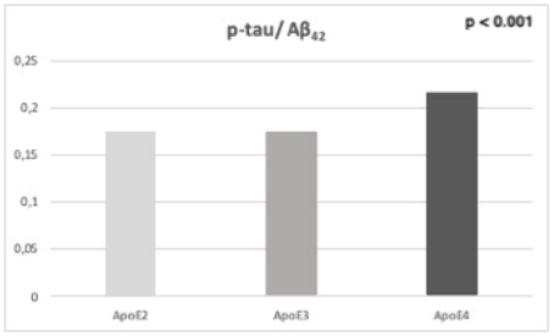
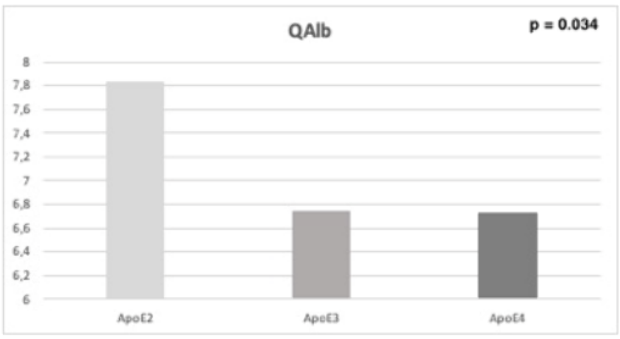
Aims: Apolipoprotein-E (ApoE) contributes to Blood-Brain Barrier (BBB) maintenance, reactivity and repair. Also, BBB impairment has been shown to play a key role in Alzheimer's disease (AD) since early stages. ApoE has three genetic variants differently associated to the risk of developing AD, with ApoE2 showing protective effects, ApoE4 increasing the risk of AD, and ApoE3, and its role on BBB regulation in AD is debated. We investigated the impact of ApoE on BBB permeability and its relationship with disease burden, evaluated as 181-phosphorylated tau protein to amyloidβ ratio (p-tau/Aβ42) as an indirect measure, in AD patients.
Methods: We recruited 895 patients belonging to the AD continuum (ADc) and stratified by ApoE genotype, who underwent lumbar puncture for diagnostic purposes and we evaluated cerebrospinal fluid (CSF) biomarkers, notably Aβ42, p-tau and total tau, the CSF/serum albumin Quotient (QAlb), as a measure of BBB permeability, and p-tau/Aβ42.
Results: QAlb levels were between the physiological range. ApoE2 showed higher QAlb levels compared to ApoE4 and E3 carriers. Also, ApoE2 and ApoE4 showed comparable levels of Aβ42, while p-tau and t-tau were higher in ApoE4 compared to ApoE3 and ApoE2. Interestingly, ApoE2 showed low p-tau/Aβ4 levels while ApoE4 showed the exact specular distribution (Fig). Thus, ApoE2, had lower levels of disease burden and higher BBB permeability. To further investigate the association of BBB and ApoE2, a regression analysis confirmed a positive association between QAlb and





ApoE2.
Conclusions: BBB is a highly dynamic structure whose role in AD pathophysiology could be influenced by

ApoE genotypes, which could play an important role in the precarious balance between toxic clearance and amyloid accumulation. ApoE2 carriers showed higher BBB permeability, participating to its protective effect, and reducing amyloid burden and neurodegeneration.

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SHIFT 01-203

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / BLOOD-BRAIN BARRIER
2-3 April 2025

HUMAN SERUM MODULATES AMYLOID-B SOLUBILITY AND NEUROINFLAMMATION IN CORTICAL ORGANOIDS: CONSEQUENCES OF BLOOD-BRAIN BARRIER DYSFUNCTION IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is the leading form of dementia histopathologically characterized by neurofibrillary tangles and aggregated Amyloid-β (Aβ). Though recent advances in monoclonal antibody therapies may slightly delay disease progression, these therapies accompany risks of micro-hemorrhages and edema. Blood-brain barrier (BBB) dysfunction is an early predictor of cognitive decline and is prominent in many neurodegenerative diseases, yet is not correlative with disease severity. This indicates that BBB breakdown may be both an exacerbator and initiator of disease. Determining the exact consequences of bloodborne products entering the brain could lead to novel preventive therapies for many neurodegenerative diseases.
Methods: Cortical organoids were generated from induced pluripotent stem cell lines derived from a healthy donor using a custom differentiation protocol. Human serum, purchased commercially, was diluted in cell culture media at concentrations ranging from 1% to 10% with treatment lasting 3 to 12 days. Additionally, comparisons in resulting shifts in Aβ solubility will be done for heat-inactivated human serum and fetal bovine serum. Amyloid-β and GFAP concentrations in cell culture media and lysate fractions will be analyzed using electrochemiluminescence-based assays from Mesoscale.
Results: Serum treatment had a dose-dependent decrease in soluble Aβ, while Aβ42/40 has differential shifts based on the concentration of serum used. Aβ was elevated in the insoluble fraction of organoid lysates, indicating that a component in serum leads to the seeding of Aβ deposits. Moreover, increased insoluble Aβ was also observed in samples treated with heat-inactivated human serum but not fetal bovine serum, but GFAP was elevated in culture media regardless of serum type.
Conclusions: These results suggest that bloodborne products can modulate both Aβ solubility and neuroinflammation, underscoring the importance of preventive methods to maintain vascular health in an aging population.

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SHIFT 01-204

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / BLOOD-BRAIN BARRIER
2-3 April 2025

CEREBROSPINAL FLUID AS A POWERHOUSE FOR PARKINSON'S RELATED METABOLISM

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Aims: Cerebrospinal fluid has been viewed as a waste disposal pathway for metabolism occurring in the brain. Little attention has been paid to its role in nutrient supply or neurotransmitter metabolism. The presence of folate metabolic enzymes and enzymes for neurotransmitter synthesis, including ALDH1L1, MTHFD1, MTHFR, DHFR and Tyrosine hydroxylase (TH), together with our previous studies showing dramatic changes in the metabolic profile of CSF in hydrocephalus, led us to explore whether metabolism was occurring in CSF and how this related to tissue metabolism.
Methods: Western blotting identified the presence or absence of enzymes in CSF and tissue. Enzyme assays for CSF and brain tissue lysates were conducted by adding the substrate and energy source for each enzyme and monitoring the reaction using a multiplate reader. Transcriptomics of brain tissue from cerebrum, cerebellum, substabtia nigra and choroid plexus, was carried out to identify location of enzyme expression.

Results: In normal brains MTHFD1and MTHFR were low in tissue, but ALDH1L1, DHFR and TH were high. ALDH1L1 and TH also showed activity in CSF and tissue. MTHFR, MTHFD1 and DHFR activity were present in CSF but not in tissue. We also investigated Parkinson's disease (PD) as it has been associated with normal pressure hydrocephalus. MTHFD1, MTHFR and DHFR were deficient in PD CSF and tissue, but ALDH1L1 and TH were present in high amounts in CSF and low in tissue. Surprisingly, only ALDH1L1 had demonstrable enzyme activity in PD with no activity detectable for other enzymes in either CSF or tissue.

Conclusions: The presence and activity of enzymes involved in important metabolism in CSF as compared to tissue demonstrates that CSF plays a significant role in metabolism and production of essential metabolites required by neurons.

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SHIFT 01-209

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

CEREBRAL MICROENVIRONMENT IN A MOUSE MODEL OF SPORADIC ALZHEIMER'S DISEASE PROMOTES TRANSTHYRETIN DEPOSITION AND AGGREGATION

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Aims: Murine models of sporadic Alzheimer's disease (sAD) induced by intracerebroventricular streptozotocin (STZ-icv) are characterized by leptomeningeal deposition of unidentified amyloids, similar to those observed in transthyretin (TTR) leptomeningeal amyloidosis. This study aimed to evaluate transthyretin deposition in the choroid plexus and leptomeningeal regions of the STZ-icv model of sporadic AD and to explore how the sAD-like cerebral microenvironment influences the tendency for TTR deposition.
Methods: Model induction was carried out by administering streptozotocin (6 mg/kg in two doses; 1 µL per ventricle) or vehicle (citrate buffer, pH 4) intracerebroventricularly to male C57BL/6 mice. After 4 weeks, the animals were euthanized, and their brains were either fixed or dissected and stored at -80°C for molecular analysis. TTR deposition in tissues was evaluated using quantitative immunofluorescence confocal microscopy. The influence of the tissue microenvironment on TTR aggregation was assessed through kinetic thioflavin T fluorescence assays and polyacrylamide gel electrophoresis of tissue homogenates with fluorescently labeled or native TTR.
Results: Both the choroid plexus and leptomeningeal space showed increased TTR deposition in the STZ-icv mouse model of sAD. Hippocampal tissue from STZ-icv animals exhibited an enhanced ability for exogenous TTR to bind endogenous insoluble aggregates, especially under conditions of solvent-induced unfolding. While exogenous TTR effectively disaggregated preformed amyloid fibrils in tissue homogenates from control animals, it demonstrated reduced disaggregation efficiency in the presence of STZ-icv hippocampal homogenates.
Conclusions: The sAD mouse model is marked by TTR deposits in the choroid plexus and leptomeningeal space, potentially driven by endogenous tissue factors that promote its accumulation.

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SHIFT 01-212

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
2-3 April 2025

ESTROGEN RECEPTOR MEDIATED NEUROPROTECTION IN MODELS OF ALZHEIMER'S DISEASE

Heba Ali, Mukesh Varshney, Per Nilsson, Ivan Nalvarte
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Aims: Middle-aged women are 2-3 times more likely than men to develop Alzheimer's disease (AD) later in life. While women tend to live longer, factors like sex hormones, genetics, and environment modulate their AD risk in relation to men. Understanding sex differences in AD has been complex. This project aims to uncover the molecular underpinnings of the female sex hormone estrogen in AD models and relate these findings to human disease.
Methods: We are using APP-NL(G)F mice, which exhibit clear AD pathology by 6 months of age, to study the effects of biological sex and sex hormones on memory and AD pathology at 6 and 12 months. Surgical menopause is induced in young adult female mice and castration in male mice. Preliminary data indicate neuroprotective effects of estrogen receptor beta (ERβ) in APP-NLGF mice. Consequently, we crossed ERβ-/- mice with APP-NL(G)F mice to study the effects of ERβ loss on AD pathology, utilizing single-cell RNA sequencing of hippocampal brain cell populations.
Results: Our ongoing analysis provides insights into ERβ's role in brain cell functions and identifies sex-dependent alterations in gene activity. Preliminary data show that ERβ activation has sex-specific neuroprotective effects in APP-NLGF mice. We will anchor our findings to human disease by studying gene and pathway regulations in human AD brains and analyzing GWAS data from women with or without AD diagnosis and with or without different menopausal hormonal treatments.
Conclusions: Collectively, these findings offer insights into the mechanisms underlying sex-specific susceptibility to AD and identifies regulatory proteins for potential treatments targeting sex-dependent AD pathology. Understanding the role of estrogen and ERβ in AD could lead to targeted therapies addressing the heightened risk in women.

SHIFT 01-213

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CHOLINERGIC
2-3 April 2025

EFFECT OF CHOLINE ALFOSCERATE (ALPHA-GPC) ON THE EFFICACY OF CHOLINERGIC HYPOTHESIS IN THE MIGRAINEURS WITH COGNITIVE COMPLAINT

Manho Kim
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Aims: Migraines are believed to be triggered by neurogenic inflammation related to peptides like CGRP and Substance P. Parasympathetic neuropeptides can also cause migraines via cerebral vasodilation. While acetylcholine (Ach) can inhibit these peptides, it may also induce pain. GPC, an Ach precursor, is used to improve cognitive function and treat cerebrovascular diseases, but its efficacy in migraine patients remain unclear. This study aims to assess the cholinergic hypothesis on MCI (Mild cognitive impairment) or SMI (Subjective memory impairment) with migraine headache.
Methods: This study was conducted with migraineurs diagnosed with either with MCI or SMI. We assessed cognitive function using the MMSE and according to the criteria as well as headache diary. The average frequency migraine days of over the past one month before taking the GPC. They were then prescribed GPC 800mg (400mg, 2 tablets) once daily for 12 weeks. After the treatment period, changes in migraine frequency and MMSE scores were evaluated during a follow-up visit.
Results: GPC was found to have a statistically significant effect in reducing the frequency of headaches. However, no further significant improvement in MMSE score was observed. The relationship between MMSE score and headaches showed a negative correlation trend both before ($p=0.112$) and after treatment ($p=0.087$). but this relationship was not statistically significant.
Conclusions: GPC demonstrated a significant effect in reducing headache frequency. However, it did not show a notable correlation on cognitive function improvement. These findings suggest that while GPC may be effective in managing headaches, its role in enhancing cognitive function may remain unclear or independent in our study subjects. However, this observation may support the cholinergic hypothesis in migraine attack.

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SHIFT 01-219

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

PLASMA CYTOKINES PROFILE IN PATIENTS WITH ALZHEIMER'S AND PARKINSON'S DISEASE: A COMPARATIVE STUDY IN TERMS OF INFLAMMATION

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Aims: Mainstream therapies for Alzheimer Disease and Parkinsonś Disease have achieved limited success. addressing inflammation may serve as a potential remedy for these conditions. Our study aims to investigate inflammation in AD and PD patients and explore their potential correlation.
Methods: the research is an interventional study. a total of 150 participants were included, divided into three groups: control, AD, and PD.
Fasting blood was collected into two different types of vacutainer tubes.
the plasma levels of tNF-α, il-1β, il-1α, il-2, il-4, il-6, il-8, il-12p70, il-10, iFN-γ were measured by sandwich-type (elisa) kits , while PGe2 level of plasma was determined using a competitive elisa kit . McP-1 and iP-10 were analyzed by elisa kits
Results: the plasma levels of il-1α, il-1β, il-4, il-6, il-12p70, il-10, tNF-α, iP-10, McP-1, and PGe2 were significantly higher in both the AD and PD groups. conversely, the levels of il-2 and il-8 were significantly lower in the AD and PD groups. No statistically significant differences were observed in iFN-γ levels. there was no significant difference in the plasma level of il-2 between the AD and PD groups the levels of il-1α, il-1β, il-4, il-6, il-8, il-12p70, il-10, tNF-α, and iP-10 in the PD group were approximately 1.5 times higher than those in the AD group. the McP-1 levels in the PD group were 3.5 times greater, while the level of PGe2 in the PD group was statistically lower (ratio: 0.7).
Conclusions: Inflammatory biomarkers, except for il-2 and il-8, increase significantly in both diseases, PD may exhibit a more impaired resolution phase in comparison to AD. current and future treatments targeting inflammation would potentially be more effective in PD than in AD.

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SHIFT 01-220

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

DIFFERENTIAL EFFECTS OF NLRP3 VS. IRAK4 INHIBITORS ON INFLAMMASOME RELATED PATHWAYS IN CELLS

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Aims: Upregulated inflammasome pathways contribute to chronic inflammatory diseases including AD and PD. Targeting inflammasome and upstream NF-κB pathways have been active efforts in anti-inflammation drug discovery. Regardless progresses, it is unclear what can be more effective to inhibit among the pathways. To address this question, we compared effects between specific inhibiting NLRP3 with MCC950 and inhibiting IRAK4 with Zimlovisertib through cellular assays.
Methods: (1) NF-κB signaling reporting assay with THP1/ASCGFP stable cell line for quantifying NF-κB signaling. **(2)** High content inflammasome formation assay with THP1/ASCGFP stable cell line pre-treated with 50 nM PMA for measuring inflammasome formation induced by LPS/Nigericine treatments. **(3)** IL-1β release assay with THP1 cells. **(4)** Quantifying inflammasome dependent cell death assay with THP1 cells.
Results: (1) NLRP3 inhibitor, MCC950, effectively inhibited inflammasome formation with high potency (<50 nM), effectively inhibited IL-1β release (about 150nM), inhibited pyroptosis (about 280nM); but inactive on NF-κB signaling. **(2)** IRAK4 inhibitor, Zimlovisertib, effectively inhibited NF-κB activation with high potency (3.8nM); partial inhibition (30%) of inflammasome formation (7.9nM), IL-1β release (about 47nM), and pyroptosis (about 12.5nM). **(3)** Combination of MCC950 and Zimlovisertib show additive effect on inhibiting inflammasome formation with increased maximal effect comparing to either individual drug.
Conclusions: There are differential effects comparing inhibition of NLRP3 vs. IRAK4. Inhibition of NLRP3 effectively blocked inflammasome formation, IL-1β releasing and pyroptosis, while no effect on NF-kB signaling. Inhibition of IRAK4 effectively blocked NF-kB activation, while only reached partial inhibition of inflammasome formation, IL-1β releasing and pyroptosis. The IL-1β releasing is dependent on inflammasome caused cell death, the pyroptosis. Results may help on evaluation of in vivo efficacy tests using these two different targeting drugs, as well as potential combination therapy with them.

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SHIFT 01-221

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

NEUROENDOCRINE CELLS TRANSCRIPTIONAL LANDSCAPE ON ALZHEIMER'S DISEASE

Patrick Da Silva[1], Toby Lanser[1], Taha Yahya[2], Rafael Machado Rezende[2], Saef Izzy[3], Howard Weiner[4]
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Aims: Alzheimer's Disease is Central Nervous System disorder, which is comprised by extracellular amyloid beta plaques deposition, Tau protein neurofibrillary tangles accumulation inside neurons and consequently neuroinflammation mediated by glial cells. Neuroendocrine (NE) cells are a rare type of cell that act as both neurons and endocrine cells, releasing hormones into the blood in response to nervous system signals. These complex cells are poorly studied, and their role on neurodegenerative diseases are unknown. In this study we aimed to track down the role of neuroendocrine cells from the pre-frontal cortex on Alzheimer's Disease.
Methods: We mined three public available single-nucleus RNAseq datasets from post-mortem pre-frontal cortex region of 47 Alzheimer's Disease patients and 40 healthy controls. The three datasets were normalized and scaled by number of counts and mitochondrial genes, and then integrated through Harmony algorithm. The cell types were annotated by gene set enrichment cell type databases together with use of well-known conventional marker genes. These steps were followed by differential expression analyses with MAST package comparing AD and healthy controls cells.
Results: We found downregulation of glutamatergic synaptic transmission, cell-cell adhesion and genes related to central nervous system development. There is high upregulation of serotonin receptors. The most profound difference was a high downregulation of IL16 on AD patients compared to healthy controls.
Conclusions: IL16 is a pro-inflamatory cytokine which mediates recruitment of monocytes through CD4 receptor. We conclude the neuroendocrine cells lost IL16 expression which in turn reduces the recruitment of monocytes to mediated amyloid beta phagocytosis and clearence.

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β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

DURAL ECTOPIC LYMPHATIC STRUCTURES ACCUMULATE DURING AGING AND ARE DYSREGULATED IN NEURODEGENERATIVE DISEASES

Amit Fruitman Davidi, Sophie Shirenova, Giulio Benedetti, Karin Vardy, Dolev Michaelovitch, Ravit Madar, Eitan Okun
Bar Ilan University, Life Sciences Faculty, Ramat Gan, Israel

Aims: This study investigates the formation and role of dural ectopic lymphoid structures (ELS) in the context of aging and neurodegenerative diseases, as these structures could serve as potential mediators of neuroimmune interactions and therapeutic targets. Using mouse models of early-onset Alzheimer's disease (EOAD), tauopathy, and Down syndrome (DS), the study examines ELS accumulation, complexity, and interactions with brain pathology to illuminate their role in disease mechanisms.
Methods: Cranial dural meninges from aged wild-type and transgenic mice (5xFAD and APP/PS1 for EOAD, K257T/P301S for tauopathy, and Dp1Tyb for DS) were analyzed. ELS were characterized by immunofluorescence using markers such as CD45R (B cells) and CD3 (T cells). Correlations between ELS dynamics and amyloid or tau pathology were assessed.
Results: Meningeal ELS accumulate with age in wild-type mice, showing sex-specific patterns. Male mice exhibited a continuous increase in ELS with age, while female mice peaked at 12 months, possibly due to age-related estrogen decline and its immunomodulatory effects. In 5xFAD mice, ELS formation intensified with pathology, whereas APP/PS1 mice displayed reduced ELS numbers with aging. Tauopathy and DS models showed significantly fewer ELS than controls. Correlations between ELS complexity and amyloid pathology varied by model, reflecting differences in how ELS relate to amyloid burden within distinct pathological contexts.
Conclusions: Dural ELS exhibit age-, sex-, and pathology-specific dynamics, reflecting their role in CNS pathology. Their differential regulation in AD, tauopathy, and DS highlights ELS as key players in the neuroimmune interface. Future research could explore manipulating ELS formation or function to mitigate neurodegenerative processes, potentially guiding immunomodulatory therapies tailored to specific diseases or patient populations.

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SHIFT 01-223

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

IN VITRO STUDY OF THE BENEFICIAL EFFECTS OF POMEGRENATE ON THE PATHOPHYSIOLOGY OF ALZHEIMER'S DISEASE

Tamas Fulop, Mehdi Aalami, Abdelouhed Khalil, Hicham Berrougui
University of Sherbrooke, Medicine, Sherbrooke, Canada

Aims: To investigate the oxidative stress, inflammatory, and Tau-phosphorylation lowering effects of pomegranate polyphenols (PP) (punicalagin, ellagic acid, peels, and arils extracts).
Methods: We used flow cytometry to quantify protein expression of proinflammatory cytokines (IL-1β) and anti-inflammatory markers (IL-10) in THP-1 macrophages, as well as M1/M2 cell surface receptors (CD86 and CD163) expression in human microglia HMC3 cells. IL-10 protein expression was also quantified in U373-MG human astrocytes. The effect of PP on $A\beta_{1-42}$-induced oxidative stress, was assessed in microglia by measuring ROS generation and lipid peroxidation, using respectively 2',7'-dichlorofluorescein diacetate (DCFH-DA) and thiobarbituric acid reactive substances tests (TBARS). Neuronal viability and cell apoptotic response to $A\beta_{1-42}$ toxicity was assayed using the annexin-V-FITC apoptosis detection kit and MTT assay; respectively. Flow cytometry analysis was also performed to evaluate the ability of PP to modulate $A\beta_{1-42}$-induced Tau-181 phosphorylation (pTau-181).
Results: Our data indicate that PP are significantly ($p<0.05$) effective to counter $A\beta_{1-42}$-induced inflammation through increasing the anti-inflammatory cytokines (IL-10) (in U373-MG astrocytes and THP1 macrophages) and decreasing pro-inflammatory markers (IL-1β) expression in THP1 macrophages. PP were also significantly ($p<0.05$) effective in inducing the phenotypic transition of THP-1 macrophages and microglial cells from M1 to M2 by decreasing CD86 and increasing CD163 surface receptors expression. Moreover, our treatments have a significant ($p<0.05$) beneficial impact on oxidative stress illustrated in the reduction ROS and TBARS generation. Our results suggest that $A\beta_{1-42}$ significantly ($p<0.05$) increases pTau-181. This effect was significantly ($p<0.05$) attenuated by arils, peels, punicalagin and drastically reduced by ellagic acid treatments.
Conclusions: Our results clearly attribute to PP an anti-inflammatory, antioxidant, anti-apoptotic and anti-Tau-pathology potential. Future studies should aim to extend our knowledge of the potential role of PP on Ab1-42-induced neurodegeneration.

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SHIFT 01-224

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

PORPHYROMONAS GINGIVALIS INFECTION INDUCES PERIPHERAL AMYLOID B PRODUCTION AND ITS CEREBRAL ACCUMULATION

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Aims: It is revealed a strong association between periodontitis and cognitive decline in Alzheimer's disease (AD), however, the mechanism of the association is unclear. In this study, we verified our hypothesis that chronic *P. gingivalis* infection expands Aβ pools in peripheral inflammatory tissues and thereby contributes to the accumulation of Aβ in the brain.
Methods: 15-month-old mice (C57BL/6J, female) were systemic *P. gingivalis* infection for 3 consecutive weeks (1×10^8 CFU/mouse, every 3 days, intraperitoneally). RAW264.7 cells (macrophage cell line) and hCMEC/D3 cells (cerebral endothelial cell line) were used for *In vitro* experiments, which were directly infection with *P. gingivalis* (multiplicity of infection, MOI=5).
Results: In comparison to uninfected mice, significantly changes were found in *P. gingivalis*-infected mice, including increased expression of IL-1β, APP_{770}, Cathepsin (Cat) B and $Aβ_{42}$ in the liver which was mainly co-localized with macrophages; increased expression of receptor for advanced glycation end products (RAGE) in the CD31-positive endothelial cells and the $Aβ_{42}$ loads around the CD31-positive cells in brains; and memory decline. In cultured RAW264.7 cells, the expression of IL-1β, APP_{770} and $Aβ_{42}$ was induced in the *P. gingivalis*-infected RAW264.7 cells which was significantly blocked by CatB specific inhibitor. In cultured hCMEC/D3 cells, the RAGE expression and a RAGE-dependent $Aβ_{42}$ influx in the hCMEC/D3 cells were elevated in the *P. gingivalis*-infected hCMEC/D3 cells. The *P. gingivalis*-upregulated RAGE expression was significantly decreased by CatB inhibition.
Conclusions: These observations suggest that inflammatory macrophages serve as a peripheral source of $Aβ_{42}$ and RAGE expression in cerebral endothelial cells mediates the $Aβ_{42}$ influx after *P. gingivalis* infection. CatB plays a critical role in regulating peripheral $Aβ_{42}$ production and its influx in brain.

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SHIFT 01-225

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

THE ROLE OF ABI3 IN LPS-INDUCED SYSTEMIC INFLAMMATION

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Aims: Human genetics studies of Alzheimer's disease (AD) have identified a rare coding variant in the *ABI3* locus associated with an increased risk of developing late-onset AD. *ABI3* is a microglia-enriched gene and is predicted to regulate the immune response. In our previous studies, we have demonstrated that deletion of the *Abi3* locus exacerbates AD-related pathologies including neuroinflammation in the 5XFAD transgenic mouse model of amyloid-beta amyloidosis. However, it remained unknown whether the increased neuroinflammation in the 5XFAD model was due to the direct effect of *Abi3* deletion on immune-regulatory genes or secondary to the increased amyloid-beta accumulation. In this study, we aimed to investigate the impact of *Abi3* deletion on inflammation independent of amyloid-beta pathology.
Methods: To assess the role of ABI3 in an inflammatory condition *in vivo*, we administered LPS (2 mg/kg) by intraperitoneal injection to *Abi3* wild-type (WT), heterozygous (HET), and homozygous knock-out (KO) mice to induce systemic inflammation. Blood and brain tissues were collected 6h and 24h after LPS injection. The cytokine and chemokine levels were assessed by qPCR and ELISA. Gliosis was assessed by immunostaining.
Results: There was no significant difference in most cytokine levels in the plasma between the genotypes. However, we detected a significant increase in CCL24, CX3CL1, and CXCL10 in *Abi3* KO mouse brain compared to *Abi3* WT. Furthermore, there was a significant decrease in CCL25 levels in the cortices of *Abi3* KO mice compared to *Abi3* WT.
Conclusions: We have demonstrated that deletion of *Abi3* modulates neuroinflammation, independent of amyloid-beta-induced inflammation, in a systemic inflammation model. Importantly, the chemokines differentially regulated in *Abi3* KO mice were also altered in the *Abi3 KO;5XFAD* mice, corroborating the direct impact of ABI3 on these immune-regulatory proteins.

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SHIFT 01-226

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

BRAIN DYSFUNCTIONS DETECTED BY A BEHAVIORAL MACHINE LEARNING ALGORITHM IN THE ALZHEIMER'S DISEASE-RELATED 5XFAD MODEL ARE AMELIORATED BY TAU REDUCTION

Sara Knowles[1,2], Rafaella Gonçalves[1,2], Pranav Nambiar[1], Kaitlyn Ho[1], Gui-Qiu Yu[1], Stephanie Miller[1], Jorge Palop[1,2], Lennart Mucke[1,2]
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Aims: Ongoing clinical trials aiming to reduce tau levels in Alzheimer's disease (AD) patients with amyloid pathology make it interesting to further dissect the interplay between tau and amyloid. 5xFAD mice, which coexpress AD-mutant human amyloid precursor protein (APP) and presenilin 1 (PS1), develop robust amyloid pathology. However, their behavioral phenotype can be variable when assessed by conventional methods. We therefore used variational animal motion embedding, an unbiased machine learning (ML) algorithm, to assess the effects of tau reduction in this model.
Methods: 5xFAD transgenic and nontransgenic mice with two, one, or no tau-encoding *Mapt* alleles were compared at 15–17 months of age. Evaluations in conventional and ML-assisted behavioral assays were followed by immunohistochemical analyses of brain sections and measurements of immune mediators in plasma.
Results: The ML algorithm detected robust behavioral abnormalities in 5xFAD mice on the tau wildtype (*Mapt*+/+) background, as compared to nontransgenic *Mapt*+/+ controls. Tau reduction effectively suppressed these abnormalities in a gene dose-dependent manner. Tau reduction also diminished deficits in balance beam performance and prevented weight loss in 5xFAD mice. Both partial reduction and complete ablation of tau decreased brain amyloid loads and plasma alterations in immune mediators in 5xFAD mice. Tau reduction had no significant effects on mice lacking human APP/PS1 with respect to the above measures.
Conclusions: Even partial reduction of tau ameliorates brain dysfunctions in 5xFAD mice. Whether these effects relate to reductions in amyloid burdens and immune mediators or other pathomechanisms remains to be determined. Since tau reduction has not reduced plaque loads in APP models lacking mutant human PS1, our results also raise intriguing questions about the relationship between tau and PS1.

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SHIFT 01-227

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β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

EXPLORING THE RELATION BETWEEN APOE AND PERIPHERAL INFLAMMATION IN ALZHEIMER'S DISEASE: A CASE-CONTROL STUDY ACROSS NEURODEGENERATIVE AND NEUROINFLAMMATORY DISORDERS

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Aims: Apolipoprotein E (ApoE) is implicated in inflammatory and neurodegenerative processes in Alzheimer´s disease (AD). It is also suggested to contribute to multiple sclerosis (MS) progression. Previous studies focused mostly on the expression in the brain. By exploring the relation between *APOE* expression and peripheral inflammatory responses in mild cognitive impairment (MCI) and AD compared to MS and non-inflammatory controls, we aim to enhance our understanding of AD-related inflammation.
Methods: RNA was isolated from whole blood of MCI (n=31), AD (n=29) and relapsing-remitting MS (RRMS, n=18) patients and age and sex-matched controls (n=26). The expression of established inflammatory genes and *APOE* was measured using quantitative PCR.
Results: We observed a trend towards decreased peripheral *APOE* expression in MCI, AD and MS samples compared to controls, which was particularly pronounced in MCI ($p = 0.027$). Among other markers, *APOE* expression was correlated with *TREM2* ($p < 0.001$) and *NLRP3* ($p = 0.013$) expression and negatively correlated with *RELA* ($p < 0.001$) and *IL-1b* ($p = 0.046$). Consistent with previous studies, AD and MCI samples revealed an upregulation of certain inflammatory markers, such as *RELA* in AD ($p = 0.023$) and *TNFα* in both AD ($p = 0.009$) and MCI ($p = 0.037$). *TREM2* was upregulated in AD (p=0.0003), especially in *APOE4* carriers, when compared to non-carriers (p = 0.001).
Conclusions: Our study provides preliminary evidence for disease-specific alterations of peripheral *APOE* and inflammatory gene expression. A complex interplay between *APOE* and peripheral inflammation seems to participate in AD pathogenesis. However, we currently perform further cell-type specific analyses in a larger number of thoroughly characterized patients, which will provide deeper insights into the interplay of *APOE*, treatment-targetable peripheral inflammatory pathways and neurodegeneration in AD.

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SHIFT 01-231

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES
2-3 April 2025

" NOVEL SMALL MOLECULE STRATEGIES FOR ENHANCING PROTEOSTASIS IN ALZHEIMER'S DISEASE (AD) USING AD CELL AND WORM MODEL"

Ajish Ariyath[1,2], Prashant Bharadwaj[1], Wmad Binosha Fernando[3], Ralph Martins[4]
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Aims: Develop novel small molecules predicted to bind USP14 and validate its neuroprotective efficacy, improve proteostasis, amyloid beta toxicity and clearance in alzheimer's disease (AD) cell and worm models.
Methods: We developed assays to screen a library of 71 novel small molecule proteostasis inhibitors and test it on AD cell and worm model. Screening resulted in identification of AA10 and AA51, two novel enhanced neuroprotective analogues of USP14 ligand IU1. The effects of these compounds on autophagy, proteasome activity, APP-C99/Aβ clearance, neurodegeneration, and behaviour were evaluated using fluorescence microscopy, toxicity, western blotting, proteasome, and lifespan assays in AD cell (MC65) and worm model (*C. elegans*).
Results: Initially, novel small molecule ligands that bind to USP14 were designed and developed through an in-silico artificial intelligence screening platform known as AtomNet and these were tested on our MC65 and *C. elegans* models of Alzheimer's disease. Positive results were achieved with compounds AA10 and AA51 from the screened library of 71 proteostasis modulators using invito cell model. In the MC65 cell model, AA10 and AA51 improved AD proteostasis impairment by 82% and 70% respectively. Cell survival improved from 40% with IU1 to 55% with AA10 and AA51. Further, study utilising the AD worm model supported these results, indicating that IU1 decreases neurodegeneration by 77%, AA10 by 83%, and AA51 by 84% (n=60 worms). Intrestingly, *C. elegans* models also exhibited enhanced behavioural responses and extended lifespans following treatment with IU1, AA10, and AA51.
Conclusions: Ours, is the first report of using IU1 in AD models as USP14 inhibitor. The novel IU1 analogue AA10 and AA51 looks more promising and hold potential as candidates for pre-clinical validation in AD. The next steps involve testing therapeutic efficacy and brain bioavailability in AD mice model.

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SHIFT 01-232

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES
2-3 April 2025

TARGETING THE UBIQUITIN-MEDIATED REGULATION OF SIRTUIN6 IN ALZHEIMER'S DISEASE: A PATHWAY TO NEUROPROTECTION

Meagan Colie, Jonathan Schisler, Michael Almeida
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Aims: Aim 1: Elucidating the Ubiquitin-Mediated Regulation of Sirt6 in the AD brain. I hypothesize that the ubiquitination and degradation of the neuroprotective Sirt6 is increased in the AD brain due to changes in the expression and behavior of E3 ligases in the presence of pathological proteins associated with AD, leading to a decrease in neuroprotection. **Aim 2: Assessing the Impact of Sirt6 Stabilization on Neuroprotection in the AD Brain.** I hypothesize that stabilizing Sirt6 expression, either through structural modifications or gene silencing/exogenous expression of E3 ligases will enhance Sirt6 neuroprotective functions in AD.
Methods: Aim 1 Methods: I will utilize biochemical approaches in cell-free ubiquitination and protein association assays using recombinant protein of two candidate competing E3 ubiquitin ligases, human stem-cell-derived cortical neuron model of AD, affinity proteomics and mass spectrometry, and post-mortem human AD brain tissue to understand the interactions and levels of Sirt6 and its proposed E3 ligase modulators via immunohistochemistry and microscopy. Aim 2 Methods: Using my neuronal AD model, I will test a ubiquitin-null Sirt6 mutant as well as targeting the E3 ligases that regulate Sirt6 to assess their influence on Sirt6 functionality and neuronal survival.
Results: I anticipate that these aims will reveal that the canonical regulation of Sirt6 via E3 ligases and ubiquitination is perturbed in the AD brain, leading to decreased Sirt6 function and increased neuronal susceptibility to inflammation and death.
Conclusions: My proposed research is poised to transform our understanding of neuronal longevity in AD. By elucidating the ubiquitin-mediated post-translational mechanisms regulating Sirt6, my work will shed light on the critical factors contributing to the loss of neuroprotection in aging. Furthermore, it will explore innovative strategies to stabilize Sirt6 expression and function within the aging brain.

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SHIFT 01-234

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METABOLISM, INSULIN
2-3 April 2025

FAULTS IN METABOLIC PATHWAY OF DOPAMINE PRODUCTION AS A CAUSE OF PARKINSON'S

Dhruti Doddaballapur
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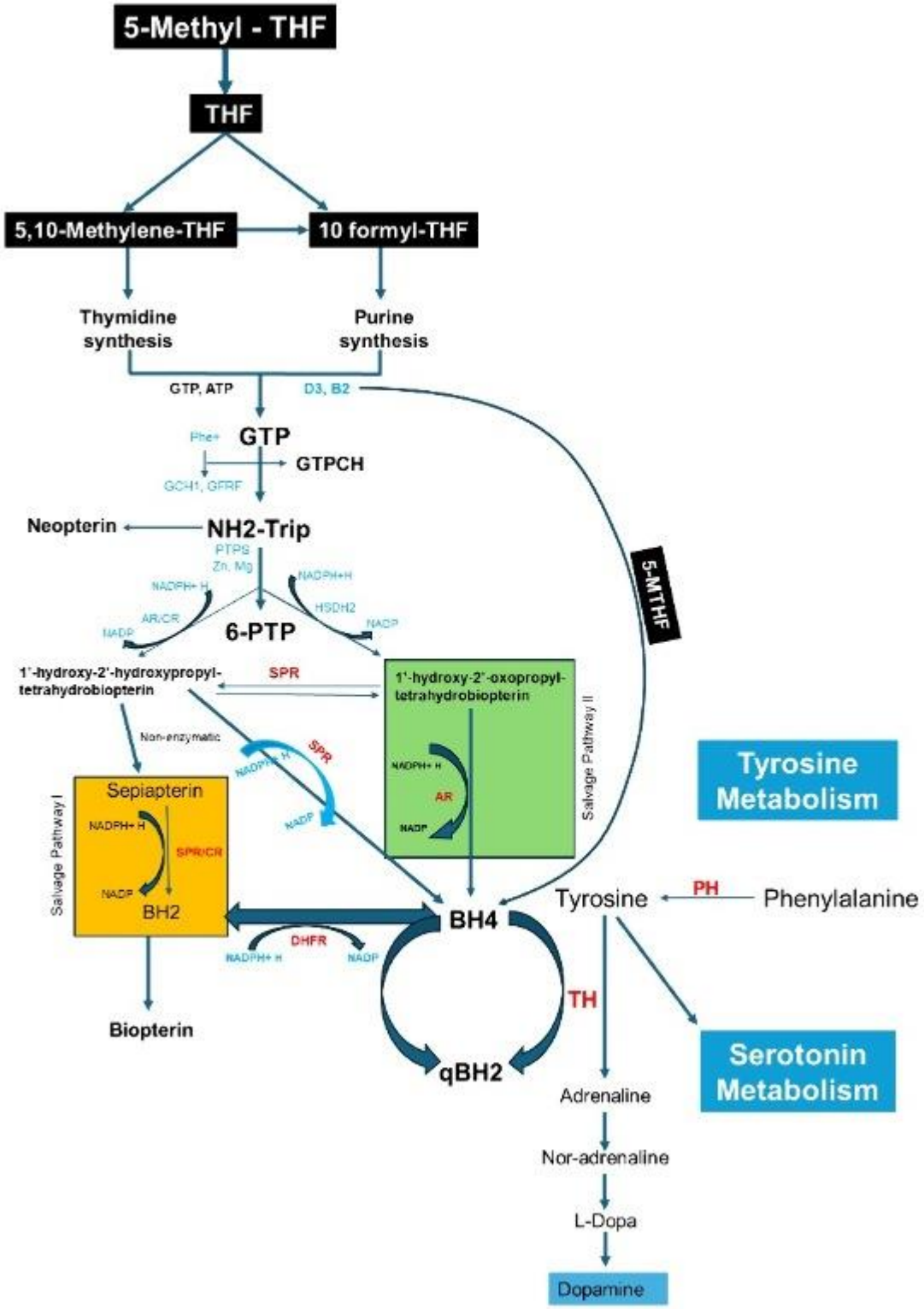
Aims: Explore metabolism of folate and TCA cycle to identify top end errors in production of dopamine



Methods: Enzyme assays: to identify errors in metabolism pathway Western blots: to identify deficiency or over expression in pathway LC/MS: to quantify proteomic and metabolic changes related to the metabolic pathway above in CSF and tissue of PD compared to controls Focus group sessions: to verify changes identified with patient experience

Results: Faults were identified in SPR, PTP, MTHFR, MTHFD1, DHFR and TH quantities of enzymes and its

respective metabolites through western blotting and LC/MS of PD tissue and CSF. Enzyme assays confirmed that these metabolic reactions were not working in CSF and tissue of PD patients. Identified faults were able to explain patient lived experience with change in taste, anaemia, hearing loss, fatigue, hair loss, issues with temperature regulation, clammy skin and incontinence.

Conclusions: Parkinson's disorder is a complicated neurodegenerative condition with significant gaps in knowledge of the underlying pathophysiology. The research has shown us a significance in the changes occurring in enzymes GCH1, SPR, PTPS, TH, MTHFR, MTHFD1 and DHFR. Genetic analysis has shown that there is no common genetic mutation related to the metabolic faults. Further testing of epigenetics and nutrigenomics is required to understand the reason for these faults.

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SHIFT 01-235

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METABOLISM, INSULIN
2-3 April 2025

BODY COMPOSITION AND BODY MASS INDEX CHANGES IN ALZHEIMER'S DISEASE ARE RELATED TO AMYLOID AND TAU BIOMARKERS

Karl Götze[1], Inès Petit-Damico[2], Manuel Sanchez[1], Sophie Lacaille[1], Théodore Decaix[3], Kany Tounkara[4], Julien Dumurgier[4], Agathe Vrillon[4], Agathe Raynaud-Simon[1], Matthieu Lilamand[3], Claire Paquet[4]
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Aims: Recent studies showed that body mass index tended to decrease prior to the diagnosis of neurodegenerative diseases. Results remains heterogenous on body composition (BC) alteration in link to cognitive diseases and amyloid and tau biomarkers. Our aim was to describe the association between BMI, BC changes and AD CSF biomarkers.
Methods: Retrospective multicentric study on patients with CSF AD biomarkers from 2 geriatric daily hospitals and 1 memory clinic, all patients having BC assessment. All patient were addressed by their physician for cognitive impairment exploration. Patients with prolongated corticotherapy, active neoplasy were excluded. BC parameters (Skeletal Muscle Mass index, SMMI; Fat Mass Index, FMI; Fat-to-muscle ratio, FMR) were measured using bio-impedancemetry. Linear regression of BC on AD CSF biomarkers was adjusted on MMSE, number of medications, age, sex and independence on activities of daily living.
Results: 236 patients, aged 76±7.5y.o, were included between 01/2022 and 10/2024. 164 (69.4%) were positive (A+) for the amyloid LCS biomarker and 72(30.5%) were negative (A-). A+ patients were significantly older than A- patients ($p<0.001$), and were mostly women ($p=0.03$). The two groups did not differ considering independence, comorbidity, or MMSE scores. A+ patients had a significantly lower BMI mean (23.4) compared to A- (25.3, $p=0.002$), lower FMI median(A- 6.85;A+ 5.41), $p=0.002$, and lower FMR median(A-=0.377;A+=0.299). A+ and A- patients did not differ considering SMI or FFMI. On multivariate analysis, Aβ42/Aβ40 was significatively associated with BMI($\beta=17.04$,$p=0.002$), FMI($\beta=16.36$,$p<0.001$), and FMR($\beta=0.67$,$p=0.02$). No association was found with SMI or FFMI. Similarly, pTau181 or total Tau were not associated with BMI or any BC parameter.
Conclusions: Aβ42/Aβ40 ratio was significantly associated with lower BMI, and fat mass diminution, with adjustment on confusion factors. Muscle mass was not associated with any biomarkers.

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SHIFT 01-238

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROBIOME
2-3 April 2025

DIFFERENCES IN THE COMPOSITION OF THE ORAL MICROBIOME IN PATIENTS WITH ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW

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Aims: Over the years, the incidence of neurodegenerative diseases has dramatically increased. People with dementia worldwide are estimated to be 50 million, with Alzheimer's disease (AD) being one of the most common subtypes of dementia. Several studies recently reported a correlation between AD and oral microbiome. The objective of this systematic review (SR) was to assess the composition of the oral microbiome in people with AD and Mild Cognitive Impairment (MCI).
Methods: Bibliographic searches were carried out to identify published literature on PubMed, the Cochrane Library databases, and ISI Web of Knowledge. The SR was developed based on the Cochrane Handbook and reported following the PRISMA statement. A specific search strategy was developed. Included studies were qualitative assessed using the Newcastle-Ottawa scale (NOS).
Results: Overall, 3,490 records were identified from the three databases. Of these, 11 met the inclusion criteria. Participants in the included studies were people with AD or MCI, and healthy controls. The most frequently performed analyses were 16S rRNA, α and β diversity, and relative abundance of taxonomic composition. The bacterial and fungal communities were not significantly different between the observed populations. However, α and β diversity appeared to be higher in people with AD or MCI compared to healthy subjects
Conclusions: The ratio between (α) the mean diversity in species at a local level and (b) the differentiation between local sites and the ratio between regional and local species diversity was higher in people with AD or MCI. Further studies with larger samples and observing more areas of the oral microbiome would be useful to confirm the observed results

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SHIFT 01-239

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROBIOME
2-3 April 2025

NASAL BACTERIOMES IN PATIENTS WITH ALZHEIMER DISEASE AND PARKINSON DISEASE: A PILOT STUDY

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Aims: Nasal microbiota and its metabolites can affect the nervous system function. Dysbiosis of nasal microbiota might be involved in the etiopathogenesis of neurodegenerative processes, such as Alzheimer disease (AD) and Parkinson disease (PD). The aim of the study is to detect the changes in human nasal bacteriomes in patients with AD and PD as compared to elderly healthy controls.
Methods: In this retrospective association case-control study, nasal swabs were collected from 26 patients with AD, 22 with PD, and 12 healthy controls. DNA was extracted using DNA Mini kit and analyzed by 16S rRNA amplicon sequencing on the Illumina platform.
Results: In nasal samples from patients with AD and PD, the number of observed amplicon sequence variants as well as the alpha diversity (Shannon index) were found higher than in healthy controls, however, the significant differences were observed only between patients with PD and healthy controls (Kuskal-Wallis test with Dunn's post hoc test, $p \leq 0.05$). As expected, the most abundant bacterial genera were *Staphylococcus, Corynebacterium, Dolosigranullum, Moraxella,* and *Streptococcus*.
Genus *Pseudomonas* was found only in patients with AD and PD, but not in healthy controls. There were no significant differences in relative abundances on the genera levels among study groups (Kruskal-Wallis test, Benjamini-Hochberg adjusted *p*-values > 0.05).
Conclusions: The pilot results suggest that the alpha diversity of nasal bacteriome is decreased in PD patients (significantly) as well as in AD patients (non-significantly). Regarding the bacteriome composition, genus *Pseudomonas* was found only in AD and PD patients, otherwise it was similar to healthy individuals.
Acknowledgements This work was supported by RECETOX Research Infrastructure (ID LM2023069) and by the project LX22NPO5107 (MEYS): Financed by European Union – Next Generation EU.

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SHIFT 01-246

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

DJ-1-MEDIATED METABOLIC EFFICIENCY REGULATES GLIAL CELL ACTIVITY IN PARKINSON'S DISEASE

Amina Abulimiti, Sarah Aunger, Jade Mello, Kambiz Alavian
Imperial College London, Brain Sciences, London, United Kingdom

Aims: Metabolic insufficiency has been identified as a key factor contributing to neuroinflammation and neurodegeneration in Parkinson's disease. Our study aimed to explore the role of the interaction between the Parkinson's protein DJ-1 (Park7) and mitochondrial F1Fo ATP synthase in modulating mitochondrial stability and its effect on microglial activity in Parkinson's disease
Methods: We examined the interaction between DJ-1 and ATP synthase in different microglial states (ramified homeostatic and reactive amoeboid) in post-mortem midbrain samples from Parkinson's disease patients and age-matched controls. Immunohistochemical and biochemical techniques were used to assess protein interaction levels and to compare them between the two groups
Results: The interaction between DJ-1 and ATP synthase was found to vary between the homeostatic and reactive states of microglia. Notably, a significant reduction in the interaction was observed in Parkinson's disease brains compared to age-matched controls. This differential interaction suggests a dysregulation of mitochondrial function, particularly in reactive microglia, which may contribute to increased neuroinflammation.
Conclusions: Our findings indicate that the interaction between DJ-1 and mitochondrial F1Fo ATP synthase is crucial for regulating microglial activity and maintaining mitochondrial membrane integrity. The altered interaction in Parkinson's disease brains suggests that impaired mitochondrial function in microglia may drive neuroinflammatory processes, contributing to neurodegeneration. This study provides novel evidence that efficient mitochondrial coupling plays a direct role in modulating midbrain glial cell function and degeneration in Parkinson's disease.

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SHIFT 01-247

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

THE IMPACT OF TREM2 POLYMORPHISM ON MICROGLIAL FUNCTION IN ALZHEIMER'S DISEASE PATHOGENESIS

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Aims: Recent genome-wide association studies highlight connections between variants of *Triggering receptor expressed in myeloid cells 2* (TREM2) and increased risk of late-onset Alzheimer's Disease (AD). TREM2, expressed in brain microglia and peripheral myeloid cells, and its cleavage product, soluble TREM2 (sTREM2), are critical for stimulating microglial activation, enhancing phagocytosis, and inhibiting amyloid beta (Aβ) aggregation, thereby protecting against AD. Recent findings in our laboratory suggest that *Abelson interactor protein family member 3* (ABI3) is a downstream regulator of TREM2 signalling. However, mouse model studies report conflicting results on ABI3's effect on microglial function. Importantly, SJL mice carry a TREM2 variant with a serine to glutamic acid substitution at codon 148 (148EE), while C57 mice retain serine (148SS). This polymorphism, which occurs near the TREM2 cleavage site, may affect microglial activity, potentially explaining discrepancies in the literature. This study aims to examine the effects of the 148EE polymorphism on microglial TREM2 shedding, Aβ phagocytosis, and phosphorylation of downstream signalling components.
Methods: Biochemical and functional assays were used to assess these aims. The phosphorylation of TREM2 pathway components in microglia isolated from 148SS and 148EE mice was analyzed by western blot. Aβ phagocytosis and sTREM2 shedding were quantified using Incucyte and ELISA (enzyme-linked immunosorbent assay), respectively.
Results: The 148EE polymorphism results in altered phosphorylation of pathway components, reduced phagocytosis of Aβ, and reduced sTREM2 shedding in murine microglia.
Conclusions: These findings indicate a possible functional interaction between TREM2 and ABI3. Understanding this interaction may provide new insights into microglial biology and contribute to the discovery of novel biomarkers and therapeutic targets for AD. This study enhances our understanding of TREM2's role in AD progression, particularly given the prevalence of the 148EE variant in humans.

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SHIFT 01-248

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

BRAIN CD163 EXPRESSION AND COGNITIVE OUTCOMES IN THE PRESENCE OF ALZHEIMER DISEASE NEUROPATHOLOGIC CHANGES

Pablo Agüero[1], Sunny Kumar[2], Charles Zachary Klein[2], Pablo Luengo[3], Cinthya Agüero[2], Teresa Gomez-Isla[2]
[1]Fundacion Jimenez Diaz, Neurology, Madrid, Spain, [2]Mass General Hospital, Neurology, Boston, United States of America, [3]Universidad Autonoma de Madrid, Medicine, Madrid, Spain

Aims: CD163+ cells, often associated with peripheral immune monocytes/macrophages, have been linked to neuroinflammation, though their origin and role in the brain in Alzheimer disease are still debated. We aimed at examining the relationship between CD163+ cells in the brain and differential cognitive outcomes in the presence of Alzheimer disease neuropathologic changes (ADNC).
Methods: CD163+ cells in post-mortem brain samples containing entorhinal cortex, temporal pole, and visual cortex from individuals at tangle Braak stages III-IV (with and without dementia**,** N=13 and 11, respectively) and non-demented individuals with no or negligible ADNC (N=9) at autopsy were quantified. Double staining with CD163 and IBA1 was conducted along with expansion microscopy to investigate potential synapse engulfment by CD163+/IBA1- cells.
Results: CD163+ cell numbers did not significantly differ between the three groups and showed a predominant perivascular and pial distribution in all brain regions examined. The highest abundance of CD163+ cells was observed in visual cortex, followed by temporal pole, with lowest abundance in the entorhinal cortex regardless of the clinical or neuropathological diagnosis. A small fraction of IBA1+ cells expressed CD163, while virtually all CD163+ cells were IBA1+. Only very rare CD163+/IBA1- cells could be identified and they lacked engulfed synaptic elements.
Conclusions: Our findings suggest that the presence of CD163+ cells in the brain does not significantly differ between cases with ADNC at intermediate stages and controls and does not correlate with cognitive outcomes in the presence of ADNC. The occurrence of CD163+/IBA1- cells in all brains examined was extremely rare. The origin and role of CD163+ cells in AD remain uncertain, warranting further research to clarify their role in disease pathogenesis.

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SHIFT 01-249

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

ADVANCED ALZHEIMER'S DISEASE MODELS USING IPSC-DERIVED MICROGLIA AND NEURONS HARBORING DISEASE-RELATED GENE VARIANTS

Elin Byman Shatri[1], Berta Sanz-Morello[1], Sofie Frandsen[1], Cameron Powell[2], Benjamin Schmid[1], Hjalte Larsen[1], Jesper Larsen[1], Ariel Louwrier[2], Bjørn Holst[1], Kenneth Thirstrup[1]
[1]Bioneer a/s, Cellular Engineering And Disease Modelling, Hørsholm, Denmark, [2]Stressmarq Biosciences Inc, Victoria BC, Canada

Aims: Alzheimer's disease (AD) is a major cause of death in people over 65, and as the global population ages, the need for effective drugs against AD is crucial. Current animal models lack key human disease traits, highlighting the need for relevant human cell models for drug screening. Recent advances in induced pluripotent stem cell (iPSC) technologies have enabled the efficient generation of functional human brain cells, providing valuable tools to model these complex diseases *in vitro*. Microglia, the brain's innate immune cells, play a key role in AD pathogenesis. Genetic mutations or variations in microglia-specific genes, such as TREM2, CD33 and APOE4 have been linked to either increased or decreased AD risk, making them promising therapeutic targets. We have developed robust protocols to generate iPSC-derived AD models, utilizing microglia carrying AD-related genetic variants in monoculture and co-culture with neurons, and evaluated key factors contributing to AD pathology such as amyloid-beta (Aβ).
Methods: Human iPSCs (BIONi010-C) were differentiated into microglia carrying specific AD-related gene variants and cultured either alone or in co-culture with iPSC-derived neurons. These models were validated and characterized through immunostaining, phagocytosis assays, and cytokine release assays. In particular, the neuroinflammatory responses and phagocytosis activity after treating the co-cultures with Aβ oligomers and fibrils were analyzed with microglia cells harboring AD risk genes.
Results: iPSC-derived microglia, both in mono- and co-culture, expressed key microglial markers and receptors. Phagocytic activity and cytokine release were observed in microglia monocultures upon stimulation, confirming their functional capacity. Microglia carrying AD-specific mutations exhibited altered inflammatory responses and phagocytic activity.
Conclusions: Human iPSC-derived microglia harboring disease-specific mutations demonstrate AD-related functional changes, making them valuable cell models for understanding disease mechanisms and testing potential treatments.

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SHIFT 01-250

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

MODULATING MICROGLIAL MITOCHONDRIA-ASSOCIATED ER MEMBRANES TO SUPPRESS INFLAMMASOME ACTIVATION AND ALLEVIATE ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) currently lacks a cure. Identifying effective therapeutic targets is challenging due to AD's diverse cellular dysfunctions. Mitochondria-associated ER membranes (MAM) are crucial regulators of these processes and are affected in AD. Neuroinflammation driven by microglia can exacerbate neurodegeneration. Inflammasomes are large cytosolic multiprotein complexes which promote neuroinflammation and are activated in microglia of AD models and patients. Although inflammasome activation has been observed at MAM, the underlying mechanisms of MAM's role in inflammasome activation remain unclear. Based on this, our project aims to: 1) examine MAM alterations in microglia from adult AD mice, 2) explore their role in NLRP3 inflammasome activation, and 3) assess the effect of microglial MAM alterations on synaptic structure.
Methods: Structural changes in MAM in microglia from adult *App*$^{NL\text{-}G\text{-}F}$ (AD) and wild-type mice were detected by a GFP reporter and transmission electron microscopy, and the associated mitochondrial function were assessed by Seahorse Analyzer. MAM modulation is currently performed and achieved by manipulating the expression of a MAM-associated protein or phytochemical treatments. Neuronal structure will be evaluated through immunostaining.
Results: We observed increased MAM number and length, and closer ER-mitochondria proximity in AD microglia, linked to the enhanced mitochondrial respiration. These changes were independent of MAM-associated protein levels. We hypothesize that these changes prime microglia for inflammasome activation, which is absent in early-stage AD microglial culture. Inflammasome activation induced by lipopolysaccharide and nigericin model was verified and will be used for future studies.
Conclusions: Microglial MAM exhibit alterations in AD that may drive cellular dysfunction and possibly inflammasome activation. Our research will shed light on MAM's role in controlling neuroinflammation, support further AD research on MAM dysfunction and highlight microglial MAM as a promising AD therapeutic target.

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SHIFT 01-251

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

PROTEOMIC CHANGES OF MICROGLIA IN ALZHEIMER´S DISEASE PATIENTS

Sonja Fixemer[1], Anouck Bahnerth[1], Stephan Müller[1], Felix Strübing[2], Anna Berghofer[1], Stefan Lichtenthaler[1,3,4], Jochen Herms[1,2,3], Matthias Prestel[1], Sabina Tahirovic[1]
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Aims: The majority of Alzheimer´s disease (AD) risk genes are associated to microglia function. While transcriptomic studies in both murine models and human samples have been extensively conducted, the proteomic signatures in human microglia remain less understood. This study aims to characterize the proteomic changes in microglia from AD patients compared to age-matched controls.
Methods: Primary microglia were isolated from the middle frontal gyrus (MFG3/4) of fresh post-mortem brain tissue from eight AD patients and eleven age-matched control subjects using magnetic-activated cell sorting with CD11b beads. Proteomic profiling of microglia lysates was performed using mass spectrometry with label-free quantification. Additionally, formalin-fixed paraffin-embedded tissue and cryopreserved samples from MFG3/4 were used for immunohistological analysis.
Results: We identified a large number of significantly dysregulated proteins in AD microglia. These included upregulated proteins associated with known AD risk genes, disease-associated microglia markers, and microglial amyloid-beta response proteins, consistent with those observed in amyloid-based murine models. Comparative analysis of the human and murine proteomes highlighted both shared and distinct proteomic signatures. Pathway analysis revealed significant alterations in energy metabolism, inflammatory responses, and the endolysosomal pathway. Notably, several proteins typically linked to astrocyte function were also upregulated in AD microglia. Upstream regulator analysis of AD microglia proteomic profiles suggested alterations at the epigenetic level. Key protein markers were further validated by immunohistochemical staining, revealing distinct spatial microglial expression patterns in relation to neuropathological features and between grey and white matter in the MFG3/4.
Conclusions: This proteome-wide study of human microglia in AD uncovers alterations in protein expression, shedding light on the molecular mechanisms underlying microglial dysfunction in AD. These findings enhance our understanding of microglial involvement in AD neuropathology and may offer novel therapeutic targets for future intervention.

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SHIFT 01-252

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

NEUROFILAMENT LIGHT CHAIN CLEARANCE THROUGH MICROGLIA AND THE IMPLICATIONS OF MICROGLIAL STATES FOR BIOMARKER INTERPRETATION

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Aims: Neurofilament light chain (NfL) is a protein released by degenerating neurons and serves as a biomarker for various neurodegenerative diseases. In these diseases, microglial activation is a hallmark of disease onset or progression. Interestingly, recent studies suggest that NfL might not be such a stable biomarker as previously thought. Studies report that patients that received the antibiotic minocycline, which is known to inhibit microglial activation, showed elevated NfL levels. Similarly, mice receiving minocycline show an increase in NfL levels. Here, we investigate how microglia can affect NfL levels.
Methods: We use human iPSC-derived cell models differentiated to microglia, neurons, or astrocytes. To investigate the role of microglia in neurofilament light chain (NfL) clearance, we measure NfL levels in co-cultures of microglia and neurons across different conditions The uptake of Alexa-Fluor-488-labeled NfL was tracked via fluorescence microscopy.
Results: We demonstrate that the presence of microglia in neuronal cultures reduces NfL levels. In co-cultures treated with minocycline, NfL levels increase. Furthermore, by tracking labelled human recombinant NfL, we observe its uptake by microglia in both monoculture and in co-culture. Pre-treatment with minocycline significantly reduces uptake of labelled NfL. Finally, RNA sequencing analysis of microglia incubated with and without minocycline reveals changes in gene expression related to microglial functions.
Conclusions: Our data suggest that microglia might play an active role in modulating NfL levels through

uptake and the inhibition of this process by minocycline may account for the elevated NfL levels observed in patients. These findings highlight the importance of considering microglial activation states when assessing and interpreting NfL levels in patients.

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SHIFT 01-253

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

USING HIGHLY VALIDATED RABBIT MABS AND HIGH-CONTENT IMMUNOFLUORESCENCE TO CHARACTERIZE IPSC-DERIVED HUMAN MICROGLIAL ACTIVATION

Jordan Hirschfeld[1], Sandra Coveney[1], Kayley Lefrancois[1], Virginia Bain[1], Rebecca Gray[1], Michelle Curtis[2], Coby Carlson[2], Scott Schachtele[2], Richard Cho[1]
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Aims: Microglia play a key role in neurodegeneration, including Alzheimer's Disease (AD). Triggering receptor expressed on myeloid cells 2 (TREM2) is a membrane receptor protein genetically linked to AD. Investigating the role of TREM2 and downstream signaling cascades using human-relevant *in vitro* models has been historically challenging but is now accessible using human induced pluripotent stem cell (iPSC) technology and protocols for differentiating into microglia.
Methods: Using highly validated rabbit monoclonal (mAb) antibodies and high-content immunofluorescence, we investigated TREM2 signaling in commercially available iPSC-derived microglia (iCell® Microglia). We first validated iPSC-microglia by staining for established microglial markers (Iba-1, TREM2, CD45), showing that the cells were highly pure and absent of non-microglia markers. We further characterized inflammatory responses using specific signaling readouts as well as inflammation-induced morphological changes.
Results: TREM2, upon ligand binding and activation, interacts with the tyrosine kinase-binding protein DNAX-activating protein 12 (DAP12) to form a receptor-signaling complex. The immunoreceptor tyrosine-based activation motif (ITAM) domain of DAP12 is phosphorylated, recruiting and binding spleen tyrosine kinase (Syk). Syk in turn is phosphorylated, leading to its activation and the mediation of a variety of downstream signaling events. To further investigate microglia TREM2 signaling, we compared TREM2 and DAP12 localization in apparently healthy normal (AHN) iPSC- derived microglia with and without stimulation with lipopolysaccharide (LPS) and IFNγ/TNFα treatment. We then compared the effects of TREM2 on microglial activation using AD-relevant iPSC-microglia, engineered with either a homozygous or heterozygous functional knockout of TREM2.
Conclusions: The antibodies used in this study can be leveraged to characterize iPSC-derived human cultures. Together, these data demonstrate the utility of high-content immunocytochemistry and iPSC-derived microglia for investigating the TREM2-signaling cascade and can be applied to AD research for early discovery and screening.

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SHIFT 01-254

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

REGULATION OF AXL RECEPTOR TYROSINE KINASE BY AMYLOID B MODULATES MICROGLIAL ACTIVITY IN ALZHEIMER'S DISEASE

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Aims: Axl, a member of the TAM receptor tyrosine kinases family, has been reported to be involved in immunological modulation and response to amyloid β (Aβ) of microglial cells. Recent RNA-sequencing data and biomarker studies on Alzheimer's disease (AD) have further suggested an association between Axl signaling and AD pathology. However, the precise mechanisms by which Aβ regulates Axl signaling in microglia remain unclear. This study aims to elucidate: (1) how Aβ regulates Axl signaling in microglia, and (2) the impact of altered Axl signaling on microglial function.
Methods: To investigate this, primary microglia were treated with Aβ to assess its effects on Axl signaling. Axl inhibitor was utilized to block the kinase activity of Axl in Aβ-treated microglia. Lactate assay and Seahorse analysis were employed to evaluate Aβ-induced metabolic changes in microglia, while bead uptake assays were conducted to measure microglial phagocytic activity. Additionally, THP-1 cells were transfected with either wild-type Axl or kinase-dead mutant Axl to further assess the role of Axl kinase activity in response to Aβ.
Results: Our findings revealed that Aβ treatment significantly increased Axl phosphorylation and downstream signaling in microglia. Inhibition of Axl kinase activity attenuated Aβ-induced microglial acute inflammatory responses, including cytokine production and enhanced phagocytic activity. Furthermore, Axl inhibition prevented the Aβ-induced metabolic reprogramming of microglia. Notably, Aβ-mediated Axl signaling was impaired in THP-1 cells expressing the kinase-dead Axl mutant.
Conclusions: These results suggest that Aβ-induced Axl phosphorylation and activation of Axl signaling are crucial for regulating microglial responses to Aβ. Inhibition of Axl kinase activity disrupts Aβ-driven metabolic reprogramming and inflammatory responses of microglia, highlighting Axl as a potential regulator of microglial function in Alzheimer's disease.

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SHIFT 01-255

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

DELETION OF SPI1 IN MICROGLIA EXACERBATES AMYLOID PATHOLOGY BY IMPAIRING MICROGLIAL RESPONSE IN ALZHEIMER'S DISEASE MODELS.

Byungwook Kim[1,2], Mason Tate[1,2], Hande Karahan[1,2], H.R. Sagara Wijeratne[1,2], Ahmad Sharify[1,2], Justin R Kim[1,2], Md Mamun Al-Amin[1,2], Luke Dabin[1,2], Sutha K John[1,2], Jungsu Kim[1,2]
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Aims: Recent human genetic studies have highlighted the potential role of microglial genes and their regulatory functions in the pathogenesis of Alzheimer's disease (AD). The transcription factor PU.1 (encoded by *SPI1*) is expressed mainly in microglia in the central nervous system and has been reported to be a genetic risk factor for AD. However, the role of microglial *SPI1* in AD etiology is still poorly understood.
Methods: Here, we demonstrate that the selective deletion of *Spi1* in microglia exacerbates AD-related pathologies in an amyloid mouse model. Specifically, microglial *Spi1* deficiency increases amyloid deposition, gliosis, and dystrophic neurites, while decreasing the microglial response to plaques. To elucidate the underlying mechanisms, we performed integrative analyses of proteomics data and functional cell biology data.
Results: We found that loss of *Spi1* in microglia impairs phagocytosis function, primarily through a few key signaling proteins. Furthermore, directly activating these proteins rescues the impaired Aβ uptake caused by *Spi1* knockdown, unveiling the potential mechanism of *SPI1* in amyloid pathology.
Conclusions: Our data provide crucial *in vivo* data to guide future therapeutic strategies for AD.

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SHIFT 01-256

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2-3 April 2025

APOE REGULATES THE TRANSPORT OF GM1

Nikolay Dokholyan, Dong Yan Zhang
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Aims: Apolipoprotein E (APOE) is responsible for lipid transport, including cholesterol transport and clearance. While the ε4 allele of APOE (APOE4) is associated with a significant genetic risk factor for late-onset Alzheimer's disease (AD), no mechanistic understanding of its contribution to AD etiology has not been established yet. Monosialotetrahexosylganglioside (GM1) is a crucial lipid component in cell membranes and has been implicated in promoting the aggregation of amyloid beta (Aβ), a key protein associated with AD. Here, we ask whether there are direct interactions between APOE and GM1 that impact AD pathology.
Methods: We employ a multifaceted approach, integrating *in vitro*, *in silico*, and cellular studies to meticulously examine the interaction between GM1 and APOE.
Results: We find that both APOE3 and APOE4 exhibit superior binding affinity to GM1 compared to cholesterol and have an enhanced cellular uptake to GM1 lipid structures than cholesterol lipid structures. APOE regulates the transport process of GM1 depending on the cell type, which is influenced by the expression of APOE receptors in different cell lines and alters GM1 contents in cell membranes. We also find that the presence of GM1 alters the secondary structure of APOE3 and APOE4 and enhances the binding affinity between APOE and its receptor low-density lipoprotein receptor, consequently promoting the cellular uptake of lipid structures in the presence of APOE.
Conclusions: Overall, we find that APOE plays a regulatory role in GM1 transport and the presence of GM1 on the lipid structures influences this transport process. Our studies introduce a plausible direct link between APOE and AD etiology, wherein APOE regulates GM1, promoting Aβ oligomerization and aggregation.

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SHIFT 01-257

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2-3 April 2025

PLASMA LIPID PROFILE IMPAIRMENT IN WOMEN WITH ALZHEIMER'S DISEASE

Laura Ferré González[1], Carmen Peña Bautista[1], Lourdes Álvarez-Sánchez[1], Mar Peretó[1], Lorena García[1], Luis Raga[1], Ana Lloret[2], Miquel Baquero[3], Consuelo Cháfer Pericas[1]
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Aims: This work aims to identify and relatively quantify the main plasma lipids altered in AD women, and correlate them with some demographic, clinical and other biochemical variables.
Methods: For this purpose, a lipidomic mass spectrometry-based method was optimized and applied to 150 plasma samples from a clinical cohort. Then, a quantification approach was developed to determine the relative lipids levels, and their statistically significant differences between AD (n=76) and non-AD (n=74) patients.
Results: As result, fatty acyls family and monoacylglycerol subfamily showed statistically significant differences between groups, being higher in AD. In the other hand, diacylglycerol subfamily showed lower levels in AD. Of 627 lipid variables detected, 45 showed significant differences between the AD and non-AD groups. These lipids correlated with plasma pTau181, Aβ42/40 ratio, glial fibrillary acidic protein, pTau217, all CSF biomarkers, triglycerides, total cholesterol/HDL ratio, weight, age and neuropsychological assessments.
Conclusions: In conclusion, the study identifies significant alterations in the lipid profiles of women with AD, relating some of them with clinical characteristics and clinical factors, and suggesting their relevance to the disease.

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SHIFT 01-258

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2-3 April 2025

MITOCHONDRIAL CALCIUM DYNAMICS: UNVEILING NOVEL MECHANISMS IN MOUSE MODELS OF ALZHEIMER'S DISEASE

Elisa Greotti[1], Nelly Redolfi[2], Mariagrazia Mancuso[1], Bedetta Martina[2], Nikita Arnst[2], Beatrice D'Orsi[3], De Stefani Diego[2], Livia Vignozzi[2], Cristina Spalletti[3], Manuela Allegra[1], Matteo Bruzzone[2], Marco Dal Maschio[2], Rosario Rizzuto[2], Tullio Pozzan[1], Paola Pizzo[2]
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Aims: Mitochondrial calcium signalling is a critical yet poorly understood pathway in Alzheimer's disease (AD) pathogenesis. It plays a key role in ATP production and cytosolic calcium regulation, both of which are essential for proper neuronal function. While mitochondrial dysfunction has been reported in AD models, the causal link between altered mitochondrial calcium handling and the disease remains unclear. Moreover, no studies have explored mitochondrial calcium dynamics in neurons during disease progression or their impact on cytosolic calcium homeostasis. Our research aims to address these gaps by investigating: 1. How mitochondrial calcium alterations contribute to neurodegeneration. 2. The potential of targeting mitochondrial calcium as a therapeutic strategy for AD.
Methods: Using transgenic AD mouse models carrying Presenilin 2 mutations, we employed two-photon imaging to investigate mitochondrial and cytosolic calcium handling in somatosensory cortex slices across presymptomatic, prodromal, and moderate AD stages. Both spontaneous and glutamate-evoked calcium transients were measured, along with synaptic remodelling.
Results: Our findings showed reduced mitochondrial calcium uptake in the early stages of AD, followed by mitochondrial calcium overload in later stages. Similar patterns were observed in cytosolic calcium dynamics, suggesting intrinsic dysfunction in its regulation. This defect is likely due to significant remodelling of glutamatergic transmission pathways in AD mice. Given the complexity and risks of therapeutically targeting the glutamatergic pathway, we are testing a method to restore cytosolic calcium homeostasis by enhancing mitochondrial calcium performance, which has shown promising in vitro results.
Conclusions: Our data indicate that mitochondrial calcium dynamics are altered during AD progression. Since mitochondria serve as a central hub for various cellular signalling pathways, improving mitochondrial calcium function could address multiple pathological processes, positioning mitochondria as a promising therapeutic target for AD.

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SHIFT 01-259

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2-3 April 2025

IRON DISTRIBUTION PATTERNS IN THE ENTORHINAL CORTEX-HIPPOCAMPUS SYSTEM.

Sonja Kagerer[1,2,3], Laetitia Vionnet[4], Jiri Van Bergen[1], Rafael Meyer[1], Anton Gietl[1,2], Klaas Pruessmann[4], Christoph Hock[1,5], Paul Unschuld[3,6]
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Aims: The entorhinal cortex-hippocampus system plays a central role in memory processing and is affected early in aging related neurodegenerative brain disorders such as Alzheimer's disease (AD). Cognitive dysfunction in AD is a result of progressive neuropathological alterations which include non-specific co-pathologies such as accumulation of non-heme iron in vulnerable brain regions. The current study used an experimental high-resolution 7 Tesla magnetic resonance imaging (MRI) setup to characterize iron distribution in hippocampal subfields and entorhinal cortex (EC).
Methods: 40 old-aged participants with full neuropsychological work-up (mean age [SD] 69.2 [7.42] years; 12 MCI, 28 cognitively healthy controls (HC)) underwent 7 Tesla MRI using turbo spin echo scanning for structural imaging and quantitative susceptibility mapping (QSM) for non-heme iron content. Image quality of high resolution ultra-high field MRI data was assured by real-time field control. Gray matter segmentation was performed with FreeSurfer Version 6.0 software. Intraclass correlation coefficients (ICCs) were calculated to characterize consistency of regional hippocampal subfield and EC susceptibility measures.
Results: ICCs for the mean regional susceptibilities were 0.61 for all subjects (n=40), 0.58 for the HC group (n=28), and 0.69 for the MCI group (n=12). Two-sample Kolmogorov-Smirnov test showed a significant difference of the ICCs between the HC and MCI group ($k=0.625$, $p \leq 0.05$).
Conclusions: Our data suggest distinctive patterns of non-heme brain iron distribution in the EC-hippocampus system that characterize MCI. Future studies are needed to confirm whether altered brain iron distribution may serve as potential biomarker of non-specific AD co-pathology.

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SHIFT 01-265

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2-3 April 2025

PERCEPTUAL LEARNING AND NEURAL CORRELATES OF VIRTUAL NAVIGATION IN SUBJECTIVE COGNITIVE DECLINE

Amir Amedi[1], Shahar Shelly[2], Nira Saporta[3], Merav Catalogna[1]
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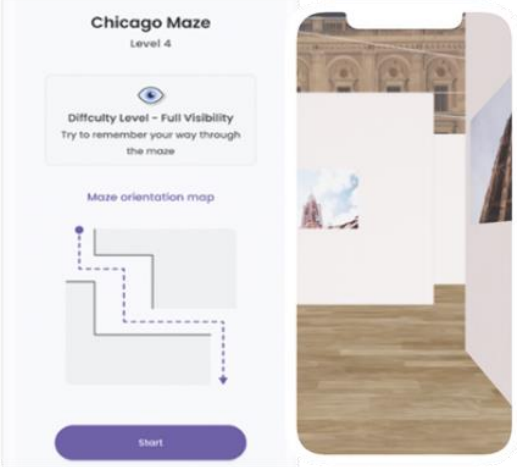
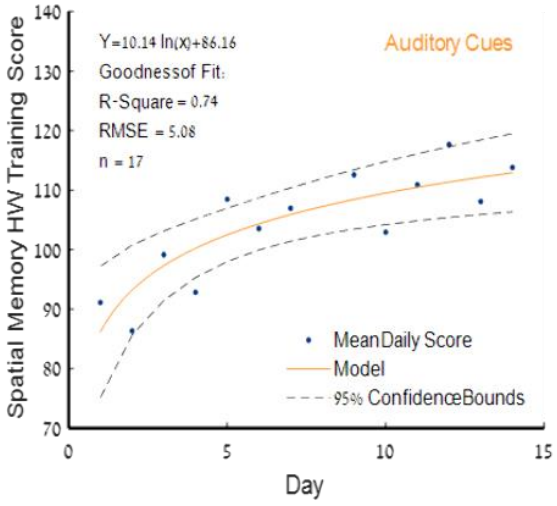
Aims: Spatial memory and navigation abilities are known to decline in both normal and pathological aging, including Alzheimer's disease (AD). We aimed to evaluate the effects of a digital navigation training protocol integrating egocentric and allocentric strategies with multisensory stimulation and visual input masking, on spatial cognition and brain connectivity.
Methods: This was a prospective, open label trial, of healthy adults aged 55-60 with subjective cognitive decline (SCD). Subjects were engaged in a two-week digital intervention using a mobile application, with daily self-training at home. This intervention uniquely incorporated both allocentric and egocentric navigation techniques through digital Hebb Williams (HW) mazes and employed an innovative protocol shifting from visual to auditory cues, with gradual vision masking.Participants were assessed for performance on the mazes using training scores, and changes in the brain's functional connectivity by fMRI.
Results: 17 adults, mean age (SD) 57.2 (1.5) completed the trial. Key results included significant improvement in spatial memory performance, shown as improved HW training score and perpetual learning. An increased connectivity between the medial temporal lobe (MTL), memory-related hub, and executive working memory frontal areas and default mode network (DMN) regions was observed, which was correlated with the spatial memory HW maze training score ($r = 0.508$, $p < 0.05$). Additionally, a significant increase in connectivity was shown between the allocentric and egocentric navigation areas through the retrosplenial complex (RSC) functional connectivity

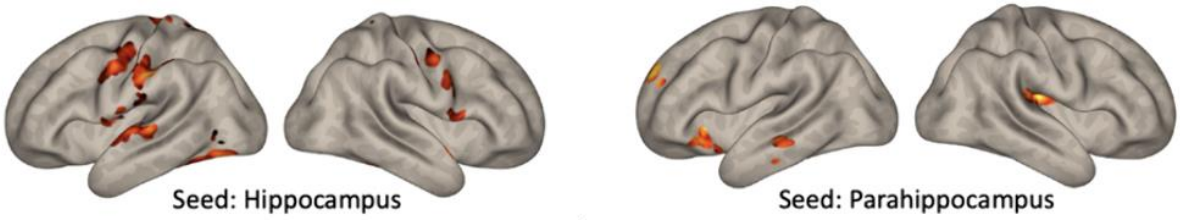
Remepy training mobile application



Perceptual logarithmic learning curve



Seed connectivity maps of longitudinal differences



hub.

Conclusions: These findings suggest that this multisensory cognitive training has the potential to induce perceptual learning and neuroplasticity through key functional connectivity hubs that are the most affected by aging (such as MTL). As spatial memory and navigation abilities are impaired early in AD, such intervention may have benefit in these patients.

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SHIFT 01-266

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2-3 April 2025

BRIDGING SINGLE-NUCLEUS TRANSCRIPTOMIC PROFILES WITH NEURAL NETWORK FUNCTIONS AND LOCOMOTOR BEHAVIORS IN AN ALZHEIMER'S DISEASE MOUSE MODEL

Fred Jiang[1], Stephanie Miller[1], Jie Pan[2], Ayushi Agrawal[3], Patrick Honma[1], Jia Shin[1], Dan Xia[4], Pascal Sanchez[4], Reuben Thomas[3], Inma Cobos[2], Jorge Palop[1]
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Aims: Objective - Alzheimer's Disease (AD) is a neurodegenerative disease characterized by pathological protein deposit in the brain. AD patients show disease-associated transcriptomic alterations in a cell-type-specific manner and display aberrant brain network activities, which eventually leads to behavioral deficits. However, few studies have revealed the relationship between transcriptomic expression at single cell resolution, neural network dynamics, and locomotor activity. The goal of our study is to bridge the transcriptomic profiles from an AD mouse model with brain network functions and animal behaviors to disentangle complex disease mechanisms and to identify therapeutic targets.
Methods: Methods - To systematically investigate how variation in transcriptomic profiles interact with neural network dynamics, we performed single-nucleus RNA sequencing (snRNA seq) on dissected hippocampi sections from AD knock-in (App KI) mice (n=39) following 14-day continuous telemetric electroencephalography recording which includes a readout of mouse locomotor activity. We utilized canonical behavioral tests including Morris Water Maze as well as novel machine-learning based unsupervised approaches to compare behavioral features among the animals.
Results: Results - We identified and quantified disease alterations in theta and gamma band power and detected multiple types of epileptiform spike activities in male and female KI mice, and we observed nocturnal locomotor hyperactivity specifically in female KI animals. Using the snRNA seq data, we found differentially expressed genes in major cell type including interneurons, oligodendrocytes, astrocytes, and microglia, corresponding to locomotive hyperactivity, gamma power alterations, and epileptiform spikes, and performed functional analysis to show potential proteomic pathways relevant to neural network dynamics and altered behaviors.
Conclusions: Conclusions - Our study provides new insights on the mechanistic relationships connecting behavioral alterations, network dysfunction and transcriptomic variations, and may support the development of treatments for AD.

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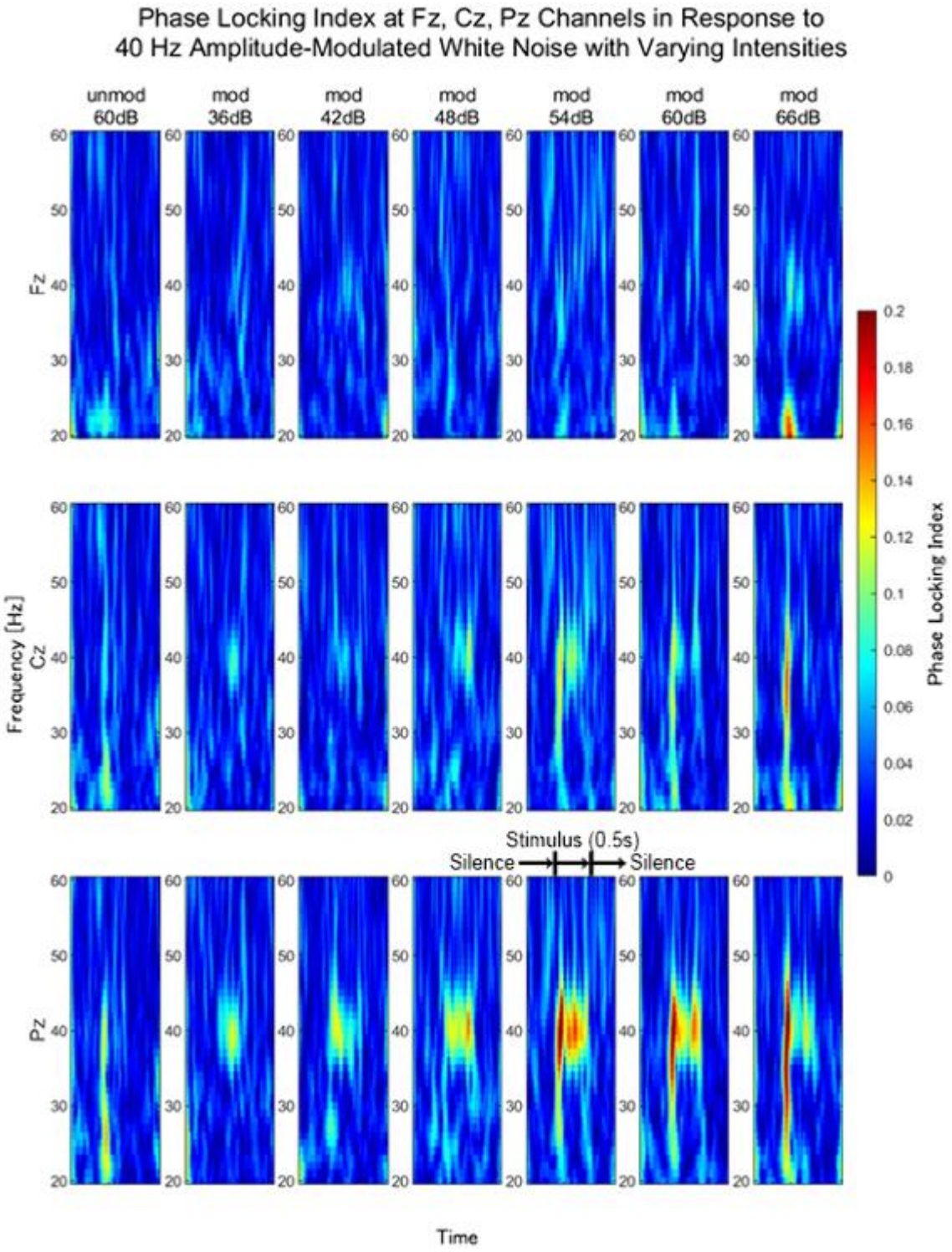
SHIFT 01-267

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / NEURAL NETWORKS, PLASTICITY
2-3 April 2025

INVESTIGATION OF EEG ENTRAINMENT WITH 40HZ AMPLITUDE-MODULATED SOUNDS AT LOW VOLUME

Taiki Kasai, Kazuki Takazawa, Yoshiki Nagatani
Pixie Dust Technologies, Inc., Development Function, Tokyo, Japan

Aims: 40Hz gamma entrainment using sensory stimuli (GENUS) is considered a potential tool against dementia. This study aimed to investigate whether 40Hz amplitude-modulated sounds below 54dB elicit higher EEG entrainment compared to unmodulated sounds.
Methods: Twenty-four participants were exposed to three types of auditory stimuli under open-eye conditions. Stimuli included a 1kHz sinusoidal wave with 100% amplitude modulation at 40Hz (36, 42, 48, 54, 60, 66dB), an unmodulated 1kHz sinusoidal wave at 60dB, white noise with 100% amplitude modulation at 40Hz (36, 42, 48, 54, 60, 66dB), unmodulated white noise at 60dB, and a 40Hz pulse train (36, 42, 48, 54, 60, 66dB). Each stimulus was presented 50 times for 0.5 seconds via insert earphones while participants watched a silent cartoon. EEG was recorded from Fz, Cz, and Pz. The pulse train's loudness was adjusted using a psychological matching test at 60dB. The experiment was approved by the Ethics Review Committee of Pixie Dust Technologies, Inc.
Results: No significant entrainment was observed for the 1kHz sinusoidal wave with 40Hz modulation at Fz. Significant entrainment was observed for white noise at all levels (36-66dB) and for the 40Hz pulse train at 48-66dB. At Cz, the 1kHz sinusoidal wave showed no significant entrainment, while white noise demonstrated significant entrainment at all levels and the pulse train at 54-66dB. At Pz, significant entrainment was observed for the 1kHz sinusoidal wave at 54-66dB, for white noise at all levels, and for the



pulse train at 48-66dB.

Conclusions: These results suggest amplitude-modulated sounds and pulse trains below 54dB can increase EEG entrainment, particularly in response to white noise and pulse trains. This highlights the brain's sensitivity to low-volume modulated sounds, including frontal areas.

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SHIFT 01-270

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
2-3 April 2025

EFFECT OF THE TREM2 R47H VARIANT ON SYNAPTIC TRANSMISSION IN HIPPOCAMPAL PYRAMIDAL NEURONES IN YOUNG MICE.

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University College London, Neuroscience, Physiology And Pharmacology, London, United Kingdom

Aims: It is well-established that the *TREM2* R47H variant raises the risk of development of Alzheimer's disease up to four-fold. Nevertheless, the exact cellular mechanisms that cause this risk are yet to be determined. Since TREM2 is a microglial receptor involved in their phagocytic activity, important for the refinement of synapses during development, we wanted to study how impaired microglial function can alter basal synaptic transmission in young mice, pre-weaning.
Methods: We used whole-cell voltage patch-clamp to record spontaneous and miniature postsynaptic currents from CA1 neurones in acute hippocampal slices from pre-weaned mice, aged 18-22 days. In addition, evoked CA3-CA1 synaptic currents paired-pulse ratios were calculated.
Results: We found that the *Trem2* R47H variant had a near significant increase in the frequency of spontaneous excitatory postsynaptic currents without affecting inhibitory inputs and without affecting miniature excitatory postsynaptic currents. Additionally, we could not find a significant change in paired-pulse ratios of evoked excitatory post-synaptic currents with the variant.
Conclusions: Increased frequency of spontaneous excitatory postsynaptic currents may be a result of reduced synaptic pruning during development, brought about by impaired phagocytosis in the *Trem2* mutants. In addition, there may be increased excitability of CA3 neurones. Together, these findings provide insight into how the *Trem2* R47H variant changes synaptic transmission during early postnatal age, which could enhance our understanding of how the variant increases the risk of developing Alzheimer's disease. These findings, along with our ongoing research on aged mice, could help us develop a better mouse model for Alzheimer's disease, opening doors to novel therapeutic approaches.

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SHIFT 01-271

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
2-3 April 2025

NOTCH-SPARING PRESENILIN 1 MUTATION'S EFFECTS ON BEHAVIOUR AND THE HIPPOCAMPAL AND CORTICAL SYNAPSE

Isabel Bestard Lorigados[1], Qinxin Zhu[2], Keenan Sterling[1], Weihong Song[1,2]
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Aims: Presenilin 1 (PS1) mutations are the main cause of familial Alzheimer's disease (AD), leading to increased amyloid beta levels and inhibition of Notch cleavage and signalling. Recent research in our lab identified a distinct mutation, $PS1_{\Delta S169}$, which does not impact Notch signalling, making it a promising target for therapeutic intervention. Our study aims to investigate the mechanisms through which $PS1_{\Delta S169}$ influences AD pathogenesis, focusing on behaviour and synaptic activity in the hippocampus and cortex.
Methods: This project involved three experimental groups: two knockin mouse models with different PS1 mutations, $PS1_{\Delta S169}$ and $PS1_{C410Y}$, and a wild-type control. We utilized Western Blots to assess the protein expression of four synaptic markers in the hippocampus and cortex, and we conducted behavioural tests such as Morris Water Maze, Y-maze, and Fear conditioning.
Results: Our results reveal significant alterations in several synaptic markers in our PS1 knockin models, indicating an overall increase in synaptic markers in 7-month-old mutant mice compared to wild-type mice. Furthermore, learning and memory-related behaviours were significantly different in our $PS1_{\Delta S169}$ knockin models compared to the control.
Conclusions: These results provide novel insights into the pathological effects of the PS1 mutations on the synapse, as well as their impact on behaviour, independently of plaque formation. These findings provide a foundation for further defining how the Notch-sparing PS1 mutations affect the AD pathogenesis process.

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SHIFT 01-272

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
2-3 April 2025

UTILITY OF HUMAN IPSC-DERIVED NEURONAL MODEL FOR EVALUATING SYNAPTIC BINDING OF AMYLOID BETA OLIGOMERS

Elizabeth Johnson[1], Hannah Maxwell[2], Miriam Scarpa[2], James Smith[2], Aitor Martinez-Zarate[2], Omar De Leon Velez[3], Kirsten Viola[3], James Cruse[4], Sanofar Abdeen[4], William Klein[3], Jasna Jerecic[1], Erika Cline[1]
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Aims: Understanding the roles of soluble amyloid beta (Aβ) conformers in Alzheimer's disease (AD) is key to developing well-targeted therapeutics. Synaptotoxicity, which correlates well with cognitive decline, of specific Aβ conformers may be directly measured in non-diseased cell cultures. This has been well-established for Aβ oligomers (AβOs) using primary rodent neurons. The next challenge is translation to human biology, due to potential differences in AβO binding sites. Previously, we demonstrated synaptic binding of synthetic AβOs to non-demented human iPSC-derived neurons. Here we examine brain-derived AβO binding and antibody-based neutralization in iPSC-derived neurons and compare our findings to literature observations in rodent neurons.
Methods: Human iPSC-derived neurons from non-demented control donors were generated and matured to ~70 days *in vitro*. Exogenous AβOs (synthetic or from human AD brain extract) were applied for 0.5-4h. For neutralization studies, AβOs were first preincubated with antibodies for 1h. Immunofluorescent co-labeling used antibodies against Aβ N-terminus (3D6), AβOs (2B4.6), synapses (drebrin), and neuronal soma/dendrites (MAP2). Binding was analyzed by high-content imaging.
Results: As described in rodent neurons, we observed punctate AβO binding colocalized with the synaptic marker drebrin, plus larger areas of AβO signal near the cell soma. Our findings with human neurons aligned with those published in rodent neurons except the puncta density observed was lower in human neurons. AβOs, both synthetic and AD-brain-derived, bound to synapses within 1h. Binding of synthetic AβOs to human neurons was neutralized by preincubation with the AβO-selective antibody sabirnetug (ACU193).
Conclusions: We observed robust binding of AβOs to human iPSC-derived neurons, demonstrating competent synaptic binding sites, synapse-binding AβO in AD brain extract, and neutralization of AβO binding by sabirnetug, an immunotherapeutic currently being tested in the phase 2 ALTITUDE-AD study.

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SHIFT 01-278

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
2-3 April 2025

EXPLORING BIOLOGICAL PATHWAYS RELATED TO ALZHEIMER'S DISEASE SUBTYPES WITH DIFFERENT LONGITUDINAL TRAJECTORIES USING RNA-SEQ DATA

Min Soo Byun[1,2], Sangyong Park[2], Dahyun Yi[3], Hyejin Ahn[4], Gijung Jung[3], Heyji Choi[2], Jaeyoung Bae[5], Yu Kyeong Kim[6,7], Yun-Sang Lee[6], Koung Mi Kang[8,9], Chul-Ho Sohn[8,9], Jun-Young Lee[1,10], Tamina Park[11,12], Yunlong Liu[13,14,15], Andrew Saykin[11,12,15], Kwangsik Nho[11,12,16], Dong Young Lee[1,2,3,4]
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Aims: It remains unclear which biological pathways are involved in the progression trajectories among cognitively impaired (CI) individuals who already have both beta-amyloid (Aβ) deposition and AD-related neurodegeneration (A+N+). We explored potential biological pathways associated with differential longitudinal clinical trajectories among A+N+ CI individuals using transcriptomic data from blood.
Methods: CI older adults with mild cognitive impairment (MCI) or mild AD dementia were recruited from the KBASE cohort, Seoul, Korea, and those who were A+N+ based on ^{11}C-PiB PET, ^{18}F-FDG PET, and MRI were included in the analysis. Group-based trajectory modeling (GBTM) was applied using the Clinical Dementia Rating Sum of Boxes scores measured at baseline and over a follow-up period of up to four years. RNA sequencing was conducted on bulk RNA from whole blood samples, followed by the application of WGCNA and over-representation analysis (ORA) using KEGG pathway database.

Results: Two AD subtypes with different longitudinal trajectories were identified among A+N+ CI individuals using GBTM—one with slow progression (A) and the other with rapid progression (B), with RNA-seq data available for 56 of these individuals (N=40 for cluster A; N=14 for cluster B). The conversion rate for MCI to AD dementia in each cluster was 33% and 100%, respectively. We detected a gene co-expression network module significantly associated with these AD subtypes after adjusting for demographic variables and APOE4 carrier status (FDR $p<0.1$). ORA found several biological pathways, including mitophagy, endocystosis, phagosome, ubiquitin-mediated proteolysis, platelet activation, and regulation of actin cytoskeleton.

Conclusions: Our finding suggests potential biological pathways related to variations in progression trajectories among A+N+ CI older adults. Further research is necessary to elucidate the molecular mechanisms linking these pathways and functional progression in individuals with AD.

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SHIFT 01-279

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
2-3 April 2025

POSTERIOR CINGULATE CORTEX MICRORNA DYSREGULATION DISTINGUISHES COGNITIVE RESILIENCE, MILD COGNITIVE IMPAIRMENT, AND ALZHEIMER'S DISEASE

Scott Counts[1,2], John S. Beck[1], Bryan Maloney[3], Michael Malek-Ahmadi[4,5], Stephen D. Ginsberg[6,7], Elliott Mufson[8], Debomoy Lahiri[3]
[1]Michigan State University, Department Of Translational Neuroscience & Family Medicine, Grand Rapids, United States of America, [2]University of Michigan, Michigan Adrc, Ann Arbor, United States of America, [3]Indiana University School of Medicine, Departments Of Psychiatry And Medical And Molecular Genetics, Indianapolis, United States of America, [4]Banner Alzheimer's Institute, Phoenix, United States of America, [5]University of Arizona College of Medicine-Phoenix, Department Of Biomedical Informatics, Phoenix, United States of America, [6]Nathan Kline Institute, Center For Dementia Research, Orangeburg, United States of America, [7]New York University Grossman School of Medicine, Departments Of Psychiatry, Neuroscience & Physiology, And The Nyu Neuroscience Institute, New York, United States of America, [8]Barrow Neurological Institute, Departments Of Translational Neuroscience And Neurology, Phoenix, United States of America

Aims: MicroRNA (miRNA) control of mRNA stability and transcription is increasingly appreciated as a key regulator of pathophysiologic pathways in Alzheimer's disease (AD). However, the role of miRNAs during the progression of AD, including prodromal syndromes such as mild cognitive impairment (MCI) and resilience, remains underexplored. To help understand which miRNAs–as well as their putative mRNA targets and associated functional pathways–are altered in AD progression, we sequenced miRNA transcripts in postmortem tissue obtained from the posterior cingulate cortex (PCC), a key hub of the resting-state default mode network (DMN).

Methods: We performed miRNA-sequencing on PCC samples obtained postmortem from Rush Religious Orders Study participants diagnosed antemortem with no cognitive impairment (NCI), MCI, or AD. NCI subjects were subdivided as low pathology (Braak stage I/II) or high pathology (Braak stage III/IV), suggestive of resilience. Bioinformatics approaches included differential expression, mRNA target prediction, interactome modeling, functional enrichment, and AD risk modeling.
Results: We identified specific miRNA groups and mRNA targets differentiating AD, MCI, resilience, antemortem neuropsychological test performance, and postmortem neuropathological burden. Select microRNAs were also associated with AD risk, with age but not *APOE* status as a significant covariate. MicroRNA-mediated pathways related to clinical diagnosis, cognitive and pathologic variables, or disease risk included insulin, prolactin, kinase signaling, protein turnover, and neurite plasticity.

Conclusions: These data from a key, vulnerable limbic region of the DMN provide new insights into the putative molecular mechanistic roles of miRNAs in AD risk, pathophysiology, and resilience. In parallel to functional studies, they add to a growing body of literature underscoring the potential of harnessing miRNA activity to manipulate disease-modifying pathways associated with AD and related dementias, with implications for precision medicine.

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SHIFT 01-280

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
2-3 April 2025

SINGLE CELL GENE EXPRESSION CHANGES UNDERLIE ABCA1 DEFICIENCY RESPONSES IN HUMAN APOE EXPRESSING MOUSE MODELS.

Nicholas Fitz, Yi Lu, Iliya Lefterov, Radosveta Koldamova
University of Pittsburgh, Eoh, Pittsburgh, United States of America

Aims: ATP-binding cassette transporter A1 (ABCA1) regulates cholesterol and phospholipid efflux to lipid-poor apolipoproteins with *Abca1* deficiency causing decreased APOE lipidation and increased catabolism. We previously shown that ABCA1 deficiency in Alzheimer's disease mouse models modulates amyloid pathology and associated pathological changes and this can be further modulated by human APOE isoform status. Recent GWAS studies identified gene variants of *ABCA1* that increase the risk of Late Onset Alzheimer's disease (AD). We hypothesize that ABCA1 regulates lipid efflux and CNS inflammatory responses, following an APOE isoform dependent manner, ultimately affecting the metabolism of Aβ.
Methods: We used APP/PSEN1dE9 mice expressing human APOE3 or APOE4 (APP/E3 or APP/E4) haplodeficient on *Abca1* (APP/E3/het, and APP/E4/het) and their non-APP WT littermates at 7 months of age, and performed single-cell RNA sequencing and assessed gene expression profiles. Transcriptional responses will be validated through FISH staining.
Results: With a total of 18,6254 cells, we identified 16 clusters. The main effects of Abca1 deficiency were observed in microglia and astrocytes. After re-clustering of microglia, we identified two clusters associated with homeostatic and two clusters of disease associated microglia (DAM). Lack of one copy Abca1 led to a significant increase of number of cells in DAM clusters in both APP/E4 and APP/E3 mice but did not have a significant effect in non-APP mice. Abca1 deficiency also increased the number of differentially expressed DAM genes between APP/E3 and APP/E4. The results for the most prominent Abca1 targets were validated using Fluorescence in situ hybridization.
Conclusions: We identified presence of two distinct subtypes of microglia and three subtypes of astrocytes, which demonstrated that Abca1 deficiency had varying impact on the transcriptome, dependent on the APOE isoform and amyloid pathology, related to phospholipids and myelin metabolism.

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SHIFT 01-283

Poster on Board - Shift 01
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS
2-3 April 2025

DISRUPTION OF THE NEURONAL RENIN-ANGIOTENSIN SYSTEM RESULTS IN BLOOD-BRAIN BARRIER LEAKAGE AND SELECTIVE VASCULAR LOSS IN THE HIPPOCAMPUS

Leah Cuddy, Mitchell Zagardo, Sohee Jeon, Miranda Salvo, Jelena Popovic, Robert Vassar
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Aims: Angiotensin I converting enzyme (ACE1) maintains blood pressure homeostasis by converting angiotensin I into angiotensin II (angII) in the renin-angiotensin system (RAS). AngII is a vasoconstrictive peptide with beneficial and pathological physiological properties that are mainly mediated through the angII type 1 receptor (AT1R). AT1R blockers (ARBs) and ACE1 inhibitors (ACEis) barrier are commonly prescribed as a first-line treatment for hypertension. Many ACEis and ARBs cross the blood brain barrier, and an intrinsic brain RAS regulates complex cognitive functions including learning and memory. ACE1 and AT1R have been implicated in neurodegenerative disorders including Parkinson's disease and Alzheimer's disease (AD) but the mechanisms remain incompletely understood.
Methods: To better understand the roles of neuronal ACE1 and AT1R, we generated two novel mouse models: ACE1 conditional knockout (cKO) mice and AT1R cKO mice, each lacking ACE1 or AT1R expression specifically in hippocampal and cortical excitatory neurons.
Results: ACE1 cKO mice exhibited hippocampus-dependent memory impairment in the Morris water maze, y-maze, and fear conditioning tests. Despite similar reductions in total ACE1 level in both the hippocampus and cortex, the RAS pathway was dysregulated in the hippocampus only. Importantly, ACE cKO mice exhibited age-related capillary loss selectively in the hippocampus. AT1R cKO mice display BBB disruption, shown as the perivascular aggregation of blood plasma protein fibrinogen. These preliminary data strongly suggest a novel role for neuronal ACE1/AT1R signaling in regulating the cerebrovascular system.
Conclusions: Here, we show selective vulnerability of the hippocampal microvasculature and RAS pathway to neuronal ACE1 and AT1R knockout. Our results provide important insights into the function of ACE1/AT1R signaling in the brain and demonstrate a connection between neuronal RAS and cerebrovascular function in the hippocampus.

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SHIFT 01-285

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / AMYLOID CLEARANCE
2-3 April 2025

IDENTIFICATION OF MOLECULAR CORRELATES WITH CT1812 TREATMENT-RELATED DECREASE IN NFL CSF LEVELS CONNECTED TO SIGMA-2 2RECEPTOR

Valentina Di Caro[1], Eunah Cho[1], Britney Lizama[1], Kiran Pandey[2], Duc Duong[2], Nicholas T. Seyfried[3], Kaj Blennow[4], Henrik Zetterberg[4], Michael Grundman[5], Anthony Caggiano[1], Mary Hamby[1]
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Aims: Neurofilament light (NfL) is a recognized biomarker of neurodegeneration, in which CSF levels are elevated in multiple neurodegenerative disorders, including Alzheimer disease (AD). Previously we reported a decrease in CSF NfL levels in AD patients treated with the sigma-2 receptor (S2R) modulator CT1812 in the SHINE Ph2 trial relative to placebo. An exploratory proteomic biomarker analysis for SHINE was performed to identify proteins and pathways that correlated with changes in CSF NfL levels.
Methods: SHINE (COG0201) was a Phase 2 randomized, double-blind, placebo-controlled trial. Participants (N=152) received a daily oral dose of CT1812 (100 or 300 mg) or placebo for 6-months. NfL in CSF was measured by Lumipulse (N=65). TMT-mass spectrometry proteomics was performed on CSF at baseline and end of the study. Pearson correlation analysis was performed between NfL levels and CSF proteomes (N=43, $p \leq 0.05$). Pathway analysis was performed using STRING to identify gene ontology (GO) term ($p \leq 0.05$).
Results: Proteins were identified to be significantly correlated ($p \leq 0.05$) with CSF NfL levels. Correlated proteins included NEFL (r=0.51), FABP3 (r=0.66), S100B (r=0.59) and OLFM3 (r=-0.60) all related to neurodegeneration. NfL (NEFL) identified among the top correlates also validates the TMT-MS proteomics as a quantitative method. Correlated proteins ($p \leq 0.05$) were associated to GO terms "Postsynaptic intermediate filament cytoskeleton" (NEFM, r=0.49)."Extracellular space" (CADPS r=0.69) and "Vesicle" (RAB4, r=-0.47).
Conclusions: Molecular correlates relevant to neurodegeneration were identified with CSF NfL levels after treatment with CT1812. Of note NEFL can interact with prion protein (PRNP), which is a component of the S2R complex. This analysis enabled additional learnings on what other changes may occur in tandem with the decrease in NfL. These findings are consistent with an impact of CT1812 on neurodegeneration through a S2R mechanism of action.

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SHIFT 01-289

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING
2-3 April 2025

SAFETY AND EFFICACY OF MELATONIN, CLONAZEPAM, AND TRAZODONE IN PATIENTS WITH PARKINSON'S DISEASE AND SLEEP DISORDERS: A RANDOMIZED, DOUBLE-BLIND TRIAL

Vajiheh Aghamollaii
Tehran Uiversity of Medical Sciences, Neurology, Tehran, Iran

Aims: Sleep disturbances are common non-motor symptoms of Parkinson's disease (PD). We aimed to compare the safety and efficacy of trazodone with melatonin and clonazepam in patients with PD and sleep complaints.
Methods: This single-center, double-blind, randomized clinical trial was conducted on PD patients with subjective sleep complaints. Eligible patients were randomized 1:1:1 to receive melatonin 3 mg/day, clonazepam 1 mg/day, or trazodone 50 mg/day for 4 weeks. The primary outcome measure was the changes in Pittsburgh Sleep Quality Index scores. The mean change in Epworth Sleepiness Scale and RBD screening questionnaire was considered as the secondary outcome measures.
Results: There was a significant decrease in PSQI scores after 4 weeks of treatment in all groups. The mean changes of PSQI from baseline were similar among the treatment arms . Mean changes of RBDSQ and ESS from baseline were significantly different between study arms. Melatonin intake was associated with a higher decrease in RBDSQ score compared to trazodone and clonazepam. Trazodone intake was associated with a higher decrease in ESS score compared to clonazepam.
Conclusions: There was a significant decrease in PSQI scores after 4 weeks in all groups. The mean changes of PSQI from baseline were similar among the treatment arms ($P = 0.325$). Mean changes of RBDSQ and ESS from baseline were significantly different between study arms ($P < 0.05$). Melatonin intake was associated with a higher decrease in RBDSQ score compared to trazodone ($P = 0.011$) and clonazepam ($P = 0.004$). Trazodone intake was associated with a higher decrease in ESS score compared to clonazepam ($P = 0.010$). Mild adverse events were reported in three patients in the clonazepam, two patients in the trazodone group, and none in the melatonin group.

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SHIFT 01-290

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING
2-3 April 2025

IDENTIFICATION OF SIGMA-2 RECEPTOR ANTAGONISTS AS NOVEL THERAPEUTICS FOR ALZHEIMER'S DISEASE THROUGH INTEGRATED PHARMACOPHORE-BASED VIRTUAL SCREENING AND MOLECULAR MODELLING APPROACH

Powsali Ghosh, Jatin Jangra, Nilesh Bajad, Sushil Kumar Singh
Indian Institute of Technology (BHU) Varanasi, Department Of Pharmaceutical Engineering & Technology, Varanasi, India

Aims: This study aimed to find novel sigma-2 receptor inhibitors to combat neuroinflammation in Alzheimer's Disease.
Methods: A comprehensive dataset of compounds was constructed from five different databases and virtually screened using a pharmacophore mapped from a sigma-2 antagonist (i.e., 'ZNC' of PDB ID: 7M95). OpenBabel was employed to remove duplicates based on InChI code and the KNIME analytics platform was used to eliminate compounds that violated the 'Lipinski Rule of Five', contained PAINS and Brenk fragments, or had a TPSA above 60 $Å^2$. Only diverse molecules, determined by Tanimoto distance using the MaxMin algorithm, were retained. Also, non-BBB permeable compounds, as predicted by SwissADME, were removed. HTVS and molecular docking studies were performed to obtain compounds exhibiting better binding affinity than standard ligand ZNC. *In silico* ADMET studies, conducted using ADMETlab and PreADMET, only retained molecules showing acceptable physicochemical properties. The best virtual hits were subjected to molecular dynamics simulations (MDS) in GROMACS to assess the stability of the protein-ligand complexes under conditions mimicking human cells.
Results: The initial dataset of 64,415,728 compounds yielded 16,864 hits through pharmacophore-based screening. After removing 4,053 duplicates, 12,811 unique compounds were identified, with 1,373 exhibiting drug-like properties. A molecular diversity filter reduced this to 250 diverse hits, 8 of which were BBB-impermeable. HTVS and molecular docking identified 15 compounds exhibiting superior binding affinities to ZNC. Three compounds (ZINC000184959872, MolPort-046-745-161, and ZINC001704299697) exhibited high selectivity for the sigma-2 receptor and are predicted to be bioavailable, BBB-permeable, and non-toxic. MDS (200 ns) and MMPBSA analysis confirmed their stable protein-ligand complexes.
Conclusions: The study identified three selective sigma-2 receptor ligands (ZINC000184959872, MolPort-046-745-161, and ZINC001704299697) with favourable drug-like properties and stable protein-ligand complexes, making them promising candidates for further development.

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SHIFT 01-291

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING
2-3 April 2025

INVESTIGATION OF THE RELATIONSHIP BETWEEN THIAMINE AND COGNITIVE FUNCTION AND CEREBRAL BLOOD FLOW IN ALZHEIMER'S DISEASE

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Aims: Previous studies have suggested that vitamin B supplementation may benefit cognitive impairment. This study examined the effects of thiamine (Vitamin B1) on cognitive function and cerebral blood flow in patients with Alzheimer's disease.
Methods: The study, conducted between 2016 and 2019, involved 71 patients (aged 52-93) who visited our memory clinic. These patients were diagnosed with either Alzheimer's disease (AD group) or mild cognitive impairment due to Alzheimer's disease (MCI group). Each patient underwent a comprehensive evaluation, including a detailed neuropsychological assessment using the Mini-Mental State Examination (MMSE), a brain perfusion SPECT to assess regional cerebral blood flow and a measurement of blood thiamine concentration. We then analyzed the relationships between these parameters.
Results: Our study revealed significant associations between MMSE scores and blood thiamine concentrations in the attention, calculation, and language subscales of the AD group. Brain perfusion SPECT showed a significant correlation between blood thiamine concentration and the right callosomarginal area in the AD group. Furthermore, we observed significant associations between blood thiamine concentration and regional cerebral blood flow in the left hippocampus and right thalamus in the MCI group.
Conclusions: These results suggest that thiamine is associated with regional cerebral blood flow and cognitive function in AD and MCI. These findings provide valuable insights into the potential role of thiamine in Alzheimer's disease. Thiamine intervention may be helpful in maintaining memory function in AD patients.

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SHIFT 01-293

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS
2-3 April 2025

WY40687 REDUCES ALPHA-SYNUCLEIN AGGREGATES IN THE BRAIN AND COGNITIVE IMPAIRMENT IN A NON-HUMAN PRIMATE MODEL

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Aims: We tested a naturally occurring molecule, WY40687, to determine if it can protect against cognitive decline and loss of executive function in an non-human primate model of Parkinson's disease dementia.
Methods: We induced alpha-synuclein misfolds and Lewy bodies in marmosets through chronic dietary exposure to beta-methylamino-L-alanine (BMAA) as well as co-exposure to BMAA and WY40687, a potential therapeutic molecule. We assessed the density of misfolded pS129 alpha-syn and Lewy bodies as well as executive cognitive function using the Detour-Reaching Task (DRT).
Results: Cognitive decline did not occur in control animals and those treated with BMAA combined with WY40687. All other animals treated with BMAA exhibited marked cognitive decline ($p=0.018$) with the interaction between group and sex also significant ($p=0.022$). Chronic dietary exposure to BMAA increased alpha-syn misfolds as much as nine-fold. The BMAA plus WY40687 group had both the best mean DRT test score and the lowest density of alpha-syn misfolds. We found that BMAA induced region-specific toxicity and increased pS129 alpha-syn expression in the frontal cortex, parietal cortex, hippocampus, and spinal cord. In the spinal cord, pS129 alpha-syn immunostaining was observed in both the anterior, lateral and posterior horns and displayed morphology and anatomical distribution reminiscent to that observed in PD.
Conclusions: These data suggest that WY40687 should be clinically evaluated. We suggest that WY40687 be considered for use during the prodromal period in PD which can start as early as 20 years before a clinical diagnosis, as well as in advanced PD stages to slow the conversion of PD patients to PD-Mild Cognitive Impairment (PD-MCI) and conversion of PD-MCI patients to PD-Dementia.

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SHIFT 01-294

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS
2-3 April 2025

A 12-WEEK, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-DESIGN CLINICAL TRIAL FOR THE EVALUATION OF THE EFFICACY AND SAFETY OF AMINOTHIONEINE ON THE IMPROVEMENT OF MEMORY MANAGEMENT

Myeong-Il Han[1], Seung-Ho Ryu[2]
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Aims: Aminothioneine, prepared from the extract of a product derived from golden oyster mushrooms (*Pleurotus cornucopiae* var. *citrinopileatus*), has been suggested to improve brain function by increasing and maintaining BDNF levels in the brain. This study aimed to evaluate the efficacy and safety of Aminothineine in the mildly cognitively impaired but not dementia.
Methods: This study was randomized, double-blind, placebo-controlled, and parallel-designed. Participants were between the ages of 50 and 75, and considering gender, age, and education level, at least one of the word list memory, word recall, and word re-recognition tests has a standardized score of -1.0 or less in the CERAD-K. They were randomized to Aminothioneine 800mg or placebo, for 12 weeks. The primary outcome measure was the Korean version of MoCA at 12 weeks. Secondary outcome measures were the Verbal Learning Test, Visual Continuous Performance Test (CPT), and Digit Span Test in computerized neurocognitive test (CNT), Subjective Memory Complaints Questionnaire (SMCQ), and BDNF (ng/ml) in serum.
Results: Aaminothioneine 800mg(n=43) increased the MoCA-K score compared to baseline (1.43±2.38), but in the control group, the MoCA-K score decreased (-0.08±2.14), showing a significant difference between the two groups ($p<0.001$). In the Verbal Learning Test, the Aminothionein increased more than the control, showing a difference between the two groups ($p<0.001$). However, no significant difference was found between the two groups in Visual CPT, Digit Span Test, SMCQ, and serum BDNF (ng/ml). In the safety measure, 4 in the test group and 11 in the control group experienced adverse reactions. Three patients had adverse reactions due to drugs, but symptoms were not severe.
Conclusions: Aminothionein increased the score of MoCA-K and Verbal Learning Test after 12 weeks, suggesting that Aminothionein may improve memory functioning, and was well tolerated.

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SHIFT 01-295

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS
2-3 April 2025

SPECTRIS™ TREATMENT PRESERVES CORPUS CALLOSUM STRUCTURE IN ALZHEIMER'S DISEASE: A COMPARATIVE STUDY

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Aims: We compared the impact of SPECTRIS™ treatment on corpus callosum structure using active treatment participants from the Overture Phase II trial and matched Alzheimer's Disease Neuroimaging Initiative (ADNI) controls.
Methods: Structural magnetic resonance imaging (MRI) data from the OVERTURE trial (NCT03556280) participants, who received daily 1-hour sessions of 40Hz gamma sensory stimulation, and controls from the ADNI database with baseline, Month 3, and Month 6 MRI data were utilized. To ensure baseline comparability with ADNI controls, OVERTURE participants with Mini-Mental State Examination (MMSE) scores of 21-26 were selected. ADNI controls were matched based on a 3d baseline distribution of age, MMSE scores, and total corpus callosum area, resulting in 22 active Overture participants and 71 ADNI controls. MRI assessments of total corpus callosum area and its subregions was performed for all visits. The baseline-matched populations showed no statistically significant differences in age, MMSE scores, or areas of interest in the total/subregion corpus callosum.
Results: After six months, the active treatment group showed a total corpus callosum area change of 0.58±0.43%. In contrast, the baseline-matched ADNI control group exhibited a change of -0.91±0.26%. The difference between the two groups (1.49±0.51%, $p<0.004$) was statistically significant. Significant differences were also observed across specific subregions of the corpus callosum, including the genu/rostrum (1.52±0.54%, $p<0.006$), anterior-body (1.69±0.74%, $p<0.025$), posterior-body (1.93±0.95%, $p<0.045$), and splenium (1.25±0.48%, $p<0.010$). The mid-body difference (0.94±0.77%) was not statistically significant.
Conclusions: We previously demonstrated that SPECTRIS™ treatment significantly reduced corpus callosum atrophy over 6 months compared to sham treatment in the OVERTURE Phase II trial. This analysis demonstrated preservation of corpus callosum integrity in active participants vs. matched ADNI controls. We plan to confirm these observations in the ongoing HOPE pivotal trial (NCT05637801).

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SHIFT 01-296

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
2-3 April 2025

INCREASING STATISTICAL POWER OF EARLY ALZHEIMER'S DISEASE CLINICAL TRIALS WITH THE AD-PX PROGNOSTIC MODEL

Angela Tam, César Laurent, Adrián Noriega, Christian Dansereau
Perceiv AI, Montreal, Canada

Aims: In Alzheimer's disease trials, many participants remain stable, which reduces power to detect treatment effects on clinical outcomes. We explored how to increase statistical power by enriching for decliners with a prognostic model.
Methods: In amyloid-positive early AD ADNI (adni.loni.usc.edu) participants, we calculated the mean and standard deviation of change on CDR-SB over 24 months. With these parameters, we estimated sample size requirements for two-arm placebo-controlled trials to detect 30% slowing on CDR-SB progression over 24 months at 80% and 90% power. These sample size estimates served as benchmarks for a typical trial without enrichment of decliners. We identified a subcohort of likely decliners using AD-Px, a model that uses demographics, APOE4, and clinical assessments to predict risk of decline. We then quantified enrichment-related increases in statistical power.
Results: The full cohort had a mean (std) change of +1.59 (2.4) points on the CDR-SB, requiring 752 participants to provide 80% power (95% CI [72, 86]) in a typical trial. The subset of likely decliners had a larger change of +2.36 (2.7) points. Consequently, enriching a trial with 752 likely decliners yielded 94% [90, 97] power (+14% power). For a typical unenriched trial to obtain 94% power, 450 additional participants were needed (+60% in sample size). To obtain 90% [85, 93] power in a typical trial, 1006 participants were required. An enriched trial of the same size yielded 98% [97, 99] power (+8% power). At this power level, a typical trial required 602 additional participants (+60% in sample

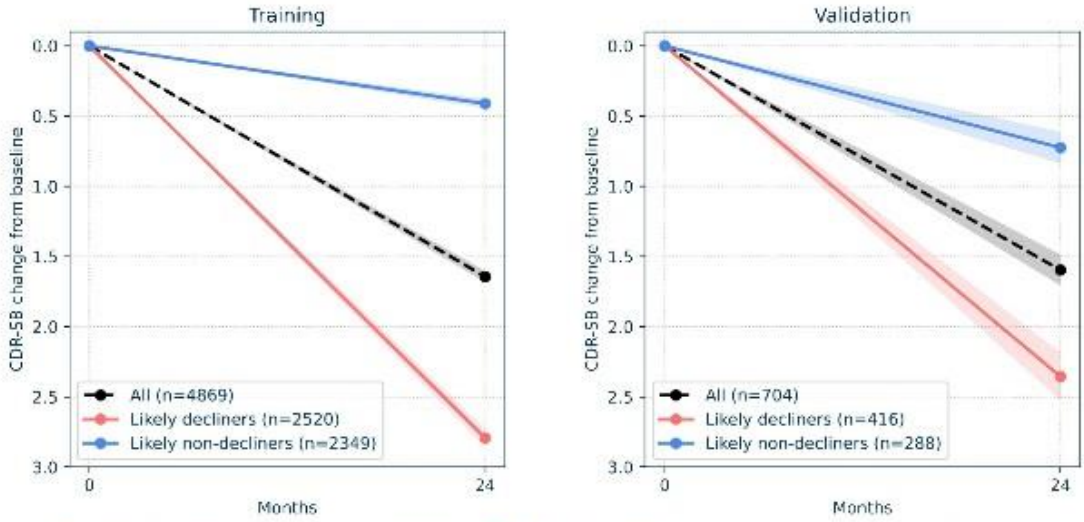

Figure 1. Clinical trajectories of the AD-Px stratified groups in the training and validation datasets.

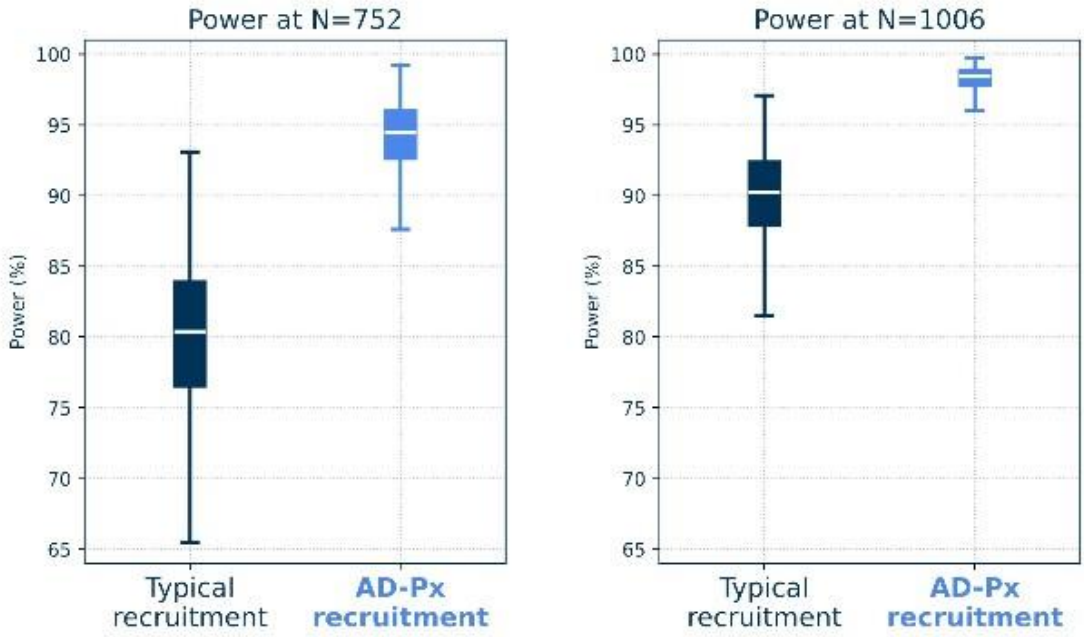

Figure 2. Bootstrapped power estimates for typical and AD-Px enriched recruitment for sample sizes of N=752 and N=1006.

size).

Conclusions: Enrichment with likely decliners by AD-Px is equivalent to recruiting 1.6 times more participants in a typical unenriched trial. AD-Px can significantly increase a trial's power and its chances of meeting its clinical endpoints.

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SHIFT 01-297

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
2-3 April 2025

DESIGNING PRIMARY AND SECONDARY ALZHEIMER'S DISEASE PREVENTION STUDIES FOR SUCCESS WITH OPTIMAL MEASUREMENT OF RISK, EARLY PATHOLOGY AND CLINICAL DECLINE

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Aims: Disease modifying Alzheimer's disease (AD) treatments face a paradox: by the time AD is diagnosed, the disease may already be irreversible, so the most treatable patients won't progress enough clinically to produce a measurable treatment effect. Treatments that work in early AD may have larger effects earlier in disease progression. Primary or secondary prevention studies that enrich based on risk assessment and early pathology may result in prevention of biomarker or clinical disease diagnosis.
Methods: We use AD risk by ApoE genotype and age to estimate clinical diagnosis rates. Timing of biomarker changes relative to clinical diagnosis are combined with event probabilities and timing to calculate sample sizes for primary and secondary prevention studies. We also consider continuous-endpoint biomarker and clinical outcome analyses. We show power for a 30% or 50% treatment reduction in events. A combination of similar risk patients across age and genotype results in homogeneity and higher power.
Results: A 1.3% annual event rate requires 20,000+ participants over 5 years for 80% power, and ~30,000 with 30% dropout. Enrichment for older patients or ApoE4 carriers reduces sample size by half. Using a continuous biomarker outcome results in sample sizes of ~10,000-15,000 participants. Secondary prevention with enrichment requires 1,000 to 6,000 subjects over a two-year treatment period. Use of a digital assessment reducing variability by 30% reduces the required sample size by half.
Conclusions: Primary and secondary prevention studies require larger sample sizes than later stages of disease, but enriching for genetic risk and targeting specific ages for primary prevention, and requiring early biomarker changes for secondary prevention can make these studies practical.

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SHIFT 01-298

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
2-3 April 2025

EXECUTING NEXT-GENERATIONAL RESEARCH IN A WORLD WITH GROWING DEMANDS FOR EFFICIENT RESEARCH DESIGN, REAL-WORLD EVIDENCE, AND PROACTIVE PLANNING IN A SHIFTING CARE ECOSYSTEM

Daniel Gautieri
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Aims: The pharmaceutical and healthcare industries face increasing demands for real-world evidence (RWE) to meet regulatory requirements, optimize patient access, and support commercial launches. Proactive planning and market-shaping activities have become critical, particularly in preparing for new care paradigms. Recent advancements in Alzheimer's Disease (AD) highlight these challenges, as the field has long faced recruitment barriers, difficulties translating trial data to real-world applicability, and slow adoption of new care paradigms. Huntington's Disease research, which leveraged RWD as comparator arms, represents an early shift toward innovative methodologies. This study explores approaches to address these challenges by integrating directly at the point of care with providers and embedding research capabilities into existing clinical workflows.
Methods: SiteRx leverages the largest decentralized neurology network in the U.S., integrating research capabilities directly at the point of care. Key methodologies include: **EHR-Enabled Recruitment:** Utilizing structured and unstructured EHR data to identify and pre-qualify eligible patients. **Remote Interventions:** Conducting remote cognitive and health assessments to reduce patient burden. **Decentralized Research Execution:** Empowering providers to execute research within routine care settings. **Synthetic Control Arms:** Leveraging RWD to create comparator arms for research designs that are difficult or impractical using traditional models.
Results: Embedding research into clinical workflows improves recruitment efficiency and accessibility for diverse populations. RWD as synthetic control arms provides a scalable alternative for complex or ethically challenging studies. Decentralized approaches minimize reliance on traditional trial sites, creating a more patient-centric, cost-effective model.
Conclusions: RWD and decentralized methodologies offer innovative, scalable solutions to meet growing demands for efficient research and evidence generation. Integrating research at the point of care enhances alignment between clinical practice and research, overcoming traditional barriers and accelerating the adoption of new care paradigms.

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SHIFT 01-300

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
2-3 April 2025

HOME-BASED TRANSCRANIAL ALTERNATING CURRENT STIMULATION OVER THE PRECUNEUS IN ALZHEIMER'S DISEASE: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED TRIAL FOLLOWED BY AN OPEN LABEL PHASE

Valeria Bracca[1], Valentina Cantoni[2], Elias Paolo Casula[3], Chiara Cupidi[4], Daniele Altomare[5], Enrico Premi[6], Elisa Zummo[4], Romina Esposito[3], Nadine Huber[7], Sanna-Kaisa Herukka[8,9], Eino Solje[8,9], Asia Ferrari[5], Maria Sofia Cotelli[2], Roberto Gasparotti[10], Alessandro Martorana[11], Giacomo Koch[3,12], Annakaisa Haapasalo[7], Alberto Benussi[13], Barbara Borroni[2,5]
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Aims: Gamma (γ) brain oscillations are involved in neural communication and synaptic plasticity, and are dysregulated in Alzheimer's disease (AD). Brain oscillations can be modulated using transcranial alternating stimulation (tACS). Here, we describe a study assessing safety, feasibility, clinical and biological efficacy, and predictors of outcome of a home-based intervention consisting of γ-tACS over the precuneus.
Methods: Sixty consecutive AD patients have been screened, and 53 randomized into two arms: ARM1, γ-tACS (frequency: 40 Hz, intensity: 2 mA; duration: 5 sessions/week 60-minutes/each; target region: precuneus) for 8 weeks; and ARM2, sham tACS (same parameters as the real γ-tACS, with the current being discontinued 5 seconds after the beginning of the stimulation) for 8 weeks. In a second phase, all participants have received γ-tACS (same parameters as the real γ-tACS in the first phase) for 8 weeks. The study outcomes will be collected at several timepoints till 24 weeks and include safety and feasibility as well as changes in cognitive functions (assessed through neuropsychological assessment), brain entrainment (electroencephalography), and biomarkers. Imaging markers (functional MRI) and cholinergic neurotransmission (transcranial magnetic stimulation) were considered as well.

Results: As of September 2024, participants successfully completed the study, and no major side effects were reported.

Conclusions: If our expected results are achieved, home-based γ-tACS, either alone or in combination with other therapies, may become a reality for treating AD.

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SHIFT 01-301

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
2-3 April 2025

TRANSCUTANEOUS VAGUS NERVE STIMULATION IS SAFE, TOLERABLE AND POTENTIALLY EFFICACIOUS IN AMNESTIC MILD COGNITIVE IMPAIRMENT

Helena Dolphin[1], Adam Dyer[1], Amparo Mogollo[2], Sean Commins[3], Ciaran Finucane[2], Sean Kennelly[4]
[1]Trinity College Dublin, Department Of Medical Geronotology, Dublin, Ireland, [2]St James's Hospital, Department Of Medical Engineering, Dublin, Ireland, [3]Maynooth University, Psychology, Maynooth, Ireland, [4]Institute of Memory and Cognition, Tallaght University Hospital, NRA, Ireland

Aims: Introduction Patients with amnestic Mild Cognitive Impairment (MCI) are at high risk of conversion to dementia. Transcutaneous Vagus Nerve Stimulation (tVNS) non-invasively stimulates the auricular branch of the vagus nerve, activating vagal brainstem nuclei and improves cognitive scores in healthy adults. tVNS has not been extensively tested in populations with MCI.
Methods: Methods A single site, single-blind, randomised three-arm crossover pilot trial of acute (60 minutes) tVNS (active, sham or baseline [no stimulation]) was conducted in an Irish Regional Specialist Memory Service. Forty participants with amnestic MCI underwent neurocardiovascular testing via the Active Stand (AS), domain-specific cognitive assessments, whole blood inflammatory cytokine and chemokines and Alzheimer Disease (AD) Blood Bio-Marker (BBM) analysis.
Results: Results tVNS was safe, tolerable and acceptable with 98% of participants stating they would use the device again. Significant improvements were noted in spatial navigation in active vs baseline (β= -8.76 [-14.91; -2.56], z= -2.78, p=0.01) and active vs sham conditions (β= -4.15 [-7.32; -0.99], z= -2.58, p=0.01). There was no significant effect of tVNS on Systolic BP, Diastolic BP, HR, Tissue Saturation Index (TSI) values during AS. There was no effect found of tVNS on circulating whole blood cytokines or chemokines. ptau-217 was the AD BBM most associated with worse cognitive performance across cognitive domains during active tVNS (β=0.18 [0.07 – 0.28], z= 1.87, p=0.02).
Conclusions: Conclusion tVNS is a safe, tolerable and potentially efficacious neurostimulation technique in participants with amnestic MCI. Future studies should explore sustained effects and feasibility of domiciliary use.

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SHIFT 01-304

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / REGULATORY ASPECTS, OTHER
2-3 April 2025

RBANS AS A PREDICTOR OF DISEASE PROGRESSION IN EARLY SYMPTOMATIC ALZHEIMER'S DISEASE

Danielle Digregorio, Selam Negash, Raymond Blattner, Christopher Randolph
WGC, Clinical Endpoint Solutions, Princeton, United States of America

Aims: The Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB) is used almost exclusively as the primary endpoint in clinical trials of putative disease-modifying therapies for early symptomatic Alzheimer's Disease (AD) clinical trials. Clinical trials of putative disease-modifying therapies typically involve very large samples of participants for large commitments of time. This is necessary to observe sufficient placebo decline to detect slowing of progression in the treatment group. Clinical factors that are predictive of placebo decline may be useful in enriching trial samples or serving as stratification variables for earlier phase trials with smaller samples.
Methods: Forward and backward stepwise regressions were carried out to identify the best model for predicting change in CDR Sum of Boxes (SB) from screening to month 18. The final model identified by the stepwise regressions was then evaluated using a linear regression to determine the magnitude and direction coefficients for the predictor variables.
Results: The final model identified by both the forward and backward the stepwise regressions included all possible variables. When subjected to linear regression, this model was found to be statistically significant (adjusted $R2 = 0.1216$; p-value < .0001).
Conclusions: Screening measures such as the RBANS, MMSE, and CDR are typically utilized in trials of disease modifying therapies. This current data show that clinical screening data including RBANS total scale index score, MMSE total, CDR-SB, and age, are predictive of disease progression. These data may be useful in future clinical trial design, either for enriching study samples for faster progression or for the purposes of stratification.

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SHIFT 01-305

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / REGULATORY ASPECTS, OTHER
2-3 April 2025

COMPARISON OF CONTEMPORARY CLINICAL DEMENTIA RATING SCALE-SUM OF BOXES (CDR-SB) DISEASE PROGRESSION MODELS IN ALZHEIMER'S DISEASE

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Aims: Emerging treatments for AD have demonstrated a reduction in the rate of disease progression, often measured using CDR-SB. Long-term extrapolation of treatment effects beyond the clinical trial period depends on the natural history of AD progression. This research sought to identify studies that model the long-term disease trajectory of AD in terms of CDR-SB using longitudinal observational data.
Methods: MEDLINE (via PubMed) was searched for articles published between January 1, 2014 and June 30, 2024 using predefined criteria. Studies were summarized on key aspects: data characteristics, modeling methods, time horizon, and endpoints including mean time to mild, moderate, and severe AD.
Results: Ten articles were identified. The majority used data from Alzheimer's Disease Neuroimaging Initiative (ADNI) (60%). Most studies (80%) used a non-linear mixed-effects framework or linear mixed-effects models with higher-order terms to capture the non-linear relationship between time and CDR-SB. Seven studies estimated mean time to different AD severity levels to take 1.5-4 years to mild AD, 3.9-7.5 years to moderate AD, and 6-12 years to severe AD from the mild cognitive impairment stage (defined as CDR-SB=2.5).

Time to Health State from CDR-SB 2.5, Years

	Jönsson 2024	Tahami Monfared 2023*	Kühnel 2021	Raket 2020	Kim 2020	Samtani 2014	Jamalian 2023
Mild AD	3.0[a]	2.3	2.2	1.5	2.4	4	1.8[a]
Moderate AD	Not available	5.7	4.8	3.9	6.4	~7.5	Not available
Severe AD	Not available	8.5	6.5	6.0	8.9	~12	Not available

*Baseline mean CDR-SB of 3.2 [a]Based on digitized plot

Conclusions: Various statistical methods have been undertaken to model AD progression using CDR-SB. Evidence supports the need for a non-linear and multivariable approach. These methods can be used to model the potential impact of treatments which modify disease progression.

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SHIFT 01-306

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / REGULATORY ASPECTS, OTHER
2-3 April 2025

REVIEWING SCIENTIFIC AND REGULATORY ASPECTS OF TAU PET IMPLEMENTATION AS A SURROGATE ENDPOINT IN ALZHEIMER'S DISEASE CLINICAL STUDIES

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Aims: Surrogate endpoints (SEs) serve to predict clinical benefit or harm, substituting direct measures of how a patient feels, functions, or survives. SEs can make clinical trials more efficient and reduce patient burden and cost. Biomarkers have recently facilitated the development of effective treatments for early Alzheimer's disease (AD), using amyloid reduction as a SE for amyloid-directed monoclonal antibody therapies. Since AD has multiple causes, additional SEs are needed to support the development of candidate treatments with different mechanisms of action.
Methods: The Critical Path for Alzheimer's Disease (CPAD) Consortium at the Critical Path Institute convened a global, pre-competitive collaboration (called the Tau PET Surrogacy Working Group), comprising subject-matter experts from academia and industry. The group evaluated the readiness of tau PET as a SE reasonably-likely to predict treatment benefit in AD clinical trials. An evidence gap analysis was conducted, based on the FDA's suggested "Considerations for Discussion of a New Surrogate Endpoint(s) at a Type C PDUFA Meeting Request."[1]
Results: The Task Force found the analysis beneficial for preparing a consortium-led initiative and establishing a proposed context of use. The information reviewed highlighted a central role for tau aggregation in AD and supports using tau PET as a SE for clinical trials in early AD. Existing AD clinical trial data generated from different tau PET tracers offer valuable data sources for future consortium efforts to tackle the identified evidence gaps, including a federated meta-analytic framework, to accelerate progress.
Conclusions: The Task Force findings outline evidentiary considerations for tau PET as a SE, inform knowledge gaps, and enhance stakeholder alignment. The CPAD consortium continues to expand opportunities to align with regulatory agencies to improve efficiency of AD clinical trials. [1]https://www.fda.gov/media/115120/download

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SHIFT 01-307

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / REGULATORY ASPECTS, OTHER
2-3 April 2025

IMPACT OF SCREENING CALL DURATION ON INITIAL EVALUATION ATTENDANCE RATE FOR ALZHEIMER'S DISEASE DRUG TRIALS

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Aims: Participant recruitment for Alzheimer's Disease (AD) drug trials is more difficult than traditional clinical trials because of the age and potential conigitive impairment of the target population. This leads to low appointment attendance rates, with typical initial evaluation appointment attendance rates across the industry being below 50%. In this study, we examine the relationship between screening call duration and the attendance rate of the initial screening appointments scheduled during the call.
Methods: From August 2023 to March 2024, 2,267 potential participants were scheduled for an in-person initial screening after passing a preliminary screening over the phone. These screening calls had an average duration of 6.59 minutes, with a SD of 4.20 minutes. Of these 2,267 potential participants, 1,258 attended their appointment, 586 canceled/rescheduled their appointment. The remaining 423 did not show up or modify their appointment.
Results: A multinomial logistic regression of initial screening appointment outcomes against screening call duration while controlling for appointment scheduling lag showed screening call duration to be statistically significant ($p = 0.028$). A separate logistic regression of no show rates against screening call duration while controlling for scheduling lag also revealed a clearly significant negative effect ($\beta = -0.0051$, $p = 0.026$).
Conclusions: There is a clear negative relationship between screening call duration and no-show rates for initial screening appointments for AD drug trials; potential participants who spend more time on the phone are less likely to outright not attend their initial screening. These findings are merely correlative and not enough to infer a causal relationship between phone screen duration and no show rates. Additional studies are necessary in order to determine causality of the relationship.

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SHIFT 01-308

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / REGULATORY ASPECTS, OTHER
2-3 April 2025

ONLINE ADVERTISING RESULTED IN MORE EDUCATED PARTICIPANTS AND NON INFERIOR SCREEN FAIL RATES WHEN COMPARED TO OFFLINE METHODS IN AN ALZHEIMER'S DISEASE CLINICAL TRIAL

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Aims: Alzheimer's Disease (AD) drug trials are slower to enroll and more expensive than trials in most other therapeutic areas. Historically, participants have been identified through offline methods - e.g. database searches, outreach events, word of mouth referrals. Sites have turned to online advertising to speed up recruitment and reach more potential participants. In this study, we investigate if recruitment modality has an effect on the education levels or screen failure rates of study participants in industry-sponsored AD drug trials.
Methods: In 2023, 208 participants screened at a commercial site in California for a clinical trial of an investigational anti-amyloid monoclonal antibody in participants with early symptomatic Alzheimer's Disease. 75.5% (157) of the participants were recruited online, 24.5% (51) were recruited offline. 48 of the participants made it through the screening process successfully and enrolled into the study. The mean years of education was 15.28 years (SD = 2.99) for the 191 participants that provided this information. 17 of the participants declined to answer questions about their education.
Results: The average years of education for a participant was 15.57 years if recruited online, 14.35 years if recruited offline. This 1.22 year difference was statistically significant (p = 0.015). The screening failure rate was 76.4% (120 of 157) if recruited online, 78.4% (40 of 51) if recruited offline. This 2.0% difference was not statistically significant (p = 0.77).
Conclusions: It is unlikely that recruitment method has any impact on a participant's ability to pass screening and enroll into an AD study. Screen failure criteria are typically clinical, which should be uncorrelated with recruitment method. The significant effect between education and recruitment method is unusual and difficult to explain. Additional investigation is necessary to identify potential causes.

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SHIFT 01-310

Poster on Board - Shift 01
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / SECRETASE INHIBITORS & MODULATORS
2-3 April 2025

SAFETY AND EFFICACY OF BACE1 INHIBITOR C3 DELIVERY USING SHORT PULSES OF FOCUSED ULTRASOUND IN 5XFAD MICE

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Aims: The blood-brain barrier (BBB) prevents 98% of small-molecule drugs from accessing the brain. This poses a significant challenge for treating Alzheimer's disease (AD), where small-molecule compounds inhibiting β-site APP cleaving enzyme-1 (BACE1), the enzyme responsible for amyloid-β production, are among the leading therapeutic candidates. Interestingly, focused ultrasound (FUS) can non-invasively and transiently increase BBB permeability; however, it is typically emitted in long-pulse sequences, which produce non-uniform drug distribution and erythrocyte extravasation. Conversely, rapid-short pulses (RaSP) of FUS produce less tissue damage and uniform delivery at 0.4MPa. In this work, we characterised BBB opening with RaSP-FUS at 0.62MPa and used it to deliver low-dose BACE1 inhibitor C3 in 5XFAD mice as a treatment for AD.
Methods: Wild-type mice were subjected to RaSP-FUS (1MHz, 0.62MPa) targeting the left hippocampus, with an intravenous injection of microbubbles (SonoVue) and 3kDa Texas-red dextran. Albumin, IgG and fibrinogen extravasation were assessed immediately post-BBB opening. Next, three-month old male 5XFAD mice were treated with 0.6mg/kg C3 delivered using the same sequence weekly for 3 weeks in three treatment groups: vehicle, C3 only and FUS+C3. Amyloid-β levels, APP processing and synaptic density in the hippocampus were assessed by western blot, ELISA and immunohistochemistry.
Results: 0.62MPa RaSP produced homogenous delivery of the 3kDa tracer throughout the ultrasound beam, with decreasing extravasation of blood proteins up to 340kDa (fibrinogen). Chronic treatment with low-dose C3 delivered by RaSP-FUS reduced amyloid-β expression and increased αCTF expression in hippocampal homogenates versus vehicle-treated mice, with no differences in PSD-95 or synaptophysin expression.
Conclusions: RaSP-FUS ensures safe, uniform drug delivery at 0.62MPa. Chronic treatment with low-dose BACE1 inhibitor C3 delivered by RaSP-FUS decreases hippocampal amyloid-β in 5XFAD mice and may promote non-amyloidogenic APP processing, without affecting synaptic density.

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SHIFT 01-311

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / AGING
2-3 April 2025

GENETIC RISK AND COGNITIVE DECLINE IN MIDDLE- AND OLDER-AGED CANADIAN WOMEN AND MEN

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Aims: Previous research indicates that age, biological sex, and apolipoprotein E (*APOE*) genotype are important sources of variation in cognitive decline; whether the *APOE* E4 allele interacts with age and sex to predict cognitive decline remains unclear.
Methods: This study examined 26,448 participants (45 to 86 years of age at baseline; 50% female; 96% self-reported white ethnic/racial background) in the Canadian Longitudinal Study on Aging who had *APOE* genotyping (24% E4 carriers). Cognitive outcomes were delayed word list recall, mental alterations, animal fluency, Stroop color-word interference, and phonetic fluency which were collected at baseline (Dec. 2011 to July 2015) and follow-up (median 5.8 years after baseline). We examined interactions between *APOE* E4 status, baseline age and sex in the context of change in cognitive performance from baseline to follow-up. Restricted cubic splines were used to allow for non-linear associations between age and cognitive change. Models were adjusted for ethnicity, study language (French/English), residential setting (urban/rural), educational attainment, and baseline cognitive score.
Results: Interactions between *APOE* E4 and baseline age were observed for delayed recall ($p = .001$) and animal fluency ($p = .014$). For both outcomes, the association between E4 carrier status and cognitive decline was amplified with increasing baseline age. For mental alterations, E4 carriers showed greater decline in performance compared to non-carriers, across age and sex ($p < .001$). Interactions between sex and baseline age were observed for delayed recall ($p = .001$) and Stroop interference ($p < .001$). Women showed less decline in these measures, especially in later adulthood. No 3-way interactions involving age, sex, and *APOE*were observed (all $p > .05$).
Conclusions: These findings show that the impact of *APOE* E4 and sex on cognitive decline may depend in part of participant age and the aspect of cognition measured.

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SHIFT 01-313

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / DISEASE-CAUSING MUTATIONS
2-3 April 2025

IMPAIRED DIMERIZATION PROPERTIES AS A COMMON MECHANISM OF PATHOGENECITY FOR A SUBSET OF ALZHEIMER'S DISEASE-ASSOCATED SORL1 VARIANTS IN 3FN-DOMAINS

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Aims: The gene *SORL1*, encoding the endosomal sorting receptor SORLA, is now recognized as a causal gene for Alzheimer's Disease (AD). A *SORL1* missense variant, p.W1862C, located at a strictly conserved sequence position in the 3Fn-domains of SORLA was identified in case-control studies to be associated with AD. Therefore, we set out for a functional characterization of the p.W1862C variant to establish its functional consequences on receptor function and how it might cause AD.
Methods: We performed an *in-silico* analysis to identify homologous pathogenic mutations in 3Fn-domains of other proteins at the same sequence position. It was suggested previously to use receptor maturation, shedding and trafficking as measures for evaluating the pathogenicity of *SORL1* mutants. Thus, we used cell-based assays combined with WB-analysis, flow-cytometry, immunocytochemistry and confocal-microscopy imaging to study maturation, shedding, cell-surface localization and intracellular trafficking of the p.W1862C variant. Finally, we utilized a bimolecular-fluorescence complementation assay to uncover how the mutation affects dimerization.
Results: We identified 7 homologous disease-causing mutations in 3Fn-domains supporting that this *SORL1* variant is pathogenic. Subsequently, we showed that p.W1862C significantly decreased receptor maturation and shedding as demonstrated previously for this and other *SORL1* variants. We found that trafficking of the mutant to the cell surface was reduced, but it was still able to sort correctly to endosomal compartments. Importantly, we found that the mutation impairs the physiologically relevant homodimerization of SORLA in endosomes.
Conclusions: We have recently described a *SORL1* mutation in the third 3Fn-domain that is causal of AD (p.Y1816C) and displays similar functional defects as the p.W1862C variant located in the fourth domain. This indicates a common mechanism of pathogenicity associated with impaired dimerization for mutations located at critical positions in several 3Fn-domains of SORLA.

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SHIFT 01-314

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

FREQUENCY OF ALCOHOL CONSUMPTION AND AMYLOID BETA DEPOSITION: RESULTS FROM THE ALBION STUDY

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Aims: The association between alcohol consumption and cognitive health is complex. In this work we move beyond cognitive status and focus on the potential associations between drinking frequency and cerebrospinal fluid (CSF) biomarkers of neurodegeneration in a cohort of dementia-free middle-aged-adults.
Methods: This analysis is part of the ALBION study (cross-sectional part). Each volunteer went through an extensive neuro-cognitive assessment. Dietary intake, including energy and alcohol intakes, was assessed through four 24-hour recalls. Diet quality was evaluated through the adherence to the modified Mediterranean diet (mMD) (without alcohol). Other sociodemographic data and lifestyle parameters were recorded, such as sleep duration (measured with a wrist actigraph for 7 days) and physical activity (assessed through the International Physical Activity Questionnaire). CSF samples were collected. Multivariable logistic regression analyses were conducted using drinking frequency (abstainers, less than 2 standard drinks/week, above 2 standard drinks/week) as independent variables and CSF Alzheimer Disease (AD) biomarkers [amyloid-β (Aβ) accumulation, Tau/Aβ and Phospho-tau/Aβ ratios] as dependent variables.
Results: Of the 195 individuals without dementia (occasional drinkers n=27, light-to-moderate drinkers n=51), 66% were female, with an average age of 65±9.4 years, 13.8±3.6 years of education, an average sleep duration (as measured with actigraphy) of 5.91±4.48 hours and an average mMD adherence score of 28.7±5.7. A weekly alcohol intake exceeding 2 standard drinks was associated with higher Aβ positivity compared to alcohol abstinence [OR:2.98(1.29-6.90)], even after adjusting for confounders (age, sex, education years, energy intake and diet quality). Alcohol consumption frequency was not associated with Tau/Aβ42 and Phospho-tau/Aβ42 ratios.
Conclusions: Light-to-moderate alcohol consumption was associated with increased Aβ accumulation in

cognitively intact adults. These findings potentially increase our understanding of how alcohol consumption might influence vulnerability to AD.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

LEAD EXPOSURE AND ALZHEIMER'S DISEASE MORTALITY AMONG US ADULTS: NHANES ANALYSIS FROM 1988-2008

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Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder with unclear etiology, although metal exposures, including lead (Pb), have been implicated. A previous study (Horton et al., 2019) using National Health and Nutrition Examination Survey (NHANES) data from 1999-2008 found a possible association between blood lead levels (BLL) and AD mortality; however, temporal biases may have influenced their findings.
Methods: We conducted a two-phase study using NHANES III (1988-1994) and Continuous NHANES (1999-2008) data linked to the National Death Index to assess the relationship between BLL and AD mortality. Phase 1 replicated and then modified Horton's competing risk approach using Continuous NHANES data, incorporating calendar effect adjustments for temporal confounding, time-window exclusions for reverse causation, and additional covariates. Phase 2 combined NHANES III with Continuous NHANES to enhance robustness.
Results: In Phase 1 (n= 8080), replication showed no association between BLL and AD mortality. Hazard ratios increased gradually across successive cycles: 0.88 (0.51, 1.52), 0.94 (0.59, 1.49), 1.17 (0.69, 1.98), 0.90 (0.46, 1.75), and 1.41 (0.71, 2.80) for years 1999-2000, 2001-2002, 2003-2004, 2005-2006, and 2007-2008, respectively. Inclusion of a calendar effect adjustment for pooled cycles yielded an inverse, though nonsignificant, association (HR, 95% CI: 0.81 (0.64, 1.04).. In Phase 2 (n = 21,308), the base analysis showed inverse associations which strengthened with calendar adjustments (HR, 95% CI: 0.86 [0.70, 1.05], P = 0.13 vs. 0.57 [0.46, 0.70], P < 0.001, respectively).
Conclusions: Our findings suggest an inverse relationship between BLL and AD mortality, previously obscured by temporal confounding. This challenges prior findings and underscores the importance of accounting for temporal patterns in BLL data within public health research. Nonetheless, findings should be interpreted cautiously due to reliance on a single BLL measurement at baseline.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

GUT-BRAIN NEXUS: MAPPING MULTI-MODAL LINKS TO NEURODEGENERATION AT BIOBANK SCALE

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Aims: Alzheimer's disease (AD) and Parkinson's disease (PD) are influenced by genetic and environmental factors. We conducted a population-scale, unbiased assessment that aimed to: 1) Investigate the association between 155 diagnoses related to endocrine, nutritional, metabolic, and digestive system disorders and the risk of AD and PD, while also accounting for established genetic factors known to influence the development of these conditions; 2) Evaluate the specificity of plasma biomarkers associated with AD or PD when individuals have these co-occurring conditions; 3) Develop a multi-modal classification model combining all these data modalities.
Methods: We utilized statistical analyses, such as polygenic risk score analyses, cox proportional hazards model, and generalized linear models, across three biobanks (UK Biobank, FinnGen, and the Secure Anonymized Information Linkage (SAIL) biobanks) to evaluate the effect of the 155 relevant disorders selected by ICD-10 (International Classification of Diseases, 10th Revision) codes and 1,463 biomarkers from the Pharma Proteome Project on AD and PD.
Results: Our findings show that certain disorders elevate AD/PD risk prior to AD/PD diagnosis. Polygenic risk scores reveal lower genetic predisposition for AD/PD in individuals with co-occurring disorders. The proteomic profile of AD/PD cases was influenced by comorbid gut-brain axis disorders. Importantly, our multi-omics prediction models perform better than single-modality paradigms in disease classification

accuracy.

Conclusions: Our integrated approach serves as a proof of concept, aligning with the expanding body of evidence that underscores the intricate etiological foundations of neurodegenerative diseases and holds promise for refining risk prediction models and devising targeted preventive strategies.

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β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

MICROSCOPIC COLITIS AND DEMENTIA: A SWEDISH POPULATION-BASED STUDY

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Aims: To examine the bidirectional relationship between microscopic colitis (MC), an inflammatory disease of the colon, and dementia.
Methods: Harnessing the nationwide ESPRESSO cohort in Sweden, we compared MC patients histologically diagnosed 1990-2017 and ≥30 years of age to their population-based MC-free comparators. MC association with incident dementia and its subtypes (Alzheimer's disease [AD] and vascular dementia [VaD]) was estimated separately in a matched cohort design using Cox models adjusting for confounding comorbidities and baseline hospital visits. Retrospective association of MC with prior dementia was also assessed via logistic models in a matched case-control design. To minimize unmeasured interfamilial confounding, MC patients were also compared to their unaffected full siblings in sensitivity analyses.
Results: Following 13,037 MC patients and 61,710 population comparators until 2021, we discovered 4674 incident dementias (85% were AD). During the first five years since diagnosis, MC was associated with a 19% higher risk of dementia overall (adjusted hazard ratio [aHR]: 1.19; 95% CI: 1.07-1.33). This short-term association was seen for both AD and VaD and appeared stronger in sibling analysis (aHR: 1.55; 95% CI: 1.22-1.97). After five years, it attenuated to null regardless of dementia subtypes. In retrospective analysis, dementia was significantly less prevalent in MC cases than population controls (adjusted odds ratio [aOR]: 0.73; 95% CI: 0.65-0.82). Such inverse association was also observed for inflammatory bowel disease (aOR: 0.70; 95% CI: 0.64-0.76), a gastrointestinal disease with similar symptoms as MC, but was not replicated in our sibling analysis (aOR: 1.11; 95% CI: 0.82-1.52).
Conclusions: MC patients may be more susceptible to dementia soon after their MC diagnosis. The intriguing inverse relation between MC and prior dementia implies an under-diagnosis of MC among demented population and warrants future studies.

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2-3 April 2025

WALKING AND ALZHEIMER'S PATHOLOGY IN PHYSICALLY CAPABLE OLDER ADULTS: A PROSPECTIVE COHORT STUDY

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Aims: This study aimed to explore the relationship between walking duration and intensity and in vivo Alzheimer's disease (AD) pathologies, including cerebral beta-amyloid (Aβ) and tau deposition, AD-signature cortical thickness (AD-CT), and white matter hyperintensity (WMH) volume. Additionally, the study examined whether the timing of walking initiation (early vs. late life) affects the association between walking and AD pathology in physically capable, non-demented older adults.
Methods: The study involved both cross-sectional and longitudinal analyses using data from the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease, an ongoing prospective cohort study initiated in 2014. A total of 340 non-demented individuals aged 55-90 years were included at baseline, with 151 completing 4-year follow-up assessments. Participants underwent structured interviews to assess their walking activity, which was then categorized by duration, intensity, or a combination of both. Multi-modal neuroimaging was used to measure cerebral Aβ and tau deposition, AD-CT, and WMH volume at baseline and the 4-year follow-up.
Results: Participants engaging in long-duration (>360 minutes/week) or high-intensity (moderate to vigorous) walking exhibited significantly lower Aβ deposition at baseline and a reduction in Aβ accumulation over four years compared to non-walkers. When combining both duration and intensity, only those in the high-combined group (both long-duration and high-intensity) showed similar protective effects. Notably, these benefits were significant only in participants who began walking before age 65. No significant differences were observed in other brain pathologies among the walking groups.
Conclusions: The results suggest that walking activity with both high intensity and long duration may reduce cerebral Aβ accumulation, potentially lowering the risk of AD and cognitive decline. Furthermore, the protective effect of walking appears more pronounced when initiated before late life.

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SHIFT 01-319

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

MODERATING ROLE OF APOE4 ON THE ASSOCIATION BETWEEN SERUM SELENIUM LEVELS AND COGNITIVE DECLINE IN OLDER ADULTS

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Aims: To examine the association between serum selenium levels and episodic memory as an indicator of Alzheimer's disease (AD)-related cognitive decline, focusing on the effect of apolipoprotein E ε4 allele (APOE4) status in older adults without dementia.
Methods: This study included 196 participants aged 65-90 years without clinical dementia from the General Lifestyle and AD (GLAD) study. Memory (episodic memory), non-memory, and global cognition scores were measured via the Korean version of the CERAD neuropsychological battery. Serum selenium levels were measured using inductively coupled plasma-mass spectrometry. APOE4 genotyping was performed with capillary electrophoresis. Linear regression analyses were used to examine the association between selenium levels and cognition, adjusting for potential confounders. Moderating effects of APOE4 on these associations were analyzed using interaction terms.
Results: Serum selenium levels were significantly associated with episodic memory scores (EMS) and total CERAD scores (TS) but not with non-memory scores (NMS). The interaction analysis revealed that APOE4 status significantly moderated the association between serum selenium levels and cognitive performance, particularly episodic memory. Subgroup analyses showed that selenium levels were significantly associated with EMS and TS in APOE4-negative participants but not in APOE4-positive participants.
Conclusions: The study suggests that APOE4 status moderates the relationship between serum selenium levels and cognitive decline, particularly episodic memory, in older adults. This highlights the importance of considering APOE4 status in studies involving selenium metabolism and cognitive decline related to AD.

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SHIFT 01-320

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

ASSOCIATION BETWEEN HDL-CHOLESTEROL AND EPISODIC MEMORY: MODERATING EFFECTS OF APOLIPOPROTEIN E E4 STATUS

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Aims: To investigate the relationship between high-density lipoprotein (HDL)-cholesterol levels and cognitive function, specifically episodic memory, in older adults, and to assess how this relationship is moderated by the presence of the apolipoprotein E ε4 allele (APOE4).
Methods: The study is part of the General Lifestyle and AD (GLAD) cohort, including 164 participants aged 65-90 without clinical dementia. Cognitive function was assessed using the CERAD neuropsychological battery, measuring immediate and delayed episodic memory, non-memory, and global cognition. Serum HDL-cholesterol levels were measured, and APOE4 genotyping was performed using PCR analysis. Multiple linear regression analyses, controlling for potential confounders such as age, sex, education, vascular risk, and physical activity, were conducted to explore the interaction between HDL-cholesterol levels and APOE4 status on cognitive outcomes.
Results: The interaction between HDL-cholesterol and APOE4 status significantly affected episodic memory and global cognition scores but not non-memory function. In APOE4-positive individuals, HDL-cholesterol levels were inversely associated with delayed episodic memory and global cognition. No significant associations were found in APOE4-negative participants.
Conclusions: The findings suggest that APOE4 status moderates the relationship between HDL-cholesterol levels and cognitive decline, particularly affecting episodic memory in older adults. These results underscore the importance of considering APOE4 status in research on HDL-cholesterol and Alzheimer's disease (AD)-related cognitive decline.

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SHIFT 01-321

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

ASSOCIATION BETWEEN ADVERSE CHILDHOOD EXPERIENCES AND SUBJECTIVE COGNITIVE DECLINE: A SCOPING REVIEW

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Aims: Adverse childhood experiences (ACEs) are linked to various health problems later in life, including cognitive decline. Subjective cognitive decline (SCD) is a self-reported perception of cognitive difficulties and is considered a potential early sign of Alzheimer's disease. The review aims to identify existing literature on how ACEs are associated with SCD and examine the roles of demographic, mental health, and social functioning factors in the relationship.
Methods: A scoping review was conducted following the PRISMA-ScR guidelines. Four databases (OVID Medline, PsycINFO, CINAHL, and Web of Science) were searched for studies published up to July 2024. The review focuses on studies measuring ACEs before age 18 and SCD in adulthood.
Results: Twelve studies were included in the final review, seven of which utilized data from Behavioral Risk Factor Surveillance System (BRFSS). The heavy reliance on the BRFSS dataset indicates a focus on U.S. populations, with only one study conducted in China. Sample sizes varied widely, ranging from as few as 46 participants to over 195,000. A strong dose-response relationship between ACEs and SCD was observed, with higher ACE counts increasing SCD risk. Subgroup analyses revealed that older adults and individuals from lower-income groups and sexual minorities showed higher rates of SCD. However, gender differences were inconsistent across studies, and the moderating effects of physical and mental health increased the risk of SCD in individuals with a history of ACEs.
Conclusions: We revealed a significant dose-response relationship between ACEs and SCD in adulthood, with various demographic and health factors moderating this association. Future research should prioritize longitudinal studies with diverse populations to better understand how ACEs lead to SCD over time and how mental health interventions might alter this trajectory.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

ASSOCIATIONS BETWEEN AIR POLLUTION AND MARKERS OF NEUROINFLAMMATION, SYNAPTIC DYSFUNCTION AND AD PATHOLOGY VARY BY APOE GENOTYPE

Kana Kimura[1], Ira Driscoll[2], Noah Cook[2,3], Tobey Betthauser[2,4], Sterling Jonhson[2,4], Sanjay Asthana[2,4,5], Catherine Gallagher[5,6], Bruce Hermann[2,4,6], Mark Sager[2,4], Kaj Blennow[7,8], Henrik Zetterberg[2,7,8,9,10,11,12,13], Cynthia Carlsson[2,4,5], Gwendlyn Kollmorgen[14], Clara Quijano-Rubio[15], Ozioma Okonkwo[2,4]
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Aims: Ambient air pollution (AP) aggravates Alzheimer's disease (AD) pathology, albeit the mechanisms remain unclear. We examined relationships between current AP exposure and biomarkers of AD pathology, neuroinflammation and synaptic dysfunction, and whether these relationships differ based on APOE status in a cognitively unimpaired cohort enriched for AD risk.
Methods: Older adults (N=444; Mage=68.7; 68% female) from the Wisconsin Registry for Alzheimer's Prevention with available data were included in analyses. Ozone (O3) and ambient fine particulate matter with diameter<2.5μm (PM2.5) levels were calculated over 13 years based on participant's zip code and Environmental Protection Agency's air quality database. Regressions, covarying for gender, race, age, education, and parental AD history, examined associations of AP with PET [PiB (Aβ); MK-6240 (tau)] and CSF biomarkers [NeuroToolKit (Roche Diagnostics International Ltd, Rotkreuz, Switzerland); AD pathology:

Aβ40/42, total tau (t-tau), and phosphorylated tau181 (pTau181); neuroinflammation: GFAP, IL-6, S100b, YKL40, and sTREM2; synaptic dysfunction: neurogranin] before and after stratifying by APOE ε4-allele carriage (APOE4+) status.

Results: AP was not significantly associated with AD pathology (PET(PiB-Aβ, MK-6240-tau); CSF(Aβ40/42; t-tau, pTau181); Ps>0.05). Higher PM2.5 exposure was associated with higher GFAP (P=0.003). There was a significant relationship between AD pathology markers and those of inflammation and synaptic dysfunction (CSF-only; Ps<0.001). APOE4+ with higher current AP exposure had higher levels of t-tau (P=0.01), pTau181 (P=0.01) and neurogranin (P=0.02).

Conclusions: AP was not significantly associated with AD pathology (PET & CSF), likely due to our cohort's generally low AP exposure compared to both the literature and national average. Current higher PM2.5 exposure was, however, associated with reactive astrogliosis (GFAP). Moreover, our results suggest a synergistic detrimental relationship between APOE4+ and AP in relation to AD pathology and synaptic dysfunction.

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SHIFT 01-323

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
2-3 April 2025

AD AND THE EXPOSOME: INVESTIGATING GENE-ENVIRONMENT INTERACTIONS IN HUMANIZED MOUSE MODELS EXPOSED TO TOXIC METALS

Kevin Kotredes[1], Olga Minaeva[2], Ravi Pandey[3], Zeynep Sarica[1], Juliet Moncaster[2], Gregory Carter[1], Lee Goldstein[2], Gareth Howell[1]
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Aims: Human data sets indicate that the complexity and heterogeneity in late-onset Alzheimer's disease (LOAD) results from dynamic interactions between genes and environment ("exposome"). Inherent risk factors, specific genotypes and molecular profiles, produce well-described phenotypes that can be altered by external variables (diets, behaviors, comorbidities, and toxicant exposures). While heavy metals have known LOAD associations, the molecular mechanisms they modulate are unknown. Here we test the hypothesis that heavy metal exposure exacerbates pathological cerebrovascular deficits, neuroinflammation, and biometal dyshomeostasis. Examination of these interactions will provide insight into the heterogeneity observed in human disease and may uncover potentially modifiable mechanisms underpinning AD pathogenesis.
Methods: Mouse models expressing humanized LOAD risk alleles (*APOE4, APP)* were exposed to heavy metal (As, Cd, Pb) drinking water. Toxicants and endogenous biometals were assayed by ICP-mass spectrometry in the brain, blood, and urine. Spatial profiling by high-resolution metallomic imaging mass spectrometry (MIMS) confirmed brain mapping of toxicants. Transcriptional and proteomics profiling of brains revealed specific changes in human-aligned, LOAD-related expression networks indicating mechanisms of disease progression. Neuropathology was evaluated for LOAD-relevant phenotypes (amyloid burden, glial activity, and neuron loss).
Results: Heavy metals accumulated in the brain and altered LOAD-relevant gene expression, including a decrease in *Vgf* and increase in *App*. Reduced *VGF* expression has been observed in all four independent AMP-AD studies and *APP* encodes amyloid precursor protein, from which Aβ peptides are generated.
Conclusions: This multidisciplinary project leverages innovative LOAD mouse models, phenotyping pipelines, state-of-the-art elemental brain mapping, and human-aligned systems biology. Results from these experiments will provide new mechanistic insights, clinically-relevant biomarkers, novel therapeutic targets, and critical environmental toxicant exposure data to inform personalized strategies for risk reduction, disease prevention, and toxicant mitigation relevant to LOAD and ADRDs.

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SHIFT 01-331

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2-3 April 2025

FROM GWAS TO FUNCTION: DISSECTING THE CELL TYPE-SPECIFIC GENE REGULATORY EFFECTS OF COMMON NONCODING ALZHEIMER'S AND PARKINSON'S DISEASE RISK VARIANTS

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Aims: Sporadic Alzheimer's (AD) and Parkinson's diseases (PD) are polygenic, driven by the cumulative influence of many disease-associated variants. Genome-wide association studies (GWASs) have identified nearly 100 loci associated with each disease. However, these studies do not identify specific causative variants. Most causative GWAS variants reside in noncoding regions, obscuring variant effects. Further, assigning effects to relevant cell types necessitates integration of functional genomics data. In this study, we aim to functionally fine-map causative variants in AD and PD risk loci, using high-throughput *in vitro* screening of allelic gene expression effects in brain cell type models and machine learning (ML)-based predictive approaches.
Methods: We utilized an allelic massively parallel reporter assay (MPRA) to assess the gene regulatory potential of cell type-specific accessible chromatin regions in AD and PD risk loci. We tested the allelic effects of common variants in these regions by applying the library across 10 *in vitro* models of brain cell types, including 4 iPSC-derived models. We separately trained ML models to predict noncoding variant effects as an orthogonal measure of variant impact.
Results: We identified variants with significant allelic expression differences in each model. Overall expression patterns are structured related to the cell type nominally being modeled. The majority of allelic effects are unique, but a number of allelic hits are shared across models. Overlapping our MPRA results with ML predictions highlights high-confidence noncoding variant drivers of neurodegenerative disease.
Conclusions: This work reveals the importance of utilizing multiple models in MPRA studies and multiple methodological approaches to fully capture the gene regulatory potential of a sequence and its allelic effects. We prioritized AD and PD-associated noncoding common variants that potentially alter gene expression in the brain and mediate GWAS associations.

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SHIFT 01-332

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2-3 April 2025

EVALUATING THE ASSOCIATION BETWEEN APOE GENOTYPES AND COGNITIVE RESILIENCE IN SUPERAGERS

Alaina Durant[1], Shubhabrata Mukherjee[2], Michael Lee[2], Seo-Eun Choi[2], Phoebe Scollard[2], Brandon Klinedinst[2], Emily Trittschuh[3,4], Jesse Mez[5], William Bush[6], Brian Kunkle[7], Adam Naj[8], Katherine Gifford[1], Alzheimer's Disease Neuroimaging Initiative (Adni)[9], Alzheimer'S Disease Genetics Consortium Adgc[10], Alzheimer's Disease Sequencing Project (Adsp)[10], Michael Cuccaro[7], Carlos Cruchaga[11,12], Jason Hassenstab[13], Margaret Pericak-Vance[7], Lindsay Farrer[5,14], Li-San Wang[15], Jonathan Haines[6], Angela Jefferson[1], Walter Kukull[16], C. Dirk Keene[17], Andrew Saykin[18,19], Paul Thompson[20], Eden Martin[7], David Bennett[21], Lisa Barnes[21], Julie Schneider[21], Marilyn Albert[22], Sterling Johnson[23], Corinne Engelman[24], Richard Mayeux[25], Badri Vardarajan[25], Paul Crane[2], Logan Dumitrescu[1], Derek Archer[1], Timothy Hohman[1], Leslie Gaynor[1]

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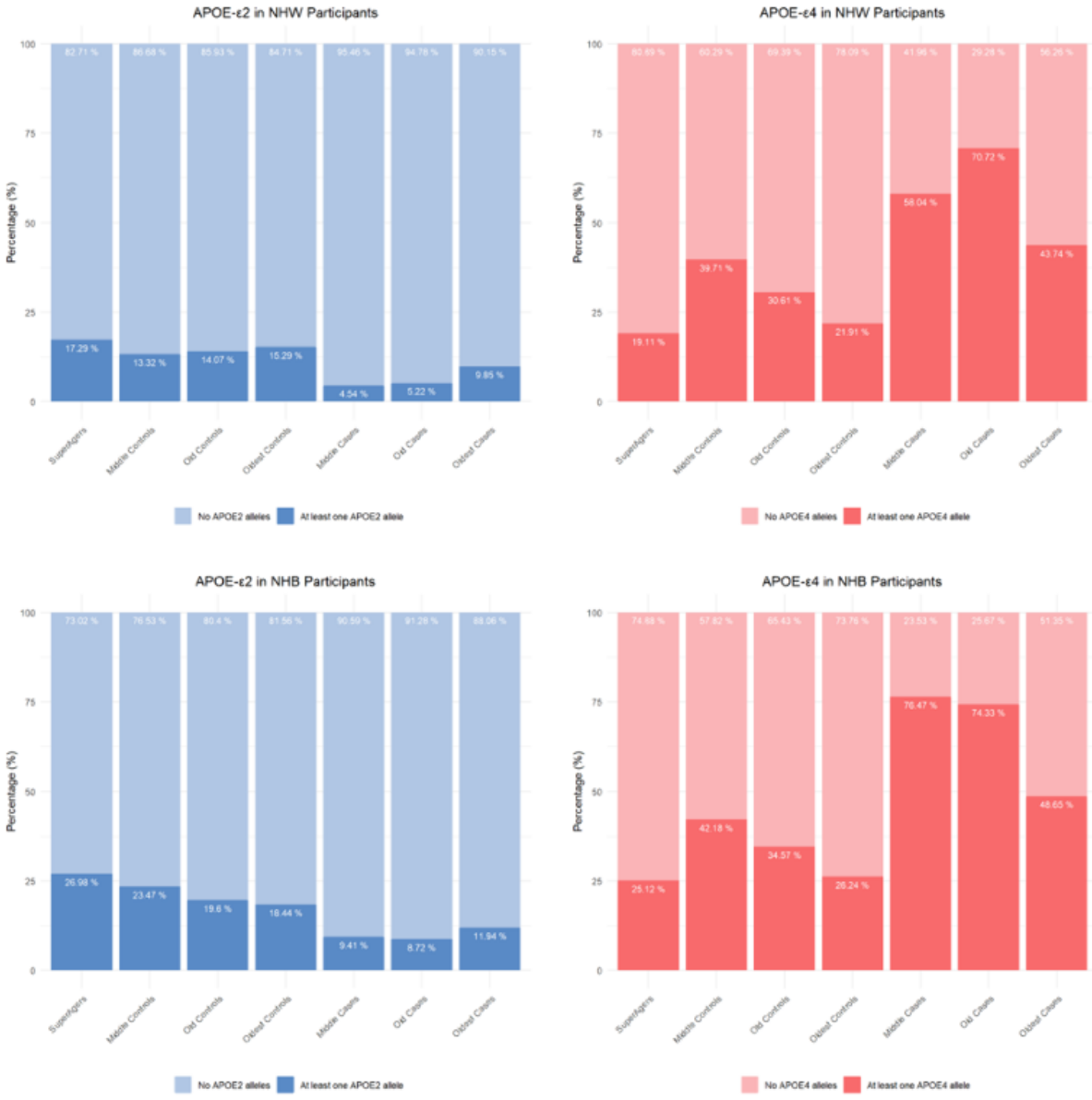
Aims: "SuperAgers" are oldest-old (ages 80+) adults with memory performance resembling adults in their 50s to mid-60s. This study explores whether the *APOE* genotype contributes to the superior memory performance of SuperAgers.
Methods: Harmonized, longitudinal memory, executive function, and language scores in Non-Hispanic White (NHW) and Non-Hispanic Black (NHB) participants were obtained from the ADSP Phenotype Harmonization Consortium. SuperAgers (NHW = 1,434; NHB = 215) also must have language and executive function domain scores within normal limits and remain cognitively normal across visits if longitudinal data was available. We compared SuperAgers to Alzheimer's disease (AD) cases (NHW = 7,887; NHB = 942) and controls (NHW = 6,130; NHB = 1,190) in age-defined subgroups (middle-aged = ages 50-64, old = ages 65-79, oldest-old = ages 80+). We performed binary logistic regression analyses comparing *APOE*-ε2 and *APOE*-ε4 allele presence among SuperAgers and counterparts, covarying for sex and education. Benjamini-Hochberg procedure adjusted for multiple comparisons.
Results: Across racial groups, SuperAgers possess significantly higher proportions of *APOE*-ε2 alleles and lower proportions of *APOE*-ε4 alleles compared to cases and middle-aged and old NHW controls. NHW SuperAgers had significantly lower proportions of *APOE*-ε4 alleles compared to oldest-old Controls; differences in *APOE*-ε2 frequency between NHB SuperAgers and oldest-old controls did not survive adjustment for multiple comparisons.
Conclusions: In a large, harmonized cohort, *APOE* genotype differed between SuperAgers and cases and controls. Crucially, NHW SuperAgers had significantly lower frequency of *APOE*-ε4 alleles than all controls including age-matched controls (ages 80+), while NHB SuperAgers had a relatively higher frequency of *APOE*-ε2 alleles than age-matched controls. This work provides the strongest evidence to date that

the *APOE* genotype is related to optimal memory in oldest-old



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Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
2-3 April 2025

GWAS USING SHORT TANDEM REPEATS EXTENDS THE GENETIC ARCHITECTURE OF ALZHEIMER'S DISEASE

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Aims: Genome-wide association studies (GWASs) are a powerful approach to decipher complex genetic traits, incl. Alzheimer's disease (AD). GWASs are mostly based on the use of single nucleotide polymorphisms (SNPs) while analyses using other types of variants are rare. In this study, we focus on short tandem repeats (STRs) which can account for a sizable fraction of complex-disease GWAS signals.
Methods: We performed GWAS analyses on diagnosed and proxy AD phenotypes in 333,446 samples of the UK Biobank (UKB) using STR genotypes imputed from SNPs. In parallel, we analyzed STR data from 107,289 overlapping UKB samples directly called from whole-genome sequencing. To distinguish between STR- vs. SNP-led GWAS signals, we performed conditional analyses on selected STR loci and compared our results to those from prior SNP-based AD GWAS.
Results: In the GWAS using imputed STRs, we found 14 loci passing genome-wide significance (α=1.49e-7). While most of these signals overlap with known SNP-based GWAS findings, we also observed one novel locus (on 11q13) previously not detected by SNPs. In addition, we observed 482 STRs in 35 loci showing suggestive association (α=1.0e-5). Conditional analyses indicated that STRs might represent the lead signal for ~6% to 25% of these loci, respectively. Comparison of effect sizes from imputed vs. genotyped STRs showed a high correlation (r=0.99, p=4.72e-71), emphasizing the high quality of the imputed STR data.
Conclusions: To the best of our knowledge, we performed the first AD risk GWAS using STRs as genetic predictors. While most observed signals were driven by SNPs, STRs represented the lead associations for 6% to 25% of all loci. Our work highlights the importance of studying non-SNP variants to fully resolve the genetic architecture underlying AD.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / METABOLIC AND CARDIOVASCULAR
2-3 April 2025

INVESTIGATING THE EFFECTIVENESS OF CAIDE SCORE IN REPRESENTING BASELINE NEUROPSYCHOLOGICAL AND NEUROIMAGING PARAMETERS

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Aims: Currently, major neurocognitive disorders are incurable and therefore risk assessment and prevention in cognitively unimpaired individuals is crucially important. Over the past decades, several studies aimed at evaluating the risk of dementia by creating risk scores for different population groups, one of them being The Cardiovascular Risk Factors, Aging and Dementia Study (CAIDE) Dementia Risk Score. In this study we aimed at assessing the effectiveness of the CAIDE Dementia Risk Score in representing baseline cognitive and structural brain status.
Methods: Every participant of this study underwent thorough neuropsychological evaluation, MRI acquisition, blood tests and risk assessment. Based on the CAIDE score we divided the participants into two groups: low and high-risk groups and completed detailed statistical analysis.
Results: We found significant intergroup differences between low and high-risk groups in neuropsychological test results, structural MRI data. Time of task completion was significantly longer in the high-risk group for the Trail-Making-Test A (t=-2.937, p=0.037) and Trail-Making-Test B (t=-4.349, p=0.0007). We also found reduced total gray matter volume (t=3.041, p=0.0289) in the high-risk group. Functional MRI results indicated a tendency of weaker large scale, and local connectivity, in addition to lower fractional amplitude of low-frequency fluctuation in subjects with high dementia risk. However, these results were no longer significant after correction for multiple comparisons was completed.
Conclusions: Our results support the use of CAIDE score in dementia risk assessment and prediction of cognitive decline as low and high-risk groups based on CAIDE score differed significantly in numerous objective parameters as well as neuropsychological test results.

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SHIFT 01-335

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / METABOLIC AND CARDIOVASCULAR
2-3 April 2025

METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE, BODY MASS INDEX, AND INCIDENT ALZHEIMER'S DISEASE: A NATIONWIDE COHORT STUDY

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Aims: The relationship between metabolic dysfunction-associated steatotic liver disease (MASLD) and risk of Alzheimer's disease (AD) remains controversial, possibly due to varying clinical implications of MASLD subtypes based on body mass index (BMI). This study aimed to investigate how MASLD and BMI together influence the incidence of AD in the general population.
Methods: Utilizing data from the "National Screening Program for Transitional Ages" conducted for 66-year-old dementia-free Koreans in 2010 and 2011, we constructed a retrospective cohort for the development of AD. MASLD was determined based on the fatty liver index (≥30) and the presence of metabolic components, and overweight was defined as BMI ≥23 kg/m^2. Primary outcome, the development of AD, was assessed until Dec 2021 through national health claims data. We performed multivariable Cox regression analyses to evaluate the risk for the development of AD according to the presence of MASLD and overweight.
Results: This cohort included 376,902 dementia-free participants with 66-years-old at baseline. Based on the presence of MASLD and overweight, participants were categorized into four groups: overweight non-MASLD, overweight MASLD, lean non-MASLD, lean MASLD with respective proportions of 30.4%, 37.0%, 29.9%, and 2.7%. During an average follow-up period of 10.38 years, 23,874 (6.3%) individuals were newly diagnosed with AD. Compared to the overweight non-MASLD (reference), the adjusted hazard ratios [95% confidence interval] for AD were as follows: lean MASLD, 1.42 [1.32–1.54]; lean non-MASLD, 1.18 [1.14–1.22]; overweight MASLD, 1.08 [1.04–1.11].
Conclusions: The results of this study indicate that normal/underweight and MASLD synergistically increase the risk of AD. In particular, lean MASLD was associated with an increased risk of developing AD compared with overweight MASLD, suggesting that the clinical relevance of MASLD for incident AD differs between the subtypes of MASLD.

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SHIFT 01-336

Poster on Board - Shift 01
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2-3 April 2025

INFLUENCE OF STATIN POTENCY AND LIPOSOLUBILITY ON ALZHEIMER'S DISEASE PATIENTS: A POPULATION-BASED STUDY

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Aims: There are several known risk factors for Alzheimer's disease (AD), such as dyslipidemia. Statins are the most prescribed lipid-modifying therapies. Recent research has suggested a relationship between statins and AD, nevertheless, their ability to prevent AD is still unclear. Therefore, this cross-sectional study aimed to examine the relationship between statin use and anti-AD drug prescription.
Methods: A database containing information on medications prescribed to patients aged 50 years or older (n = 233183) between 2018 and 2020 was used. Defined daily doses (DDDs) were calculated according to the ATC/DDD index 2023. Of the initial population, those patients aged more than 70 years who were prescribed at least one antihypertensive, antidiabetic or lipid-modifying agent were included in the study. Statistical analyses, with logistic regression and cumulative incidence, were carried out to assess statins and anti-AD drug consumption.
Results: A total of 47852 patients who met the inclusion criteria were studied. Of these, 45345 patients were classified within the cardiovascular risk group and 2483 were classified as patients with only hyperlipidemia. Patients using low potency or hydrophilic statins had lower odds of anti-AD usage when compared to high potency or lipophilic statins, respectively. Similarly, rosuvastatin and pitavastatin had lower odds of anti-AD medication intake when compared to atorvastatin. Finally, pitavastatin DDDs were prone to lower the odds of anti-AD medication usage when compared to rosuvastatin.
Conclusions: A potential association between statins and the intake of AD medication has been observed. Specifically, low-potency (pitavastatin) and hydrophilic (rosuvastatin) statins were associated with less use of anti-AD medication.

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SHIFT 01-337

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / METABOLIC AND CARDIOVASCULAR
2-3 April 2025

IMPACT OF DIETARY FIBER ON DEMENTIA RISK: EVIDENCE OF NONLINEAR EFFECTS

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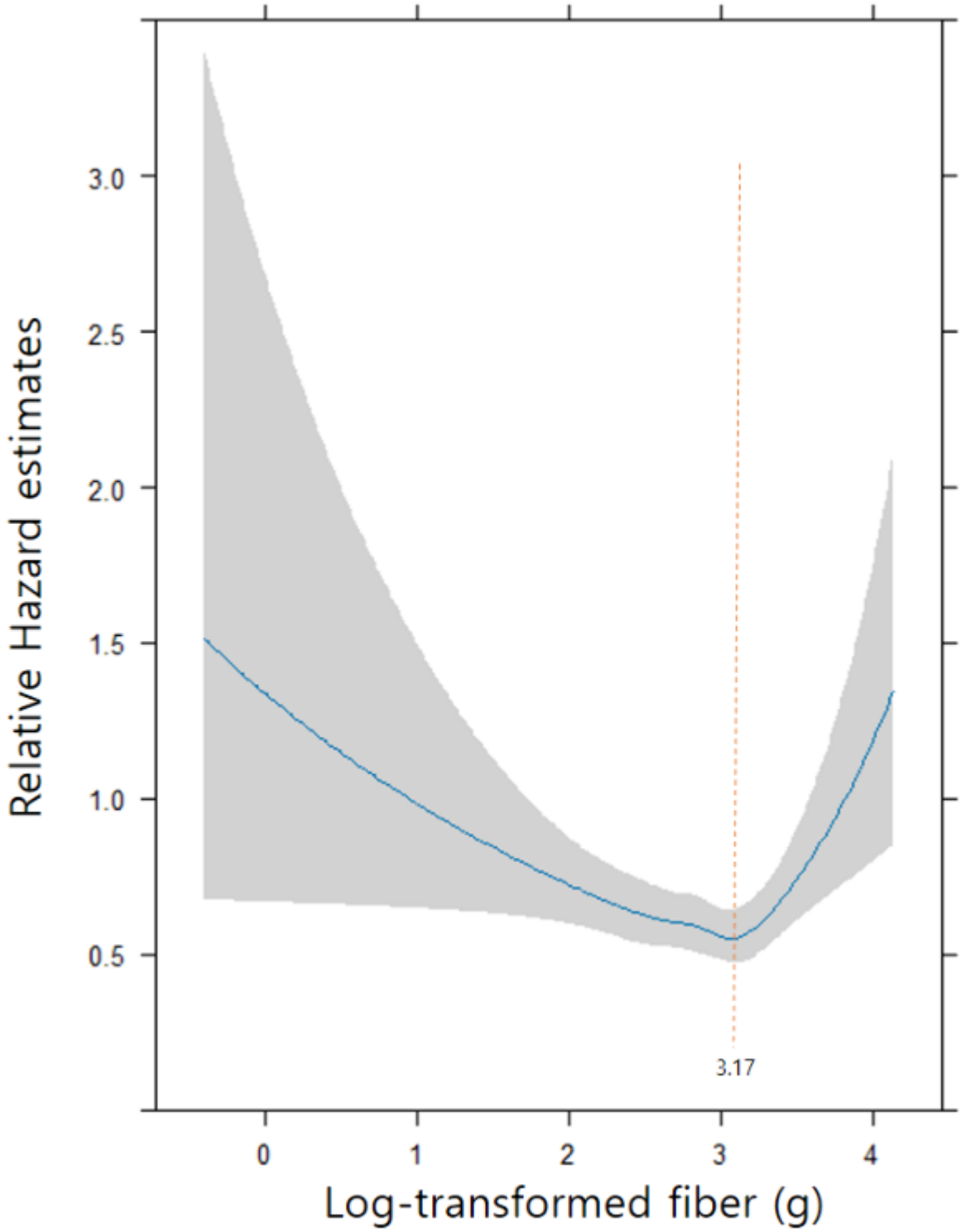
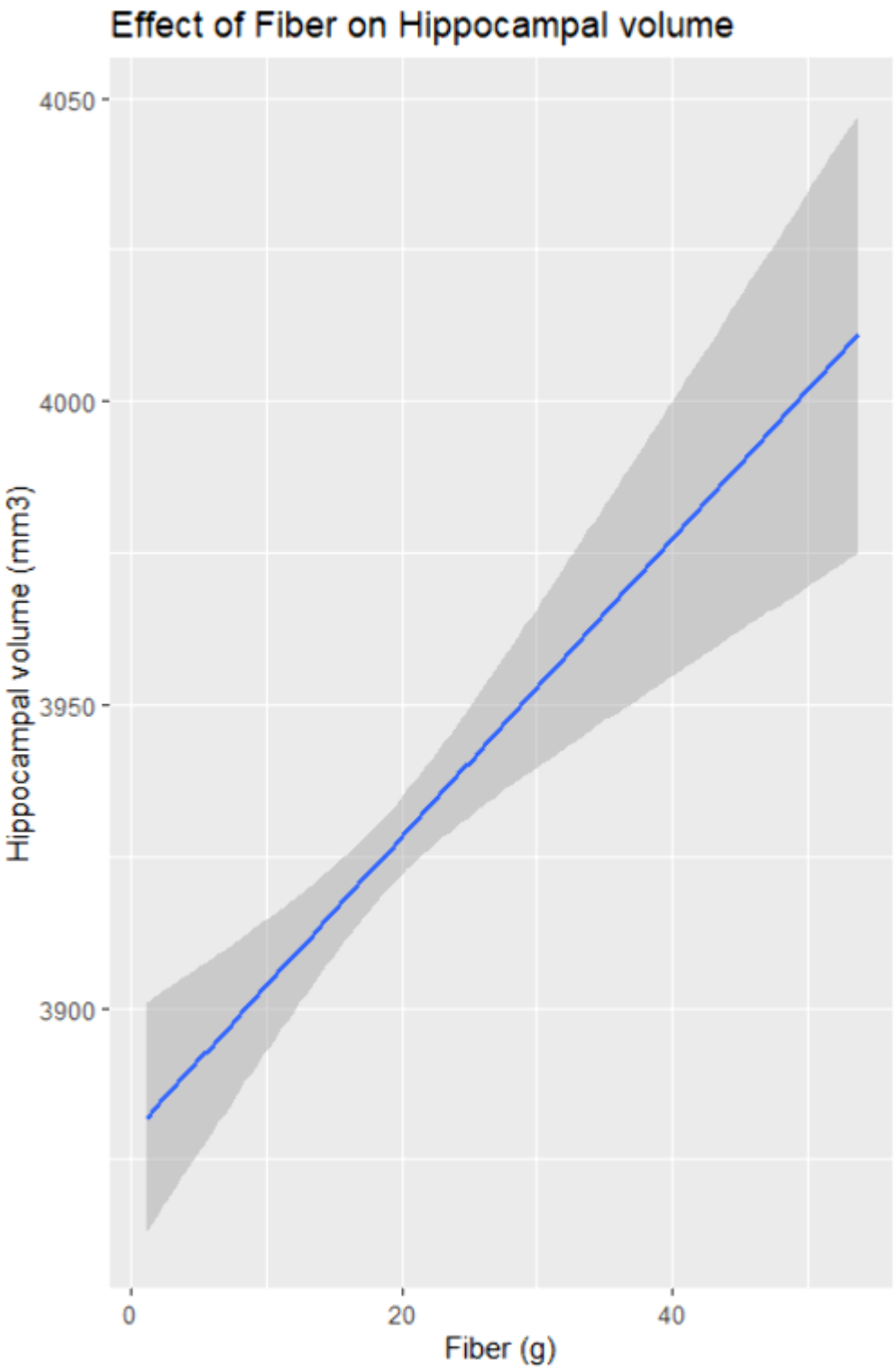
Aims: Dietary fiber is known to benefit for cognitive function. Previous studies have predominantly explored cross-sectional associations between fiber-rich diets and dementia. This study focuses on the association between dietary fiber intake and dementia
Methods: We utilized data from the UK Biobank, focusing on participants aged 55 and older who completed a 24-hour dietary recall survey. Fiber intake, quantified from these survey data, was log-transformed and used as the primary exposure variable. The main outcome of interest was all-cause dementia incidence, identified through self-reported interviews, linked hospital-admission data and death register data. Hippocampal volume and entorhinal cortical thickness from brain MRI were analyzed as secondary outcomes. Cox proportional hazards models with restricted cubic splines were used to account for the relationship between fiber intake and dementia risk, while multiple linear regression examined the effect of fiber intake on MRI measurements.
Results: During a median follow-up period of 12.02 years, a total of 1,997 participants developed dementia in a cohort of 109,043 participants with a mean age of 61.74 years. The mean fiber intake was 18.46g. The results showed a significant nonlinear U-shaped effect (p-value < 0.0001) of fiber on dementia risk, with an inflection point around 23.81g (log-transformed fiber=3.17) (Figure 1). Among 14,764 participants who underwent brain MRI, higher fiber intake was correlated with larger hippocampal volume (covariate coefficient [95% CI]: 1.051 [0.01, 2.09], p =0.045, Figure 2) but not with entorhinal cortex thickness. F1. A restricted cubic spline curve between fiber intake and dementia risk: evidence from relative hazard



estimates

F2.



Conclusions: In summary, moderate fiber intake was associated with a reduced risk of dementia and increased hippocampal volume, though higher intake did not confer additional benefits on dementia risk.

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SHIFT 01-340

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

DECODING THE GENETIC NEXUS: IN SILICO ANALYSIS OF PICALM SNPS IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline, marked by the accumulation of amyloid-beta plaques and hyperphosphorylated tau proteins. Genome-wide association studies (GWAS) have identified PICALM as one of the key genes in the context of late-onset Alzheimer's disease (LOAD), playing critical roles in cellular processes such as vesicular transport and autophagy. Vesicular transport is essential for synaptic function and neuronal communication, while autophagy is crucial for the clearance of damaged cellular components. By analyzing single nucleotide polymorphisms (SNPs) in PICALM, this study aims to uncover variants that may disrupt these functions and facilitate the pathogenesis of Alzheimer's disease. This research aims to identify SNPs in the PICALM gene through in-silico analysis and investigate their potential impact on disease progression.
Methods: SNP data was obtained from dbSNP, and pathogenicity was evaluated using tools such as CADD, DynaMut, HOPE, I-Mutant 2.0, M-CAP, Missense3D, MuPro, PANTHER, PMut, PolyPhen-2, and SIFT. Conservation scores from Consurf were used to identify conserved protein sites and non-synonymous SNPs. Protein modeling was performed using Phyre2 and Swiss-Model.
Results: Our analysis identified rs145115354, rs759277181, and rs1316349561 SNPs in the *PICALM* with potentially harmful effects. Notably, variants affecting the lipid-binding domain of the PICALM (Phosphatidylinositol-binding clathrin assembly protein) protein have been found to increase the instability of this protein, which may impair its normal function. This disruption could impact the functions of protein in vesicular transport and autophagy.
Conclusions: The in-silico analysis highlights three SNPs in the *PICALM* gene that could affect Alzheimer's disease molecular etiopathogenesis. Further experimental validation is needed to confirm these results and explore their implications for targeted interventions and possible therapies for Alzheimer's disease.

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SHIFT 01-341

Poster on Board - Shift 01
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

INCIDENCE OF DEMENTIA IN SWEDEN 1988-2017 (THE BETULA PROJECT)

Eva-Stina Hemmingsson[1], Fredrik Elgh[2], Jan Olsson[2], Bodil Weidung[3], Rolf Adolfsson[4], Maria Josefsson[5], Lars Nyberg[6], Hugo Lövheim[1]
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Aims: Several studies from different countries have indicated a decreasing age-adjusted incidence of dementia in recent years. The cause of this decrease is not known but several factors have been proposed. The aim of the study was to examine the incidence of dementia, as well as Alzheimer's disease and vascular dementia specifically, in the Betula epidemiological cohort study.
Methods: The incidence of dementia from 1988 to 2017 was investigated in the Betula cohort, a population-based cohort study in Umeå, Sweden, with 4.425 thoroughly investigated initially dementia-free participants. Dementia incidence (a total of 650 new dementia diagnoses) were recorded during a total of 66.140 person-years of follow-up.
Results: A significant decrease (-55.9% since its peak in about 2000 until 2017) in age-adjusted dementia incidence was found. The decrease was seen both for Alzheimer's disease and vascular dementia, although more pronounced for Alzheimer's disease.
Conclusions: The result supports existing trends that dementia incidence may be decreasing and indicate that this is not entirely driven by improved treatment of cardiovascular risk factors.

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2-3 April 2025

AROMHA BRAIN HEALTH TEST: A REMOTE OLFACTORY ASSESSMENT AS A SCREEN FOR COGNITIVE IMPAIRMENT

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Aims: Cost-effective, noninvasive screening methods for preclinical Alzheimer's disease (AD) and other neurocognitive disorders remain an unmet need. The olfactory neural circuits develop AD pathological changes prior to symptom onset.
Methods: To probe these vulnerable circuits, we developed the digital remote AROMHA Brain Health Test (ABHT), an at-home odor identification, discrimination, memory, and intensity assessment.
Results: The ABHT was self-administered among cognitively normal (CN) English and Spanish speakers (n=127), participants with subjective cognitive complaints (SCC; n=34), and mild cognitive impairment (MCI; n=19). Self-administered tests took place remotely at home under unobserved (among interested CN participants) and observed modalities (CN, SCC, and MCI), as well as in-person with a research assistant present (CN, SCC, and MCI). Olfactory performance was similar across observed and unobserved remote self-administration and between English and Spanish speakers. Odor memory, identification, and discrimination scores decreased with age, and olfactory identification and discrimination were lower in the MCI group compared to CN and SCC groups, independent of age, sex, and education.
Conclusions: The ABHT revealed age-related olfactory decline, and discriminated CN older adults from those with cognitive impairment. Replication of our results in other populations would support the use of the ABHT to identify and monitor individuals at risk for developing dementia.

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2-3 April 2025

THE POWER OF REPEATED ASSESSMENTS – WHO CARES ABOUT PRACTICE EFFECTS?

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Aims: Intra-individual fluctuations in cognitive and neuropsychiatric symptoms are a core feature of Alzheimer's disease. This variability can hinder the reliability of neuropsychological performance to detect treatment effects in clinical trials, requiring large sample sizes and long studies. While repeated assessments are routinely employed in other therapeutic areas to minimize endpoint variability, their utility in measuring cognition has been underexplored due to concerns that practice and learning effects could compromise the validity of repeated testing.
Methods: This work will present the results of a 6-month Phase 2 clinical trial in Alzheimer's disease, assessing cognition, neuropsychiatric symptoms and function every month using standard neuropsychological tests. Firstly, a conventional change from baseline to 6 months analysis will be performed. Then, averaged scores from multiple repeated assessments (at screening and baseline, as well as at 5-month and 6-month time points) will be calculated to explore their impact on endpoint variability. Descriptive statistics (mean, SD) and inter-correlation coefficient (ICC) analysis between monthly assessments will be presented for both methods. The effect size (Cohen's D) will be compared between the two methods. Furthermore, we will simulate and compare study designs based on a cognitive decline model leveraging the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu), showing that repeated assessments across the study duration can reduce the required sample size.
Results: The data from the Phase 2 clinical trial is currently being analyzed.
Conclusions: There is an urgent need for methodologies to improve the efficacy endpoints in Alzheimer's disease. Reducing variability in cognitive testing is crucial for designing smaller, more efficient clinical trials. Repeated assessments emerge as a promising and robust method to reduce variability, thus facilitating faster delivery of medicines to patients.

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2-3 April 2025

SEEKING OPTIMAL REPEATED FLUID BIOMARKER ASSESSMENTS TO ENHANCE PRECISION AND SAMPLE SIZE POWER IN CLINICAL TRIALS

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Aims: Plasma biomarkers are increasingly being used for clinical trial inclusion/exclusion criteria and as surrogate outcomes. However, these biomarkers exhibit within-subject variability. One way to cope with the within-subject variability is to assess biomarkers repeatedly within short intervals. Multiple measurements per individual can enhance biomarker precision, improving the signal-to-noise ratio and increasing statistical power. However, the impact of repeated biomarker measurements on sample size power in clinical trials is poorly understood. This study aims to determine the number of within-subject repeated measures needed to enhance sample size power for detecting pre-post trial changes in biomarkers.
Methods: Published data (Brum et al., 2023; Pontecorvo et al., 2022) and data from a pilot project conducted at the Massachusetts Alzheimer's Disease Research Center were used to estimate the within-subject mean and variability of repeated measures for plasma biomarkers (p-tau217, NfL, GFAP, Aβ42/40). We simulated data under various assumptions and analyzed the effects of increasing the frequency of within-subject assessments across both placebo and experimental conditions or groups. We evaluated the impact on sample size estimates.
Results: Increasing the number of assessments improved the statistical power to detect treatment efficacy using a generalized linear mixed-effects model. For example, raising the assessment frequency from one (the conventional approach) to three assessments during each placebo and experimental stage in cross-over design resulted in an average 20% increase in statistical power.
Conclusions: Repeated measures of biomarkers can enhance statistical power. Additional data is needed to validate the assumptions used in this study's simulations. As more trials incorporate plasma biomarkers as primary outcomes (e.g., Phase I) and surrogate outcomes (Phases II and III), optimizing the use of repeated biomarker assessments is crucial for designing efficient clinical trials.

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2-3 April 2025

DIAGNOSTIC PERFORMANCE OF ACTIGRAPHY IN ALZHEIMER'S DISEASE USING A MACHINE LEARNING CLASSIFIER – A CROSS-SECTIONAL MEMORY CLINIC STUDY

Mathias Holsey Gramkow[1], Andreas Brink-Kjær[2,3], Frederikke Kragh Clemmensen[1], Gunhild Waldemar[1,4], Poul Jørgen Jennum[2,4], Steen Gregers Hasselbalch[1,4], Kristian Steen Frederiksen[1,4]
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Aims: Movement activity, sleep and circadian rhythm are altered in Alzheimer's disease. These aspects can be determined with actigraphy using wearable sensors. We wanted to determine the diagnostic value of actigraphy in patients with AD in a memory clinic setting.
Methods: Single-center cross-sectional study. In total, 70 patients with AD (mean age 76.2 years), 29 with dementia with Lewy bodies (DLB) (76.2 years), 23 patients with cerebrovascular disease (CVD) (79.7), and 48 aged healthy controls (71.1 years) were included. Participants underwent 1-week actigraphy in home settings using two body-worn sensors (lateral femur and sternum) (SENS Motion). Activity patterns (amount of time spent walking, running, resting, etc.) were derived using a proprietary algorithm. By evaluating the distribution of these activity patterns during day- and nighttime, 510 activity-related features were extracted. These features were used to train a machine learning classifier using logistic regression with a minimum redundancy maximum relevance algorithm for feature selection. Performance was evaluated with nested leave-one-out cross-validation and compared to single feature classification using mean overall daily activity levels.
Results: Activity patterns (time spent walking, running, cycling, resting) as well as the robustness and fragmentation of the circadian rhythm differed across diagnostic groups (all P-values<0.05). Discriminatory performance was best (accuracy 80-89 % and precision 69-84 %) when machine learning was applied to actigraphy data to discriminate between dementia etiologies (AD vs. DLB + AD vs. CVD), while the AD vs. healthy model had a lower accuracy and precision of 66 %, similar to single feature classification.
Conclusions: Actigraphy revealed a lower activity level in AD and may serve as a supplement to diagnostic investigations in patients with suspected AD, especially for differential diagnostic purposes.

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2-3 April 2025

A COHORT STUDY ASSESSING THE FREQUENCY OF HEARING IMPAIRMENTS AND ASSOCIATIONS TO COGNITIVE DECLINE IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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Aims: Based on previous population-based studies hearing loss has been identified as one of the greatest modifiable risk factors for dementia in mid-life. This study sought to examine if the frequency of hearing loss among patients with mild cognitive impairment (MCI) are different than among healthy older adults, and if hearing impairments are associated with cognitive decline in MCI-patients.
Methods: This cohort study examined the hearing ability and cognitive performance of forty patients with MCI as well as sixty healthy older adults. All participants were assessed with objective measures of hearing and cognition, including pure-tone audiometry and a speech-in-noise test, as well as comprehensive cognitive tests examining memory functions, processing speed, executive functions, attention, and language.
Results: Hearing impairment when categorized as a pure-tone average (PTA) above 20 was found in 77.5% of patients with MCI, while 60% of healthy older adults had impaired hearing. There was no significant difference between the average PTA in the two groups, and the score on the speech-in-noise test was not worse in the MCI-patients when compared to healthy older adults. Only the Symbol Digit Modalities Test showed a significant association with measures of hearing in the MCI group, but this association did not reach significance when controlling for age.
Conclusions: Hearing impairment was present in 77.5% of MCI-patients, but the hearing ability was not different or worse in MCI-patients when compared to healthy older adults. That audiological measures did not differ between the groups suggests that there was no clear association between hearing impairment and the cognitive status of the MCI-patients and healthy older adults of this study. Age might be an important common factor in the association between hearing and cognition.

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NEUROPSYCHOLOGICAL TEST PERFORMANCE IN FOUR AFRICAN COUNTRIES: A CALL FOR LOCAL NORMS

Andrew Zaman[1], Pedro Mena[1], Katalina Mcinerney[1,2], Larry Adams[1], Goldie Byrd[3], Allison Caban-Holt[3], Christiane Reitz[4], Giuseppe Tosto[4], Paula Ogrocki[5,6], Brian Kunkle[1,7], Jonathan Haines[8,9], Jeffery Vance[1,7], Olusegun Baiyewu[10], Rufus Akinyemi[10], Margaret Pericak-Vance[1,7], Michael Cuccaro[1,7]
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Aims: Neuropsychological test results used to define clinical stages in dementia require normative adjustments. For instance, US researchers use nationally representative normative adjustments for age, education, and sex. It is widely accepted that normative values should be population-specific. This study examined country-specific differences in neuropsychological test performances in four AfDC countries to assess the need for local norms.
Methods: As part of the AFDC arm of the DAWN Alzheimer's Disease study, we recruited 448 Non-Cognitively Impaired individuals from Nigeria (N=249, 48% Female; mean age=72.9, mean education=8.7), Ghana (N=60, 75% Female, mean age=73.1, mean education=15.6), Kenya (N=93, 71% Female, mean age=80.1, mean education=4.3), and Ethiopia (N=46, 13% Female, mean age=66.4, mean education=9.3). An ANCOVA examined performance differences between countries with age, sex, and education as covariates on a multi-domain battery derived from the National Alzheimer Coordinating Center (NACC) Uniform Data Set V3 and tests developed for use in Africa.
Results: Our results yielded mixed findings. On tests such as Animal Naming, participants from the four countries showed no statistically significant differences. However, for most tests, there were significant

effects of country but no clear patterns. For example, participants from Nigeria and Ethiopia performed better than those from Ghana and Kenya on the Africa-specific Stick Design Test and IDEA Cognitive Screen. The opposite trend was seen for the Benson Complex Figure-Copy task as participants from Kenya and Ghana performed the best.

Conclusions: We found country-specific performance differences on several neuropsychological tests but no consistent pattern. This finding suggests the need for local normative values in Africa. Further studies will examine whether variables such as rurality could explain country-specific differences. Ensuring that neuropsychological test data are interpreted accurately will enhance diagnostic classification.

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SHIFT 01-369

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PROSPECTIVE EVALUATION OF PLASMA PTAU217 STABILITY AND DIAGNOSTIC ACCURACY FOR THE DETECTION OF ALZHEIMER'S DISEASE IN A MEMORY CLINIC

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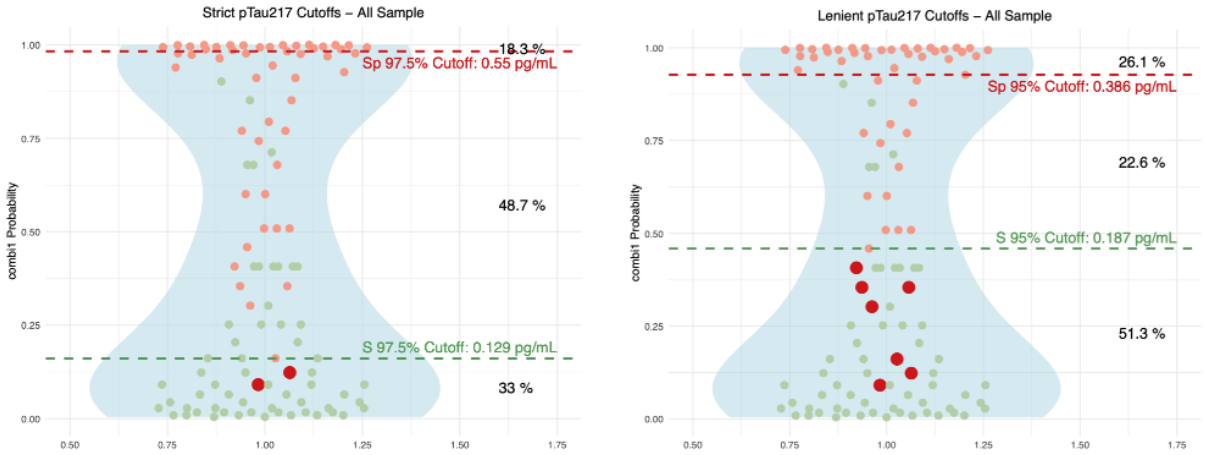
Aims: Understanding the impact of analytical variability and storage conditions is crucial for implementing plasma pTau217 in clinical settings. **Aims:** To investigate the pre-analytical and analytical stability of plasma pTau217 measured with LUMIPULSE and assess its diagnostic performance in detecting Alzheimer's disease (AD).
Methods: We prospectively measured pTau217 using the LUMIPULSE automated platform in consecutive patient samples collected between May and November 2024 at the Sant Pau Memory Unit (Barcelona). A subset underwent lumbar puncture for CSF AD biomarkers. We compared biomarker concentrations under different storage conditions (4ºC vs -20ºC) and assessed lot-to-lot variability. In participants with CSF biomarkers, logistic regression evaluated the association between plasma pTau217 and CSF amyloid status (A+ vs A-). Using ROC analysis, we evaluated the accuracy of established thresholds in this prospective cohort.
Results: We included 332 participants, classified into groups with CSF (n=126) and without CSF (n=206); mean age was 74 (±8) years, and 52% were female. Differences in biomarker concentrations between groups were attributed to variations in age, sex, and GDS distribution. Among those with CSF, 49% were A+, showing a fold-change of 5x in plasma pTau217 compared to A-. Plasma pTau217 concentrations were similar across storage conditions. The overall coefficient of variation was 3.2% (low control) and 1.8% (high control). Using a two-threshold approach, confirmatory testing (grey zones) was required for 48.7% of patients (strict cutoffs, 97.7% accuracy) and 22.6% (lenient cutoffs, 92.9%



accuracy)(Fig1).

Conclusions: The robust stability and low lot-to-lot variability of plasma $pTau_{217}$ measurement in an automated plaftorm result in high diagnostic performance of this biomarker in the prospective evaluation of patients in a memory clinic setting. These findings support its implementation into clinical routine, offering clinicians an accessible biomarker for AD diagnosis.

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SHIFT 01-370

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA EXTRACELLULAR VESICLES SHOW ALZHEIMER'S DISEASE PROTEOMICS HALLMARKS IN PATIENTS OF A MEMORY CLINIC

Maria Capdevila Bayo[1], Raquel Puerta Fuentes[1], Rosanna Rossi[2], Laura Montrreal[1], Álvaro Muñoz-Morales[1], Claudia Olivé[1], Itziar De Rojas[1], Pablo García-González[1], Pamela Martino-Adami[3], Laura Guzmán[4], Marina Carrasco[4], Marta Marquié[1], Montserrat Alegret[1], Antonio Camins[4], Alfredo Ramirez[3], Mercè Marti Ripoll[2], Maria Isabel Pividori Gurgo[2], Mercè Boada[5], Agustín Ruiz[6], Miren Ettcheto[4], Amanda Cano[1]
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Aims: Alzheimer's disease (AD) is commonly diagnosed when neuronal damage is already established and irreversible. A differential diagnosis in the mild cognitive impairment (MCI) stage is one of the greatest challenges nowadays. Blood biomarkers, and specifically plasma extracellular vesicles (pEVs), are gaining much interest as a new biomarkers' source for the early stages of AD. This work aims to evaluate the proteomic profile of pEVs from patients with MCI and AD to explore their potential as AD screening tools.
Methods: pEVs were isolated by ultracentrifugation from patients with MCI Aβ(+) (n=50), MCI Aβ(-) (n=50), and AD dementia (n=43). Nanoparticle tracking analysis (NTA) and cryo-TEM were used to characterize the pEVs. CSF, serum and pEVs proteomics were carried out by using the multiplex PEA technology of Olink© proteomics, Inflammation and Neurology Explore 364 panels (728 proteins).
Results: Characterization results showed that isolated plasma fraction corresponded in shape, size and concentration to EVs. pEVs' biomarkers correlated with common AD signatures (CSF Aβ42 and pTau181, plasma pTau181, MMSE, Age and Qalb) with the same pattern than CSF biomarkers as previously described. Several neurology proteins of the pEVs (e.g. MMP-8, MMP-9, IGF2R or NDRG1) didn't exhibit differences between the MCI Aβ(+) vs AD dementia groups, whilst MCI Aβ(-) vs AD dementia did. Likewise, many pEVs neurology proteins significantly correlated (rho>0.30 and p<0.05) with their CSF homonyms, not instead with their serum homonyms (e.g. APP, NOS1, CXCL11, SOD2, BCAN...).
Conclusions: Preliminary results suggest that the biomarkers signature of pEVs could inform about the AD

pathology in the prodromal stages of AD continuum. However, further experiments are still needed for a better understanding of the EVs' role in the AD development and pathology dissemination.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA BIOMARKERS FOR NEUROCOVID AND COGNITIVE DECLINE

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Aims: SARS-CoV-2 infection can lead to neurological deficits in a significant number of patients. NeuroCOVID seems to be associated with an increased risk of developing a neurodegenerative disorder or could accelerate its progression. The aim is to investigate a potential link between NeuroCOVID and cognitive decline in blood samples from patients to understand this phenomenon and develop new therapeutic strategies
Methods: 15 healthy subjects, 8 affected by NeuroCOVID and 7 with Mild Cognitive Impairment were selected. RNA was extracted and reverse transcribed from the patients' plasma. The concentration of miRNAs was assessed by RT-qPCR. For the analysis of circulating mitochondrial DNA (ccfree-mtDNA), DNA was extracted using the Norgen Kit. The number of copies/microliter of ccfree-mtDNA was determined by Digital droplet PCR using Taqman probes from Life Technologies.
Results: A study published by us identified three circulating miRNAs (miR-92a-3p, miR-320a and miR-320b) that regulate the MAPT gene differentially expressed in patients with frontotemporal dementia (FTD) compared to healthy controls and/or patients with Alzheimer's disease (AD). The analysis of these miRNAs carried out in our population highlighted a significant increase in the expression of miR-320a and miR-320b in NeuroCOVID patients compared to controls and a significant increase in miR-320b also in patients with MCI. There is no significant increase for miR-92a-3p. The number of copies of circulating mtDNA in plasma is significantly lower in MCI compared to controls and a similar trend is also observed in the group of patients with NeuroCOVID.
Conclusions: The results suggest that the parameters examined are associated with both the MCI and NeuroCOVID groups. Further analyses on these possible biomarkers could be useful to define common mechanisms between the two pathologies.

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SHIFT 01-372

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PREDICTING AMYLOID AND TAU PATHOLOGY WITH PLASMA BIOMARKERS IN ALZHEIMER'S DISEASE

Hanna Cho[1], Han-Kyeol Kim[2], Jae Hoon Lee[3], Joong-Hyun Chun[4], Tim West[5], Kris Kermess[5], Philip Verghese[5], Daniel Connell[5], Joel Braunstein[5], Young Hoon Ryu[3], Chul Hyoung Lyoo[1]
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Aims: This study aimed to evaluate the diagnostic value of plasma biomarkers to predict amyloid and tau pathology stages, as determined by positron emission tomography (PET)-based Thal phases for amyloid and Braak stages for tau in Alzheimer's disease (AD).
Methods: A total of 232 participants underwent ^{18}F-florbetaben and ^{18}F-flortaucipir PET imaging, as well as plasma biomarker assessments, including phosphorylated-tau217 (p-tau217), p-tau217/non-phosphorylated-tau217 (np-tau217) ratio, and amyloid-beta 42/40 (Aβ42/40) ratio. PET results were classified into Thal phase for amyloid and Braak stages for tau.
Results: For Thal phase for amyloid, participants with Thal phase I-II had significantly higher p-tau217 (η^2p = 0.285) and p-tau217/np-tau217 (η^2p = 0.418), and lower Aβ42/40 (η^2p = 0.069) compared to Thal phase 0. P-tau217 demonstrated strong predictive accuracy for distinguishing Thal phase I-II from Thal phase 0, with an AUC of 0.964, followed closely by p-tau217/np-tau217 (AUC = 0.965) and Aβ42/40 (AUC = 0.726). For Braak stage for tau, participants with Braak stage I-II had significantly higher p-tau217 (η^2p = 0.525) and p-tau217/np-tau217 (η^2p = 0.513) compared to Braak stage 0, with minimal differences observed in Aβ42/40 (η^2p = 0.015). P-tau217 showed moderate predictive accuracy for differentiating Braak stage I-II from stage 0 (AUC = 0.866), as did p-tau217/np-tau217 (AUC = 0.864), while Aβ42/40 had a lower predictive value (AUC = 0.595). For predicting Braak stage III or higher, both p-tau217 (AUC = 0.935) and p-tau217/np-tau217 (AUC = 0.925) showed high accuracy, with Aβ42/40 performing poorly (AUC = 0.586).
Conclusions: Both p-tau217 and p-tau217/np-tau217 ratio showed high accuracy in predicting PET-based amyloid and tau pathology stages in Alzheimer's disease. In particular, they were highly accurate in distinguishing Thal phase I-II and Braak stage III-IV, which are key stages for early intervention and treatment.

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SHIFT 01-373

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA BD-TAU AND RATIO P-TAU217/BD-TAU IN A MIXED MEMORY CLINIC COHORT

Frederikke Clemmensen[1], Fernando Gonzalez Ortiz[2], Mathias Holsey Gramkow[1], Nicholas Ashton[2,3], Kaj Blennow[2,4], Henrik Zetterberg[2,4], Gunhild Waldemar[1,5], Steen Hasselbalch[1,5], Kristian Frederiksen[1,5], Anja Simonsen[1]
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Aims: Aiming for better blood-based biomarkers reflective of Alzheimer's disease-type neurodegeneration, plasma brain-derived-tau (BD-tau) has shown promising results targeting non-peripheral tau compared to T-tau. This study examines short-term performance of plasma BD-tau compared to T-tau and corresponding ratios with p-tau217 in a memory clinic setting.
Methods: In memory clinic patients (AD n=27, non-AD n=20), we collected cerebrospinal fluid (CSF) and blood from a baseline visit and repeated blood samples twice within 36 days. We investigated the stability of plasma BD-tau and T-tau over time, the correlations between plasma and CSF, and calculated biological variation (BV) within- and between-subjects.
Results: We found significant correlations across visits and no effect of time on plasma T-tau or BD-tau. No significant correlations were found between plasma and CSF T-tau or BD-tau in this sample set, however the P-tau217/BD-tau ratio in plasma and CSF revealed a significant correlation (p-value 0.015, rho=0.39) compared to no correlation for P-tau217/T-tau (p-value 0.57, rho=0.09). Within-subject BV was similar for T-tau (9.6%[7.5;11,6]) and BD-tau (9.3%[7.5;11.3]) in the AD-group, however different from each other in non-AD (T-tau 12.5% [9.5;15.3], BD-tau (7.5%[5.8;9.2])). Regarding between-subject BV we found different variation between T-tau (17.4%[13.2;21.6]) and BD-tau (11.1%[9.0;13.1]) in AD, but not regarding non-AD (T-tau 18.7%[14.3;23.3], BD-tau 23.8%[16.6;30.3]).
Conclusions: BD-tau and T-tau levels in plasma were stable over the short time span. Significant correlation between plasma and CSF for the P-tau217/BD-tau could indicate that plasma BD-tau works better than plasma T-tau in reflecting AD-specific neurodegeneration in the CNS. Low within-subject BV for BD-tau in the non-AD group may reflect absence of AD-neurodegenerative processes in these patients,

whereas low between-subject BV for BD-tau in AD is promising considering possible application of BD-tau as a marker for AD-specific neurodegeneration.

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SHIFT 01-374

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

METHODOLOGICAL VALIDATION OF FOUR CHLIAS FOR ALZHEIMER'S DISEASE-RELATED BIOMARKER DETECTION IN CSF

Alessandro Dario Confettura[1], Katharina Römpler[1], Philipp Arendt[1], Britta Brix[1], Viola Borchardt-Lohölter[1], Anette Schulz[1], Mandy Busse[2], Stefan Busse[3]
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Aims: Determination of $A\beta_{1-42}$, tTau and pTau(181) concentrations and the $A\beta_{1-42}/A\beta_{1-40}$ ratio in cerebrospinal fluid (CSF) supports diagnosis of Alzheimer's disease. Certified reference material (CRM) used to evaluate the trueness of novel assays can increase standardization and comparability between diagnostic laboratories. Due to lack of CRMs for tTau, pTau(181), and $A\beta_{1-40}$, comparability may be assessed by comparing assays from different manufacturers. This study compares the performance of chemiluminescence immunoassays (ChLIAs) developed by EUROIMMUN with established chemiluminescence assays.
Methods: Biomarker concentrations were determined in 110 CSF samples (patients without known diagnosis; mean age 57.2 years, range 11–94 years; 49 female, 60 male, 1 unknown) using the Beta-Amyloid (1-42), Beta-Amyloid (1-40), Total-Tau and pTau(181) ChLIAs (all EUROIMMUN) and the corresponding Lumipulse G assays (Fujirebio). The assays were performed according to the manufacturers' instructions on the fully automated random-access devices IDS-i10 (Immunodiagnostic Systems) and LUMIPULSE G 600II analyzer (Fujirebio), respectively. Agreement of results obtained with the two chemiluminescence systems was calculated.
Results: Overall agreement ranged from 89.0% to 97.3%. Agreement for the determination of normal biomarker concentrations was 93.4%–100% and 57.7%–94% for abnormal concentrations. The level of agreement was highest for $A\beta_{1-42}$ determination. Pearson's regression coefficient revealed high correlation of results (R=0.82 to R=0.99 for $A\beta_{1-42}$ determination). While concentrations determined using EUROIMMUN assays were generally higher, numerical differences had minor influence on the diagnostic evaluation.
Conclusions: Using the EUROIMMUN ChLIAs, AD-specific biomarkers can be measured with high precision and stability on fully automated random-access devices. The highest level of agreement and correlation was found for $A\beta_{1-42}$ determination as assays are aligned to the respective CRMs. This indicates the need to introduce CRMs for standardization of $A\beta_{1-40}$, tTau, and pTau(181) assays.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

CHEMILUMINESCENCE IMMUNOASSAYS SUPPORT CATEGORIZATION OF ALZHEIMER'S DISEASE-RELATED BIOMARKER PROFILES ACCORDING TO THE ATN SYSTEM

Alessandro Dario Confettura[1], Philipp Arendt[1], Katharina Römpler[1], Britta Brix[1], Viola Borchardt-Lohölter[1], Anette Schulz[1], Mandy Busse[2,3], Stefan Busse[3]
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Aims: The ATN system categorizes results of Alzheimer's disease (AD)-related biomarker determination into three main categories: beta-amyloid (A), tau-pathology (T), and neurodegeneration (N) (Jack et al., 2016). Initially, this ATN system was developed for research purposes, but classifying results of biomarker determination also has the potential to support differential diagnosis of AD (e.g. identification of incipient AD or mixed dementias, Eckerstrom et al., 2021). This study analyzed residual cerebrospinal fluid (CSF) samples using four newly developed chemiluminescence immunoassays (ChLIAs) to measure established biomarkers and categorize the results according to the ATN system.
Methods: AD-related biomarker concentrations were determined using Beta-Amyloid (1-40), Beta-Amyloid (1-42), Total-Tau and pTau(181) ChLIAs (all EUROIMMUN) in CSF samples from 219 clinically characterized AD patients, 74 patients with mild cognitive impairment (MCI), and 220 disease control patients (DC) with various neuropsychiatric disorders. Biomarker concentrations were evaluated as normal (−) or abnormal (+) based on the respective assay's cut-off.
Results: ATN profiles consistent with AD were found in 83.1% of AD patients (A+T+N+: 73.1%, A+T+N−: 9.6%, A+T−N+: 0.5%) and inconsistent with AD in 77.0% of MCI (A−T−N−: 67.6%, A−T−N+: 5.4%, A−T+N−: 0%, A−T+N+: 4.1%) and 85.5% of DC patients (A−T−N−: 74.6%, A−T−N+: 7.3%, A−T+N−: 0.9%, A−T+N+: 2.7%).
Conclusions: Biomarker profiles were clearly distributed between AD versus DC and MCI patients. More MCI than DC patients revealed biomarker profiles indicative of pathological values for all three biomarkers. Thus, AD biomarker profiles determined in CSF using these ChLIAs effectively support differential diagnosis of AD and related disorders with neuropsychiatric symptoms.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

NEWLY DEVELOPED LC-MS/MS ASSAY FOR NEUROFILAMENT-LIGHT CHAIN (NFL) QUANTIFICATION: HEAD-TO-HEAD COMPARISON WITH IMMUNOASSAYS

Salomé Coppens[1], Etienne Mondesert[1], Anthony Fourier[2], Isabelle Quadrio[2], Jérôme Vialaret[1], Sylvain Lehmann[1], Christophe Hirtz[1]
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Aims: To develop, validate and compare with available immunoassays a new LC-MRM assay for NfL quantification.
Methods: A *multiple reaction monitoring* (MRM) method was developed on a triple quadrupole coupled to a liquid chromatography system (LC-MRM) to monitor four NfL tryptic peptides. The quantifier was GMNEALEK (324-331). CSF samples were spiked with the heavy labelled recombinant protein, oxidised with hydrogen peroxide, immunoprecipitated using ADx209 monoclonal antibody and tryptic digested overnight prior analysis. This protocol was analytically validated according to ICH guidelines and compared to available immunoassays. First, 12 pools CSF were analysed with the LC-MS assay, Lumipulse (Fujirebio) and the Simoa (Quanterix). Then, the comparison focused on LC-MS and Lumipulse with the analysis of 70 additional CSF samples.
Results: The LC-MS/MS method was successfully validated in terms of linearity [r^2 = 0.98-0.99], accuracy [76-98 %], repeatability [2-12 %CV] and intermediate precision [6-11 %CV]. Limit of detection and quantification were respectively 103.81 pg/mL and 207.62 pg/mL for the quantifier peptide. The correlation coefficient obtained between the LC-MRM and Simoa or Lumipulse were r^2 = 0.94 and r^2 = 0.98 respectively demonstrating a great correlation but the obtained absolute values were slightly higher with the LC-MRM assay.
Conclusions: To conclude, we developed and validated a new LC-MRM assays that allowed the analysis of 80 CSF samples. Good correlations were obtained with immunoassays for NfL quantification, but the absolute values were different. These observations pave the way and reinforce the need for standardization of this marker, with the development of a reference measurement procedure for CSF before moving on to blood.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

UNDERSTANDING SOURCES OF VARIATION IN ALZHEIMER'S DISEASE PLASMA BIOMARKERS TO OPTIMISE PRE-SYMPTOMATIC DISEASE DETECTION.

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Aims: Plasma biomarkers can identify early signs of Alzheimer's disease (AD). They may be able to play a role in stratifying pre-symptomatic individuals for anti-amyloid therapies. To better exploit these biomarkers, genetic and phenotypic contributions to their variation need to be accounted for. Here we characterise clinical, genetic and health associations of major AD plasma biomarkers in a cohort from the UK Biobank and assess if a broader panel of plasma proteins can model confounding factors.
Methods: We analysed Quanterix Simoa plasma AD biomarkers for Aβ40, Aβ42, pTau-181, NFL and GFAP in 1252 UK Biobank participants (46-80 years) across two assessments comprising the UK Biobank COVID imaging sub-study. We used linear models to assess associations with health, genetic, and OLINK proteomics data. Further models assessed how factors affected changes in biomarkers across the interval between sessions.
Results: Individuals with *PICALM* AD risk *v*ariants showed differences in all biomarkers. However, *APOE, SORL1, ABCA7* and *CLU* variants were associated only with differences in Aβ42 and GFAP concentrations. *APOE* predicted accelerated Aβ42 reductions between assessments. Plasma pTau-181, NfL and GFAP concentrations showed the most extensive associations with lifestyle factors and co-morbidities, many associated with AD risk (including obesity, hypertension and alcohol intake). Estimated renal glomerular filtration rate was significantly associated with levels of all biomarkers except Aβ42:Aβ40 ratio and GFAP. A simultaneously measured OLINK plasma proteomic panel of 1453 proteins could predict a substantial proportion of the variation in biomarkers associated with the assessed factors.
Conclusions: Plasma biomarkers appear differentially sensitive to genetic risk factors in mid-life and may be influenced by confounding effects of co-morbid disorders and other health factors. Extended plasma

proteomic panels may be useful to predict these sources of variance enhancing early and specific detection of AD pathology.

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EVALUATION OF THE FIRST BLOOD BASED CE-IVD CERTIFIED TEST FOR MORBUS ALZHEIMER – A REAL LIFE EXPERIENCE

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Aims: The accelerated development of disease modifying therapies targeting β amyloid for the treatment of Alzheimer's disease has increased the need for rapid and reliable biomarkers for the rapid screening and diagnosis of the disease. Current diagnostic biomarkers (amyloid PET-Scan or CSF analysis for Aβ42/40 and P-tau181) are limited to specialised institutions due to high costs and low availability. Recently, the first CE-IVD certified blood based test measuring amyloid ß42/40 ratio in plasma, has become available in Europe, allowing screening for Alzheimer in patients with clinical signs of dementia in Europe. We firstly report the application of this test in a large outpatient laboratory in Vienna.
Methods: Methods Determination of plasma amyloid ß42/40 ratio was performed by fully automated high-sensitivity chemiluminescence enzyme (HISCL) immunoassay. This is a magnetic bead enhanced capture chemiluminescence assay allowing high precision measurements in minimal quantities.
Additionally, a standardized pre-analytical pathway for the K_2EDTA sample tubes was established to ensure reliable measurement.
Results: Results The strict preanalytical standardisation resulted in >90% valid results, only 4 samples had to be excluded due to inappropriate material. Up to now ~50% of the patients had an amyloid ß42/40 ratio >0,102 with a low probability of Alzheimer disease, 34% had a ratio <0,093 indicating a high probability of a ß amyloid pathology, and 16% of the results within the grey zone of the assay.
Conclusions: Conclusions Plasma ß42/40 ratio has proven its practical applicability in outpatient routine and represents a valid screening tool in outpatient care. Due to its excellent negative predictive value, this assay allows valid exclusion of individuals without ß amyloid pathology.

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DIAGNOSTIC PERFORMANCE OF RT-QUIC ASSAY FOR DETECTING ALPHA-SYNUCLEIN IN CSF AND ASSESSING CO-PATHOLOGY EFFECTS IN A COHORT OF COGNITIVELY IMPAIRED INDIVIDUALS.

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Aims: This study evaluated the diagnostic performance of the RT-QuIC assay for detecting alpha-synuclein (aSyn) in CSF for the diagnostic of Dementia with Lewy Bodies (DLB) in a clinical cohort of cognitively impaired individuals.
Methods: A convenience sample of subjects with cognitive impairment (neurodegenerative and non-neurodegenerative) was selected, with available CSF samples at their first evaluation. Participants underwent clinical follow-ups ranging from 6 months to 12 years, with current diagnoses established according to consensus criteria. We assessed the diagnostic performance of the RT-QuIC aSyn for DLB diagnosis and the impact of AD copathology in biomarkers and clinical profile.
Results: The study included 600 subjects (mean age 67.5y (SD 11), mean MMSE 25 (SD 4.5), 49% female). The RT-QuIC assay detected aSyn in 85/89 (93%) of DLB, 30/304 (10%) of AD, 4/76 (5%) of FTLD, 0/61 of n-nd MCI, 1/43 (2%) of SCD and 0/32 healthy controls. The assay exhibited a sensitivity of 95.5% and specificity of 93.1% for DLB diagnosis, with a PPV of 71% and a NPV of 99%. Among the 265 patients with a CSF A+T+ AD biomarker pattern, 44 also tested positive for aSyn. No significant differences were found in MMSE scores, age, or age at onset between A+T+Asyn+ and A+T+Asyn- groups. The clinical diagnosis of the A+T+Asyn+ subjects were 8 DLB, 27 AD and 9 suspected AD+DLB copathology. A higher frequency of neuroleptic use was observed in patients with co-pathology (56.1% vs 36.5%, p=0.023). Both A+T+Asyn+ and A+T+Asyn- groups exhibited higher levels of CSF neurofilament light chain (p=0.025) and plasma GFAP (p=0.011) compared to the A-T-Asyn+ group, with no differences in plasma neurofilaments.
Conclusions: The RT-QuIC assay shows strong performance identifying DLB and detecting aSyn co-pathology in subjects diagnosed with AD.

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PLASMA VS. SERUM: WHICH IS BETTER FOR PROTEOMIC BLOOD BIOMARKER ANALYSIS? EVALUATION OF THE NOVEL NULISA PLATFORM

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Aims: Blood biomarker studies most often use plasma samples. Suitability of serum as an alternative sample type remains unclear, despite many clinical chemistry laboratories preferring it over plasma. We compared the technical performance of the novel NUcleic acid-Linked ImmunoSandwich Assay (NULISA) blood-based targeted proteomic biomarker assay in plasma and serum samples processed from identical blood draws in a memory clinical cohort.
Methods: Paired plasma and serum samples from 43 donors (75.2±7.8 years, 41.9% female, 32.6% clinically-assessed Alzheimer's Disease (AD)) from the University of Pittsburgh ADRC were analyzed using the NULISAseq CNS disease panel 120 (v2) on an Alamar ARGO™ system, following manufacturer protocols. Protein levels were quantified by NGS, normalized, scaled, and transformed to log2 NULISA Protein Quantification (NPQ) units. Spearman's rank correlation assessed concordance between plasma and serum NPQs, while the Wilcoxon rank-sum test evaluated differences in protein detection levels.
Results: The assay achieved high analyte detectability (95.7% ± 14.2%) with low variability (%CV: 4.9%). Strong correlations (Spearman rho: 0.75-0.96) were observed for traditional AD biomarkers (Aβ42, p-Tau217, p-Tau231, p-Tau181, GFAP, NEFL) across both matrices. ANXA5, NRGN, and Oligo-SNCA were significantly more detectable in plasma (log2 fold change: 9.72, 9.48, and 4.99), while TIMP3, S100A12, and BDNF showed higher levels in serum (log2 fold change vs. plasma: -2.91, -2.66, and -2.42). Notably, Aβ42, p-tau181, p-tau217, and p-tau231 levels were significantly higher in plasma than serum ($p<0.001$). Contrarily, GFAP and NEFL levels were similar in plasma and serum ($p>0.05$).
Conclusions: NULISAseq-based AD blood biomarkers in paired plasma and serum are highly correlated; however, the absolute levels significantly vary by matrix type. These findings highlight the importance of considering specimen type in clinical study designs to ensure the reliability and accuracy of AD biomarker diagnostics.

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SHIFT 01-381

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COMPARATIVE QUANTIFICATION OF NEUROFILAMENT ISOFORMS (NFM, NFL, NFH) IN CEREBROSPINAL FLUID OF NEURODEGENERATIVE PATIENTS

Badrieh Fazeli[1], Veronika Klose[1], Franziska Bachhuber[1], Paula Klassen[1], Sarah Jesse[1], Sarah Anderl-Straub[1], Albert Ludolph[1], Markus Otto[2], Hayrettin Tumani[1], Steffen Halbgebauer[1]
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Aims: Neurofilament isoforms, including neurofilament light (NfL) and heavy (NfH) chains, serve as valuable biomarkers in neurodegenerative diseases by reflecting neuronal damage, aiding in early diagnosis, tracking disease progression, and informing prognosis. However, the neurofilament medium chain (NfM) is less well characterized. This study aimed to evaluate NfM levels in a cohort of patients with neurodegenerative diseases using a newly developed NfM ELISA assay and to examine the correlation between the measured NfM, NfL, and NfH levels in cerebrospinal fluid (CSF).
Methods: We deployed a novel ELISA assay for the detection of NfM. For NfL and NfH the commercial Ella cartridges were applied. We measured a clinical cohort of 276 patients including amyotrophic lateral sclerosis (ALS) (n=91), Alzheimer's disease (AD) (n=30), Parkinson's disease (PD) (n=18), behavioral variant of frontotemporal dementia (bvFTD) (n=17), primary progressive aphasia (PPA) (n=21), control patients with initial diagnostic suspicion of ALS but finally diagnosed with another condition (Con.DD)(n=48) and non-neurodegenerative controls (Con) (n=51).
Results: NfM levels were significantly elevated in the ALS ($p<0.0001$), AD ($p=0.0003$), PPA ($p<0.0001$), and bvFTD ($p=0.0005$) cohorts compared to control patients. Additionally, all of these patient groups exhibited significantly higher NfM levels compared to the Con.DD group. Correlation analysis revealed a strong positive relationship between NfM and NfL ($r = 0.94$, 95% CI = 0.93-0.96, $p<0.0001$), and between NfM and NfH ($r = 0.71$, 95% CI = 0.64-0.76, $p<0.0001$).
Conclusions: In conclusion, the study demonstrated significantly elevated NfM levels in patients with ALS, AD, PPA, and bvFTD compared to control patients, and in comparison to the Con.DD group. Additionally, a strong correlation was observed between NfM and NfL levels, and between NfM and NfH levels, indicating a consistent relationship between these neurofilament subtypes across neurodegenerative conditions.

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DEVELOPMENT AND VALIDATION OF SANDWICH ELISA ASSAYS FOR DETECTING SYNTAXIN 1A AND 1B ISOFORMS IN CEREBROSPINAL FLUID

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Aims: Functional and morphological alterations of synapses are early pathological events in Alzheimer's disease (AD), occurring before major neurodegeneration. As essential components of the synaptic vesicle machinery, syntaxin 1A (STX1A) and syntaxin 1B (STX1B) are promising candidate cerebrospinal fluid (CSF) biomarkers for the detection of synaptic dysfunction in AD. This project aimed to develop sensitive enzyme-linked immunosorbent assays (ELISA) to detect STX1A and STX1B in human CSF samples.
Methods: We have developed two novel sandwich ELISA assays, one specific for STX1B and another for the detection of both isoforms. The established assays were validated regarding analytical performance, and subsequently, a cohort of AD patients (n=25) and non-neurodegenerative disease controls (n=15) were screened with the novel assays.
Results: The intra- and inter-assay coefficients of variation were below 15% for both assays. The lower limit of quantification (LLOQ) and limit of detection (LOD) for the STX1A&B assay were determined to be 96 pg/mL and 20.4 pg/mL, respectively, while the LLOQ for the STX1B assay was 19.7 pg/mL. A significant increase of both syntaxin isoforms was observed in the AD cohort (STX1A&B: median 1300 pg/mL, IQR 1044 -2046 pg/mL, STX1B: median 1486 pg/mL, IQR 1123 -1894 pg/mL) compared to the controls (STX1A&B: median 713 pg/mL, IQR 426 -1197 pg/mL, STX1B: median 792 pg/mL, IQR 698 -1255 pg/mL) ($p<0.05$).
Conclusions: We have successfully developed two sensitive assays for the detection of syntaxin 1A and 1B. The assays were technically validated and showed reliable performance. Preliminary results showed slightly higher levels of both isoforms in Alzheimer's disease samples compared to controls. A larger cohort of patients is required to further investigate and confirm these findings.

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IDENTIFYING CIRCULATING PROTEIN SIGNATURES FOR MILD COGNITIVE IMPAIRMENT IN PAIRED CSF AND PLASMA

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Aims: Aging is the most significant risk factor for Alzheimer's disease (AD), yet the biological pathways that differentiate healthy aging from pathological aging, which leads to neurodegeneration, remain unclear. Current clinical biomarkers for mild cognitive impairment in early AD focus primarily on a limited set of disease-related proteins and peptides (e.g., Aβ, Tau/pTau, NFL), which do not fully capture the complex pathology of early neurodegenerative stages. To address this gap, we employed a combination of proteomics tools leveraging quantitative mass spectrometry-based workflow as well as multiplexed ligand-binding assays.
Methods: Matched CSF and plasma samples were obtained from individuals at the same visit. Samples were collected from young control subjects (n= 53), subjects with mild cognitive impairment (MCI) (n = 40), age-matched healthy control subjects (n = 40) and subjects with autopsy-proven AD (n = 21). Cinical biomarkers were assessed using the Lumipulse G1200 system in all CSF samples. All plasma and CSF samples were analyzed on Biognosys' TrueDiscovery platform using DIA-MS. Selected plasma samples from MCI and age-matched healthy control subjects were profiled with multiplexed NULISAseq CNS panel 120.
Results: We employed mass spectrometry to investigate protein- and peptide-level changes associated with cognitive decline with aging. We identified novel patterns of alternative protein cleavage, splicing, and phosphorylation in key proteins involved in lipid metabolism, ECM structure, axonogenesis, and synaptic activity, including APP, APOE, COL4A2, NRXN1, and NRCAM. Additionally, plasma-based signatures for mild cognitive impairment were identified, reducing the need for invasive CSF collection.
Conclusions: By analyzing matched plasma and cerebrospinal fluid (CSF) proteomes from individuals undergoing healthy aging and those experiencing cognitive changes associated with early Alzheimer's, we generated an unbiased, quantitative map of proteoforms linked to both healthy and pathological aging.

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THE SERUM-BASED PROTEOME OF INCIDENT ALZHEIMER'S DISEASE USING THE SOMASCAN 7K PLATFORM

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Aims: As the incidence of late-onset Alzheimer's disease (LOAD) increases, there is a soaring need for effective diagnostic tools and disease-modifying therapies. As proteins in the blood can predict a variety of pathologies and have a regenerative function in both peripheral and central organs, the objective of this study was to capture blood-based proteomic signatures associated with incident LOAD using the SOMAscan 7K platform.
Methods: This study assed the abundance of 7,523 serum-based proteins using the SOMAscan v4.1-7K platform in 5,377 participants of the Age, Gene/Environment Susceptibility Reykjavík Study (AGES-RS). The proteins were measured from blood drawn at study baseline and their association with incident LOAD over a 16.9-year follow-up period was assessed using Cox Proportional Hazards models. Associations with Benjamini-Hochberg false discovery rate < 0.05 were considered statistically significant.
Results: We identified 94 serum proteins associated with incident LOAD in AGES-RS. Compared to our recently published study using the SOMAscan v3-5K platform, 48 of the proteins were novel.
Conclusions: Circulating proteins can inform on future risk of LOAD. In assessing proteins associated with LOAD prior to its diagnosis we aim to narrow down on biomarkers that could be useful for the diagnosis and monitoring of the disease. Future work will require evaluating the predictive performance of these novel proteins compared to established biomarkers. As the levels of these proteins change prior to LOAD diagnosis, they may point to therapeutic candidates for LOAD.

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CLINICAL AND BIOLOGICAL HETEROGENEITY IN EUROPEAN MCI POPULATIONS: INSIGHTS FROM THE AI-MIND PROJECT

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Aims: Mild cognitive impairment (MCI) represents a critical transition between normal aging and dementia, where early detection and risk assessment are essential, especially with emerging treatments for Alzheimer's disease (AD). The AI-Mind project, funded by the EU Horizon 2020 Research and Innovation Programme, seeks to reduce dementia's burden by developing AI-driven tools to support MCI diagnosis and early dementia risk assessment using accessible, cost-effective, non-invasive methods such as blood biomarkers, APOE genotyping, high-density EEG, and cognitive tests. The present study aims to investigate the differences in cognitive performance, ApoE genotype, and novel AD blood biomarkers within the AI-Mind MCI cohort.
Methods: Across five clinical sites in Norway, Finland, Italy, and Spain, 1022 MCI participants were enrolled. Baseline measures included neuropsychological tests, APOE genotype and plasma p-tau levels: p-tau181 was measured using the NeuroToolKit (Roche Diagnostics International Ltd), while p-tau217 was measured using the MesoScale S-PLEX Human Tau Kit on a MESO QuickPlexSQ 120MM instrument.
Results: APOE ε4 carriers constituted 36.2% of the analysed subjects, with a higher prevalence in Northern Europe. Cognitive performance varied significantly by country, revealing heterogeneous MCI profiles. Both plasma p-tau biomarkers were independently influenced by APOE ε4 status, clinical site, and age. Episodic memory and set-shifting tasks emerged as the most significant independent predictors of both p-tau levels.

Conclusions: This study highlights the diversity of clinical and biological MCI characteristics across Europe, emphasizing the need for standardised diagnostic tools. The AI-Mind project aims to address this need by developing AI tools for personalised dementia risk estimation. Future analyses will incorporate EEG data and monitor dementia progression in this cohort, providing critical insights into the mechanisms underlying cognitive decline and enhancing the precision of the AI-Mind predictive tools.

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2-3 April 2025

PLASMA AMYLOID PREDICTS AMYLOID ACCUMULATION IN PET A- NON-DEMENTED PARTICIPANTS

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Aims: As plasma biomarkers are increasingly used for Alzheimer's disease studies, the associations of plasma and PET biomarkers of β-amyloid (Aβ) in relation to Aβ accumulation and conversion from PET A- to A+ must be better understood.
Methods: We evaluated 58 non-demented participants from ADNI and 170 from the University of Pittsburgh (UPitt) who had plasma Aβ42 and Aβ40 outcomes and longitudinal PET Ab values. All participants were PET A- at baseline. Plasma Aβ42/40 values, analyzed through either the C_2N mass spectrometry-based assay (ADNI) or the Single molecule array (Simoa) methods on a Quanterix HD-X (UPitt). Aβ42/40 status was determined with a cut-off value of 0.15 in the ADNI set and 0.11 in the UPitt set. Kaplan-Meyer survival models evaluated the association of plasma Aβ42/40 status with risk of conversion to PET A+. Linear regression models, adjusting for baseline PET Aβ values, sex, age, and APOE*4 status, assessed the association of plasma Aβ42/40 values with Aβ accumulation.
Results: Kaplan-Meyer survival analysis results showed that plasma Aβ status distinctly differentiates PET A- trajectories. Linear regression models of the continuous measures revealed that, even with the inclusion PiB PET and the other covariates, plasma Aβ42/40 was significantly associated (ADNI: β=-142.29, p=0.002; UPitt: β=-0.27, p=0.02) with Aβ

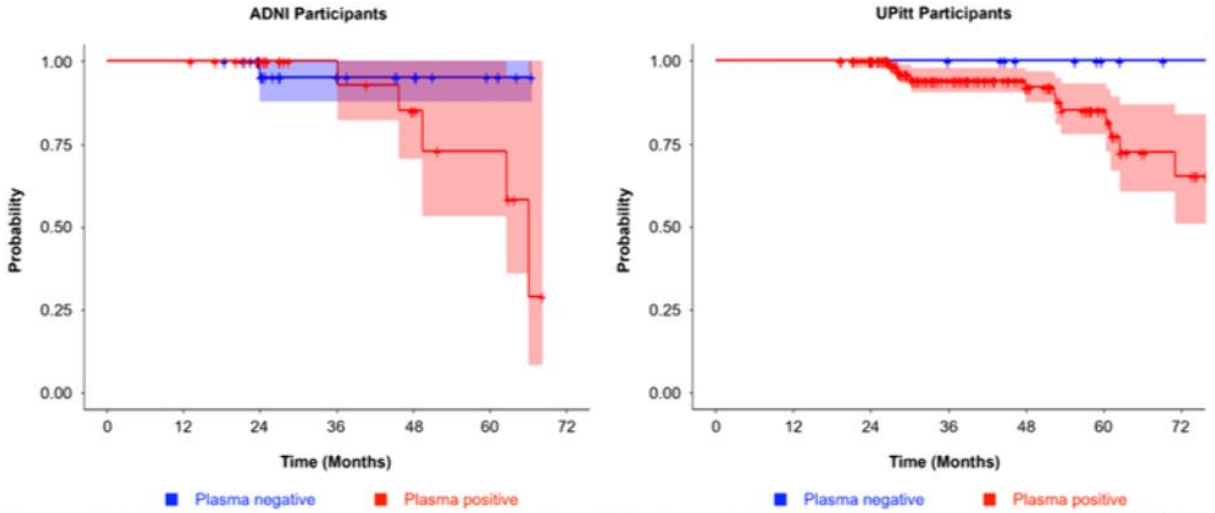

Figure 1. Kaplan-Meyer survival curves for PET A- subjects' risk of converting to PET A+, split into plasma A+/- groups.

accumulation.

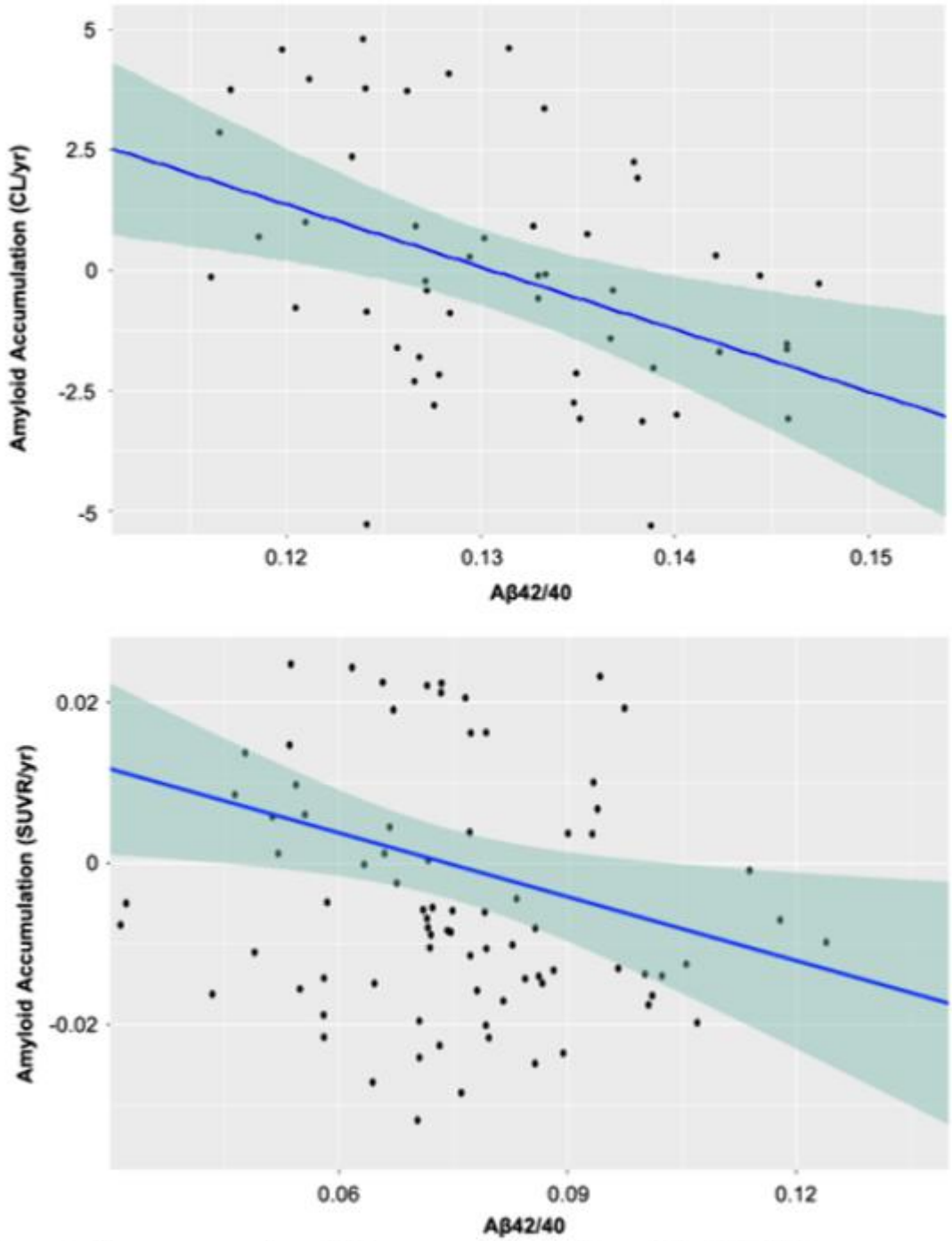

Figure 2. Linear regression of Aβ accumulation, adjusted for PiB PET, sex, age, and APOE*4 status, with plasma Aβ42/40. ADNI participants are on the top, UPitt are on the bottom.

Conclusions: The models suggest that plasma Aβ in PET A- participants predicts Ab accumulation, and eventual conversion from PET A- to PET A+. This follows the notion that soluble Aβ, measured in plasma or CSF, becomes abnormal before insoluble Aβ measured with PET does. Therefore, plasma Aβ-positive, Aβ-PET negative identify individuals at the very early stages of Aβ accumulation, at risk of progression, and likely to benefit the most from anti-Aβ therapy.

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SHIFT 01-387

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA PHOSPHORYLATED TAU181 AS A BIOMARKER FOR ALZHEIMER'S CO-PATHOLOGY IN LEWY BODY DISEASE

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Aims: Plasma phosphorylated tau181 (pTau181) is proving to be a useful predictor of Alzheimer's disease (AD). AD co-pathology is frequently observed across the Lewy body disease (LBD) spectrum. Here, we sought to determine whether pTau181 in LBD is associated with postmortem AD neuropathologic changes (ADNC) and with antemortem PET measurements of β-amyloid and tau deposition.
Methods: We studied 53 participants with LBD who underwent plasma pTau181 assessment, contrasting with 129 healthy control participants and 67 participants with AD. Postmortem assessments were conducted on 24 LBD cases. Spearman correlation analyses were used to assess the association between plasma pTau181 and the severity of amyloid deposits, tau accumulation and neurodegeneration (A/T/N) measured at autopsy or via neuroimaging.
Results: Plasma pTau181 in LBD participants was higher than in healthy participants and lower than in AD participants. Plasma pTau181 in LBD was moderately correlated with Thal stage, Braak NFT stage and CERAD scores but not Lewy body Braak stage. Plasma pTau181 was associated with cortical PiB retention. Elevated plasma pTau181 levels were associated with greater cortical thinning, particularly in later Braak NFT regions. The addition of plasma pTau181 improved models that included age, sex and APOE ε4 to detect amyloid and tau positivity.
Conclusions: Plasma pTau181 reflects β-amyloid and tau pathology but not α-synuclein pathology in LBD. Plasma pTau181 is a useful indicator in LBD for neurodegeneration in cortical regions vulnerable to NFT pathology and adds value in identifying Alzheimer's co-pathology. These findings support plasma pTau181 as a cost-effective screening tool for AD co-pathology in LBD.

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SHIFT 01-388

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA PHOSPHORYLATED TAU 217 IN RELATION TO ALZHEIMER DISEASE IN A CARIBBEAN HISPANIC POPULATION

Yian Gu[1], Lawrence Honig[2,3], Min Suk Kang[2], Angel Piriz[3,4], Dolly Reyes-Dumeyer[3,4], Cory Weinfeld[3], Badri Vardarajan[2,4,5], Richard Mayeux[1]
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Aims: Plasma-based phosphorylated tau 217 (P-tau217) has been increasingly used to identify Alzheimer's Disease (AD). We aimed to examine the association of plasma P-tau217 and other biomarkers with AD in an underrepresented population.
Methods: This cross-sectional study included 1,817 participants of a population-based cohort of Caribbean Hispanics. We measured P-tau217, P-tau181, P-tau231, amyloid beta (Aβ) 40, Aβ42, Glial Fibrillary Acid Protein (GFAP), and Neurofilament Light Chain (NfL). Participants went through consensus diagnosis of AD. Logistic regression models were used to examine the association of biomarkers with cognitive status, adjusting for age, sex, education, and *APOE*. ROC analyses were performed to examine the diagnostic value of P-tau217 and other biomarkers. An optimal cut-point derived based on the Youden index was used to define P-tau217 positivity.
Results: The participants were on average (SD) 71.3 (8.7) years old, had 6.5 (5.8) years of education. 67% were women, and 22.2% met criteria for AD. All biomarkers were significantly associated with odds of AD, with the highest odds ratio [OR (95%CI), p value] being 2.21 (1.91-2.57, p<0.0001) for P-tau217. The [OR (95%CI), p] was 0.88 (p=0.036) for Aβ42/40 ratio and ranged from 1.47 to 2.00 for other biomarkers (p<0.0001). A cut-point of 0.525 for P-tau217 was derived from ROC analysis (AUC = 0.718). Among P-tau217 negative individuals, higher level of NfL, and in P-tau217 positive individuals, higher level of GFAP, were significantly associated with increased odds of AD, adjusted for covariates. Replacing P-tau217 with P-tau181 or P-tau231 showed similar results.
Conclusions: Plasma P-tau217 is strongly associated with clinical AD, suggesting its value of identifying individuals with amyloid pathology. Additional biomarkers such as NfL and GFAP might help explain the heterogeneity of dementia.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

CLINICAL IMPLEMENTATION OF AGE-DEPENDENT SERUM GFAP REFERENCE VALUES FOR ALZHEIMER'S DISEASE

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Aims: Studies have demonstrated the usefulness of blood glial fibrillary acidic protein (GFAP) levels in the context of Alzheimer's disease (AD). Elevated levels of GFAP are however also observed in elderly individuals, highlighting the need for age-dependent reference values. Therefore, we aimed to establish age reference curves for serum GFAP based on a large cohort of control patients. In addition, we calculated age-dependent cut-off values for AD.
Methods: 952 non-inflammatory and non-neurodegenerative control, in addition to 321 AD patients were analyzed using the 2nd gen. ELLA GFAP assay.
Results: Regression curves for serum GFAP were constructed using percentiles and z-scores for the association with age. We observed a non-linear increase in GFAP from around 50 years of age in the control cohort, in contrast to a more linear increase in AD. Serum GFAP levels showed a moderate to strong correlation with age in controls ($r=0.62$ (95% CI: 0.58-0.66), $p<0.0001$) and a weak correlation in AD patients ($r=0.24$ (0.15-0.33), $p<0.0001$). GFAP levels were significantly higher in AD compared to controls ($p<0.0001$) with an AUC of 0.88 (0.86-0.90). Subsequent stratification of the cohorts into decades revealed age-dependent serum GFAP cut-offs. Furthermore, GFAP levels showed only a weak correlation with CSF ATN markers, but a more pronounced correlation with cognitive tests (MMSE $r = -0.32$ (-0.44 - -0.22), $p < 0.0001$ and CDR $r = 0.27$ (0.11-0.42), $p < 0.0011$).
Conclusions: Our results show that serum GFAP levels increase significantly after the age of 50. In addition, z-scores may be applicable across platforms and may provide valuable insights for patient follow-up to monitor disease progression and response to treatment. In the differential diagnosis of AD, the established age-dependent cut-offs may be more accurate than a single cut-off.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

CEREBROSPINAL FLUID AQUAPORIN 4 AS BIOMARKER FOR ALZHEIMER'S DISEASE

Steffen Halbgebauer[1], Nerea Gómez De San José[1], Petra Steinacker[2], Sarah Anderl-Straub[1], Samir Abu Rumeileh[2], Lorenzo Barba[2], Patrick Oeckl[1], Giovanni Bellomo[3], Lorenzo Gaetani[3], Andrea Toja[3], Sara Mravinacová[4], Sofia Bergström[4], Anna Månberg[4], Alberto Grassini[5], Innocenzo Rainero[5], Peter Nilsson[4], Lucilla Parnetti[3], Hayrettin Tumani[1], Markus Otto[2]
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Aims: Aquaporin 4 is a water channel located in the endfeet of astrocytes. Semi-quantitative studies have detected an elevation of AQP4 in CSF of Alzheimer's disease (AD) patients. In this multicenter study we aimed to establish a novel assay for the quantification of AQP4 levels in cerebrospinal fluid. Furthermore, we performed a technical and clinical validation in three independent patient cohorts.
Methods: In total 333 neurodegenerative (AD, amyotrophic lateral sclerosis (ALS), frontotemporal dementia, Lewy body disease (LBD)) and control patients (CON) from three independent centers (Ulm University Hospital (discovery), University of Perugia (validation cohort I), University Hospital of Torino (validation cohort II)) were analysed using the newly developed CSF AQP4 ELISA.
Results: CSF AQP4 was increased in the discovery cohort in AD patients compared to CON ($p < 0.001$), ALS ($p = 0.015$), and LBD ($p = 0.012$) patients. In validation cohort I, AD-MCI ($p = 0.011$) and ADD ($p = 0.002$) patients had significantly higher AQP4 concentrations than CON. In cohort II, AQP4 levels were also higher in AD-MCI ($p < 0.001$) and ADD ($p = 0.028$) patients compared to controls. CSF AQP4 distinguished AD from Con with an AUC of 0.81 (95% CI: 0.71-0.90, $p <0.001$) in the discovery cohort, 0.70 (95% CI: 0.60-0.81, $p<0.001$) in validation cohort I and 0.82 (95% CI 0.71-0.94, $p <0.001$) in II. Patients with AD-MCI could be distinguished from non-AD MCI with an AUC of 0.79 (95% CI: 0.65-0.93, $p = 0.002$).
Conclusions: Three independent cohorts consistently showed elevated AQP4 levels in AD. These findings contribute to understanding AD neuropathology and propose AQP4 as a potential early biomarker of AD. Further investigations are needed to proof AQP4 as a fluid blood brain barrier damage marker.

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BLOOD-BASED SIGNATURE OF ALZHEIMER´S PATHOLOGY IN PATIENTS WITH MILD BEHAVIORAL IMPAIRMENT DUE TO LATE-LIFE DEPRESSION

Niels Hansen[1], Sandro Ambrosini[1], Barbara Morgado[1], Anke Jahn Brodmann[1], Imke Amanzada[1], Chris Bauer[2], Johannes Schuchhardt[2], Hermann Esselmann[1], Hans-Wolfgang Klafki[1], Jens Wiltfang[1]
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Aims: Blood-based biomarkers are an excellent future tool to diagnose Alzheimer's disease (AD) early. Late-life depression is potentially AD's first manifestation in patients with major depressive disorder (MDD). Our goal is to find a blood-based signature of AD that can distinguish mild MDD-associated behavioral impairment (MBI) in elderly patients.
Methods: We chose 9 patients with MBI due to MDD in old age and a cerebrospinal fluid (CSF)-supported AD diagnosis (MBI-AD) compared to 9 patients with MBI due to MDD (MBI-MDD) in old age from our biomaterial bank. To identify an AD signature in CSF, we relied on a reduced Aβ1-42/Aβ1-40 ratio (<0.08) originating from the DELCODE [DZNE Longitudinal Cognitive Impairment and Dementia Study] cohort. We assessed Aβ1-40, Aβ1-42, p-tau181, p-tau217 and NfL immunoassays for EDTA plasma on the automated Lumipulse G600II system to determine blood-biomarkers. GFAP was measured via the SiMOA HD-1/HD-X analyzer platform. For statistical analysis we used Wilcoxon test to compare plasma levels of biomarkers between groups.
Results: The Aβ1-42/Aβ1-40 ratio revealed lower plasma levels in MBI-AD than MBI-MDD patients ($p<0.05$). Plasma p-tau217, the Aβ1-40/Aβ1-42 x p-tau 217 (AT^{217}-term) and p-tau217/p-tau181 ratios exhibited higher plasma levels in MBI-AD than MBI-MDD groups ($p<0.01$). However, the Aβ1-40, Aβ1-42, p-tau181, NfL and GFAP plasma levels did not differ significantly between groups. Among other plasma biomarkers we analyzed, the AT^{217}-term proved best able to predict CSF amyloid positivity with high diagnostic accuracy (AUC=0.914).
Conclusions: The Aβ1-42/ Aβ1-40 ratio, p-tau217, AT^{217}-term, and p-tau217/p-tau218 ratio seem to be diagnostically suitable to identify a blood-based signature of AD in MBI. Large-scale studies should be conducted to investigate the usefulness of these biomarkers for clinical diagnostics and patient care.

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SHIFT 01-392

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2-3 April 2025

USING PLASMA P-TAU FOR PRIMARY EFFICACY IN A 1-YEAR PHASE 1B PROOF-OF-CONCEPT STUDY BASED ON PREDICTION OF CLINICAL BENEFIT

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Aims: The past 5 years have seen an increased incorporation of plasma biomarkers into clinical research and practice related to Alzheimer's disease (AD). These biomarkers are now being used in clinical trials throughout the field. Aducanumab and lecanemab were approved based on PET amyloid for accelerated approval. Considering the potential of blood biomarkers to serve as predictors of clinical benefit, we modeled the relationship between plasma ptau-181 and 217 and clinical outcome in trials of anti-amyloid monoclonal antibodies (mABs) in AD.
Methods: We identified four randomized, placebo-controlled trials of mABs that included plasma p-tau outcomes. Clinical outcomes were combined in a Global Statistical Test (GST). A linear regression model was then applied to model the relationship between the biomarkers and clinical GST.
Results: Aducanumab, donanemab, and lecanemab data for plasma p-tau biomarkers and clinical assessments were obtained from the literature. Plasma p-tau is a strong predictor of clinical outcome (GST) at both 6 and 12 months, and the biomarker effect is approximately 2 times as sensitive as the clinical effect, resulting in a reduced sample size for similar power. A single/multiple ascending dose (SAD/MAD) study with 3 active doses in 3 cohorts of 36:12 active:placebo, with 20% dropout with 12 months duration can detect a Cohen's d effect size of 0.8 (the magnitude observed in Trailblazer 2) for plasma p-tau217 with 85% power at alpha=0.05 two-sided.
Conclusions: Our analysis suggests that the linear correlation between p-tau and clinical outcome GST can be utilized to facilitate trial design and even to estimate clinical benefit based on treatment effects on ptau-217.

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AGE, APOE4, AND BLOOD-BASED BIOMARKERS ARE RELATED WITH AMYLOID DEPOSITIONS IN SUBJECTIVE COGNITIVE DECLINE: RESULTS OF THE COSCO STUDY

Yun Jeong Hong[1], Seong Hye Choi[2], Sangyun Kim[3], Jee Hyang Jeong[4], Kee Hyung Park[5], Min Jeong Wang[6], Sungmin Kang[7], Dong Won Yang[8]
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Aims: The prediction of Alzheimer's disease (AD) pathologies is clinically important in subjective cognitive decline (SCD), given that clinical progression varies depending on the underlying pathologies. In this study, we investigated the cross-sectional relationships between clinical factors and amyloid PET positivity using multicenter cohort data.
Methods: The Cosco study, a Korean prospective multicenter cohort on SCD, was conducted between 2018 and 2021. Demographic data, lab results (including apolipoprotein epsilon [APOE] genotype and blood-based biomarkers), MRIs, and florbetaben PET scans were collected. The blood-based biomarkers included amyloid beta 42/40 (Aβ42/40), phosphorylated tau 181 (p-tau181), neurofilament light chain (NFL), and glial fibrillary acidic protein (GFAP). We assessed both direct and indirect relationships between age, APOE4, blood-based biomarkers, and amyloid PET positivity using path analyses.
Results: Aβ-positive SCDs (n=18) were older and had more APOE4 carriers than Aβ-negative SCDs (n=85). Amyloid positivity was associated with age, APOE4, and sex. A combination of age, APOE4, and plasma p-tau181 provided the best prediction for amyloidosis. Path analyses revealed that age was related to amyloidosis both directly and indirectly, mediated by p-tau181 and GFAP. The APOE4 allele was indirectly associated with amyloid positivity through mediation by p-tau181, GFAP, and Aβ42/40. Among the blood-based biomarkers, p-tau181 and GFAP showed the strongest association with amyloidosis. P-tau181 was also directly related to medial temporal volumes.
Conclusions: Age, APOE4, and plasma p-tau181 demonstrate favorable prediction for amyloid deposition. P-tau181 shows strong associations with both amyloidosis and neurodegenerations, making it a promising predictive biomarker for AD-related pathologies in SCD.

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AMYLOID B-REACTIVE T CELL POLYFUNCTIONALITY RESPONSE AS A NEW BIOMARKER FOR MILD COGNITIVE IMPAIRMENT

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Aims: Alzheimer's disease involves neuroinflammation and amyloid plaque deposition, yet the role of amyloid-reactive immune response in neurodegeneration remains unclear. We investigate amyloid-reactive T cell levels in the EMCIT and TPMIC cohorts.
Methods: Using diverse amyloid peptide formulations, we established a polyfunctionality assay for five T cell functions and compared MCI patients with control subjects in both cohorts.
Results: We established a T cell polyfunctionality assay using different amyloid peptide formulations to induce five immune functions. Samples from both cohorts showed enhanced amyloid-reactive T-cell responses in individuals with MCI. In the EMCIT cohort, the individual's amyloid peptide pool-reactive CD4+ and CD8+ total response frequencies were significantly larger in MCI patients (n=69; CD4+: 0.79%; CD8+: 0.67%) than in control individuals (n=69; CD4+: 0.27%; CD8: 0.4%; both $p < 0.05$). Notably, CD4+ T cell total response discriminated MCI versus control (AUROC, 0.72) with significantly higher accuracy than p-Tau181 (AUROC: 0.59, $p < 0.01$). In the TPMIC cohort, both amyloid peptide pool-reactive CD4+ and CD8+ total response frequencies were also higher in MCI individuals (n=41; CD4: 1.3%, CD8: 1.91%) than in control (n=79, CD4: 0.15%, CD8: 0.28%; both $p < 0.001$). Impressively, amyloid peptide pool-reactive total CD4+ and CD8+ T cell response frequencies outperformed p-Tau181 in their discriminative accuracy of MCI (CD4+ AUROC, 0.97; CD8+ AUROC, 0.96; p-Tau181 AUROC, 0.72; both $p < 0.001$). Other amyloid peptide formulations similarly increased T cell response in MCI individuals and demonstrated superior discriminative accuracy than p-Tau181.
Conclusions: Our findings implicate that circulatory amyloid-specific T cell responses can potentially be used to monitor disease activity and predict the prognosis of patients with cognitive decline. Amyloid-reactive T cell polyfunctional response distinguishes MCI from normal aging and could serve as a novel MCI biomarker.

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DEVELOPMENT OF A HIGHLY SPECIFIC P-TAU205 ASSAY USING A FULLY AUTOMATED IMMUNOASSAY SYSTEM

Kengo Ishiki[1], Takeo Kamakura[2], Shun Murakami[1], Aoi Tanaka[1], Kazuto Yamashita[1], Masahiro Miura[1], Kazuyoshi Shuta[2], Kanta Horie[2], Toshiyuki Sato[1]
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Aims: Recent advances in fluid biomarkers for Alzheimer's disease (AD) diagnosis are expected to enhance patient classification in clinical practice. Phosphorylated tau (p-tau), with multiple molecular species at different phosphorylation sites, exhibits concentration changes at various AD stages. Among these, p-tau205 measured by immunoprecipitation-mass spectrometry (IP-MS) method with high specificity showed the association with the tau pathology. In this study, to develop a convenient and automated method for p-tau205 measurement, we established a new immunoassay that demonstrates high correlation with the IP-MS method.
Methods: We developed p-tau205 immunoassay using Automated Immunoassay System HISCL™-5000 (HISCL). The IP-MS method for p-tau205 was developed in-house based on previously established methods. The correlation between p-tau205 levels measured by HISCL and IP-MS was evaluated in commercially available cerebral spinal fluids samples (n=17). To confirm the disease stage dependency, p-tau205 levels were measured by HISCL and compared between cognitively normal (CN, n=18) and clinically diagnosed AD groups (n=20).
Results: A significant correlation was observed between p-tau205 levels measured by HISCL and IP-MS, with Spearman's rank correlation coefficient at 0.97 ($p<0.001$). p-tau205 levels were significantly higher in the AD group than in the CN group ($p<0.001$).
Conclusions: Our p-tau205 assay showed high correlation with IP-MS method, suggesting excellent specificity of the assay. It also demonstrated higher levels of p-tau205 in the AD group, reflecting progression of tau pathology and highlighting the utility of this assay. We previously developed immunoassays for detecting plasma amyloid beta, p-tau181 and non-phosphorated tau using same approach. This p-tau205 assay can also be applicable for plasma samples. Such combinatorial measurement of biomarkers by simple immunoassays would contribute to the diagnosis of AD for patient classification based on the biomarker levels in clinical practice.

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PLASMA PROTEOMIC ASSOCIATIONS WITH ALZHEIMER'S DISEASE ENDOPHENOTYPES

Erik C. B. Johnson[1], Shiva Afshar[1], Eric B. Dammer[1], Shijia Bian[2], David Bennett[3], Richard Mohs[4], Doug Beauregard[4], John Dwyer[4], Nicholas T. Seyfried[1], Cecelia Manzanares[1], James J. Lah[1], Allan I. Levey[1]
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Aims: Alzheimer's disease (AD) is characterized by cerebral neurodegeneration associated with multiple neuropathologies. The peripheral protein changes associated with these AD endophenotypes are poorly understood.
Methods: We analyzed the plasma proteomes of four cohorts (*n*=2,103 participants) to identify proteins and pathways associated with cerebral β-amyloidosis and multiple other neuropathologies commonly associated with AD, as well as cognitive function.
Results: Plasma proteins positively associated with cerebral β-amyloidosis were enriched in synaptic and extracellular matrix (ECM) pathways, whereas proteins negatively associated with amyloidosis were enriched in metabolism and proteostasis pathways. The proteins most strongly associated with β-amyloidosis included kinetochore protein Spc25 (SPC25) and complexin-2 (CPLX2), linking amyloid pathology with markers of microtubule and synaptic function in blood. Many proteins strongly associated with cerebral β-amyloidosis were influenced by *APOE* ε4 genotype. Proteins positively associated with cognitive function were enriched in protein translation, vesicular transport, and mitochondrial pathways and included synaptic vesicle membrane protein VAT-1 homolog (VAT1) and amyloid beta precursor like protein 1 (APLP1), whereas proteins negatively associated with cognitive function were enriched in inflammation, fatty acid metabolism, and ECM pathways and included alpha-1-antichymotrypsin (SERPINA3). Analyses in a cohort with paired brain data showed that known neuropathologies could account for only half of proteins associated with cognitive function, and that many proteins in plasma associated with these neuropathologies are not strongly correlated to levels in brain.
Conclusions: Peripheral factors are associated with AD neuropathological endophenotypes. Biological pathways represented by these peripheral proteins may be targets of modifiable risk for AD.

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2-3 April 2025

DIAGNOSTIC VALUE OF SERUM GFAP, NFL, AND UCH-L1 IN NEURODEGENERATIVE DISEASES – DATA FROM CBAS

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Aims: This study aimed to assess the diagnostic utility of serum biomarkers—glial fibrillary acidic protein (GFAP), neurofilament light (NfL), and ubiquitin C-terminal hydrolase L1 (UCH-L1)—in differentiating Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD), and probable dementia with Lewy bodies (DLB).
Methods: Participants with MCI-AD (n=53), AD dementia (n=49), MCI-FTLD (n=25), FTLD dementia (n=21), probable DLB (n=29), and cognitively unimpaired (CU) individuals (n=37) were recruited from the Czech Brain Aging Study. Biomarker levels were analyzed using the Simoa technology. Analysis of covariance (ANCOVA) with post hoc Tukey's HSD and the receiver operating characteristic (ROC) curve analysis with age and sex as covariates were performed using the R statistical software.
Results: Serum GFAP levels were significantly elevated in patients with AD and DLB compared to CU individuals and in patients with AD compared to FTLD. NfL levels were higher in FTLD compared to AD and DLB. UCH-L1 levels were elevated in AD compared to FTLD, but less effective in differentiating AD from DLB. ROC analysis demonstrated moderate diagnostic accuracy for GFAP and UCH-L1 in distinguishing AD from FTLD, with Area Under the Curve (AUC) values of 0.80 and 0.85, respectively. NfL had lower diagnostic accuracy for differentiating AD from FTLD (AUC=0.64). Combining serum biomarkers improved diagnostic performance across all neurodegenerative conditions.
Conclusions: Our findings suggest that serum GFAP, NfL, and UCH-L1 are promising biomarkers for differentiating between AD, FTLD, and DLB, with GFAP showing the most potential. These biomarkers, particularly when used in combination, could enhance clinical diagnosis and patient stratification in neurodegenerative diseases. Further validation in larger cohorts is needed to confirm these findings.

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SHIFT 01-398

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PREVALENCE OF ABNORMAL PTAU217 IN AGING POPULATION

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Aims: Blood pTau217 is recognized as a good indicator of amyloidosis and may serve as an accurate tool for the diagnosis of Alzheimer's disease. Before implementing this biomarker in clinical practice, data on the general population are required. In this study, we evaluate the prevalence of abnormal pTau217 in an unsuspected Alzheimer population of autonomous aging subjects.
Methods: The SarcoPhAge cohort is a Belgian cohort of community-dwelling older adults. pTau217 was measured in 218 plasma samples collected at the second follow-up visit using the Lumipulse pTau217 kit. According to cut-offs previously reported by Arranz et al., negative amyloidosis subjects are <0.130 pg/mL, equivocal amyloidosis subjects are between 0.130 and 0.552 pg/mL and positive amyloidosis subjects are >0.552 pg/mL.
Results: In our cohort, 64.2 % were negative for pTau217, 33.5 % were in the intermediate zone and 2.3 % were positive for pTau 217. pTau217 was independently associated with age (rho: 0.252, p=0.0002), renal function (rho: 0.295, p<0.0001), MMSE (rho: -0.210, p=0.0019) and body mass index (rho: -0.156; p=0.0210). The percentage of doubtful patients was significantly higher in patients with chronic kidney disease (GFR< 45) (61.5 %) compared to patients with GFR > 60 (30.6 %). Regarding cognitive status, pTau217 was increased in patients with an MMSE score of 28-29 or an MMSE score ≤ 27 compared to subjects with an MMSE score of 30 (p=0.0029).
Conclusions: According to our data, one third of the aging population is eligible for neurological evaluation for amyloidosis. Our data support the notion that specific cut-offs or alternative methods should be developed for patients with chronic kidney disease.

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SHIFT 01-399

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

ANALYTICAL PERFORMANCE OF NOVEL CSF AND PLASMA NPTX2 PROTOTYPE ASSAYS ON THE FULLY AUTOMATED LUMIPULSE® G PLATFORM

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ADx NeuroSciences NV, Ghent, Belgium

Aims: Synaptic dysfunction is an early-stage indicator of pathology progression and neurodegeneration, and correlates to the degree of cognitive decline. NPTX2 could be a relevant synaptic biomarker for observing disease evolution or treatment response in patients with neurodegenerative diseases such as DLB, FTD, PD and psychiatric disorders such as schizophrenia (Das et al., 2023; Göverti et al., 2022). In addition, it may represent an important therapeutic target for TDP-43 proteinopathies (Hruska-Plochan et al., 2024). We aimed to develop and qualify a prototype Lumipulse G assay for quantification of NPTX2 in CSF, plasma and serum.
Methods: A prototype assay was developed using proprietary monoclonal antibody (mAb) ADx410 to capture NPTX2 combined with an alkaline phosphatase-conjugated Fab fragment digested from mAb ADx409. Extended analytical performance of the prototype assay was assessed.
Results: The assay demonstrates robust inter- and intra-run precision below 10% CV. CSF, plasma and serum can be diluted up to 10 times and NPTX2 can be measured accurately above the analytical LLOQ of 3.6 pg/mL in all three matrices. Parallelism was demonstrated from DF 2 and 4 to 20 for CSF and plasma, respectively. Spike recovery was obtained within the 80-120% interval. Analyte stability in CSF is proven up to 5 F/T-cycles. Testing of 20 paired serum-plasma samples for correlation resulted in a Pearson rho of 0.98 (slope 0.991).
Conclusions: A highly performant and automated prototype Lumipulse G assay for measuring NPTX2 in CSF, plasma and serum was developed using in-house NPTX2 specific mAbs. Given the high precision, this assay should allow to detect subtle differences between baseline and follow-up samples in a clinical trial context. Next step is evaluating the clinical performance of the marker, using the current assay in well-characterized cohorts.

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SHIFT 01-400

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA BIOMARKERS ASSOCIATED WITH LONGITUDINAL VOLUME CHANGE IN ALZHEIMER'S DISEASE SIGNATURE REGIONS AMONG SUBJECTIVE COGNITIVE DECLINE PATIENTS

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Aims: Plasma biomarkers are emerging tools for predicting amyloid positivity and future cognitive decline in Alzheimer's disease (AD). However, few studies have investigated their value in predicting future brain atrophy. This study aimed to identify which plasma biomarkers are associated with longitudinal atrophy rates in AD signature regions in patients with subjective cognitive decline (SCD).
Methods: This study included 103 participants from a cohort of 120 Korean SCD patients, with available plasma biomarker data (amyloid β ratio [Aβ40/Aβ42], glial fibrillary acidic protein [GFAP], neurofilament light chain [NFL], and phosphorylated tau [pTau181]) and follow-up MRI data (median interval of 721 days). The association between atrophy rates in regions of interest and each plasma biomarker was analyzed using linear regression models, adjusted for age, sex, education, and either APOE status, global standardized uptake value ratio (gSUVR) from [18F]florbetaben (FBB) PET, or the other plasma biomarkers. Analyses were also stratified by FBB PET positivity.
Results: The atrophy rate of the parahippocampal cortex was significantly associated with baseline Aβ40/Aβ42 after adjusting for age, sex, education, APOE status, gSUVR, or other plasma biomarkers. Aβ40/Aβ42 and its interaction with FBB PET positivity also predicted atrophy in the superior parietal cortex. GFAP was associated with volume loss in the amygdala, adjusted for age, sex, education, and APOE status. In the FBB PET-positive group, pTau181 predicted entorhinal cortex atrophy after adjusting for age, sex, education, APOE status, and gSUVR, while Aβ40/Aβ42 predicted superior parietal cortex atrophy even after full covariate adjustment.
Conclusions: Plasma biomarkers predicted future volume changes in AD signature regions in SCD patients.

In particular, baseline Aβ40/Aβ42 levels were associated with prospective atrophy rates in the parahippocampal and superior parietal cortices.

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SHIFT 01-401

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA AB42/P-TAU RATIO PREDICTS CSF ALZHEIMER'S PATHOPHYSIOLOGY IN SUBJECTIVE COGNITIVE DECLINE AND MILD COGNITIVE IMPAIRMENT IN A BRAZILIAN POPULATION

Marcio Balthazar[1], Isadora Ribeiro[1], Marjorie Silva[1], Liara Rizzi[2], Italo Aventurato[1], Luis Eduardo Santos[3], Gustavo Fernandes[4], Fernanda De Felice[3]
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Aims: To evaluate if plasma measurements of Aβ42/Aβ40, Aβ42/p-Tau181, and Aβ42/T-tau ratios can predict cerebrospinal fluid (CSF) Alzheimer's disease pathophysiology alterations in patients with Subjective Cognitive Decline (SCD) and Mild Cognitive Impairment (MCI) in a Brazilian population.
Methods: We evaluated 78 individuals (13 diagnosed with SCD, 48 MCI and 17 controls). All participants underwent neuropsychological assessment, magnetic resonance imaging and blood tests. MCI and SCD individuals performed cerebrospinal fluid tests. Roche's Elecsys immunoassay measured the quantification of CSF Aβ42 peptide, p-Tau 181, p-Tau231 and t-Tau. Plasma biomarkers Aβ42, Aβ40, p-Tau 181, and t-Tau were measured on an automated SIMOA HD-X immunoassay equipment. Logistic regression models considering Aβ42/Aβ40, Aβ42/p-Tau181and Aβ42/t-Tau ratios in plasma, age, sex and APOE E4 status were performed, as well as ROC curve analysis to evaluate sensitivity and specificity.
Results: There were no differences between CSF and plasma biomarkers in the groups. Moderate correlations were found between: CSF Aβ42 and plasma Aβ42/Aβ40 ($r = 0.441$, $p = 0.0009$); CSF p-Tau231/Aβ42 and plasma t-Tau ($r = 0.429$, $p = 0.019$); CSF Aβ42 and plasma Aβ42/p-Tau181 ($r = 0.426$, $p = 0.0015$); CSF p-Tau231 and plasma t-Tau ($r = 0.408$, $p = 0.002$). The full regression model was significant, $\chi^2(4, N = 50) = 16.30$, $p = 0.006$. Only plasma Aβ42/p-Tau181 was significant as predictor ($p = 0.01$). ROC curve considering plasma Aβ42/p-Tau181as predictor of CSF alteration showed an AUC = 0.849 (95% CI: 0.72-0.97), $p = 0.001$. At the threshold of 0.329, sensitivity of 80% and specificity of 88.4%.
Conclusions: The plasmatic Aβ42/p-Tau181 ratio could predict CSF amyloid alteration with good sensitivity and specificity in subjects at prodromal dementia in a racial admixed population. It is crucial to validate these findings across diverse populations of the Global South.

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SHIFT 01-402

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

A PROSPECTIVE, OBSERVATIONAL STUDY INVESTIGATING THE REAL-WORLD IMPLEMENTATION OF CONFIRMATORY DIAGNOSTIC BLOOD-BASED BIOMARKERS FOR EARLY ALZHEIMER'S DISEASE: A FEASIBILITY ASSESSMENT

Daryl Jones[1], Marwan Sabbagh[2], Jo Vandercappellen[1], Leah Zullig[3], Nicholas Giordano[4], Feride Frech[1], Christine Divers[1], Soeren Mattke[5], Harald Hampel[1]
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Aims: This study aims to assess the feasibility of implementing blood-based biomarkers (BBMs) as amyloid pathology confirmatory diagnostic tools for early Alzheimer's disease (AD) in real-world settings.
Methods: This prospective, multi-clinic, observational, real-world study is being conducted in three US memory clinics using confirmatory BBMs and receiving referrals for patients with suspected cognitive decline. The study evaluates the reach of confirmatory BBMs, i.e., the proportion and representativeness (e.g., sex, race, age) of patients with a first referral for cognitive decline who receive a BBM-confirmed diagnosis over a 6-month study period vs. standard of care. The time and number of visits from initial assessment for mild cognitive impairment (MCI) to confirmed diagnosis for confirmatory BBMs vs. standard of care will also be investigated. The BBM studied is Precivity AD2™, which analyses the Aβ42/40 ratio and p-Tau217 ratio with a performance meeting the confirmatory BBM criteria established by the Global CEO initiative on AD. Secondary data from ~60 patients aged 55 years or over presenting with suspected cognitive decline will be collected using electronic medical records. Data include date of biomarker-confirmed diagnosis (with BBMs or other diagnostic modalities) or clinical diagnosis, date of clinical assessment for MCI, dates of diagnostic procedures, adverse events associated with diagnostic procedures, and patient characteristics.
Results: This interim analysis will review patient baseline characteristics and available data on the reach, time to and number of visits required for a BBM-confirmed diagnosis vs. standard of care.
Conclusions: Findings will provide insight into the feasibility of and potential barriers to the implementation of confirmatory BBMs into routine care, including information on the representativeness of patients accessing BBMs and time to a BBM-confirmed diagnosis of early AD.

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SHIFT 01-403

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

HEALTH CARE PROVIDERS' PERSPECTIVES ON THE REAL-WORLD USE OF CONFIRMATORY DIAGNOSTIC BLOOD-BASED BIOMARKERS FOR EARLY ALZHEIMER'S DISEASE

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Aims: This study aims to assess the feasibility of implementing blood-based biomarkers (BBMs) for amyloid pathology confirmation to diagnose early Alzheimer's disease (AD).
Methods: A prospective, multi-clinic, real-world evidence study is being conducted at three US memory clinics using confirmatory BBMs and receiving referrals for patients with suspected cognitive decline. The study assesses implementation science outcomes, including clinician acceptability and appropriateness, and investigates perceived barriers and facilitators for the implementation of confirmatory BBMs utilising the Consolidated Framework for Implementation Research model. The BBM studied is Precivity AD2™, which analyses the Aβ42/40 ratio and p-Tau217 ratio with a performance meeting the confirmatory BBM criteria established by the Global CEO initiative on AD. Clinicians and other providers recruited from the three clinics will complete three quantitative validated questionnaires: the Feasibility of Intervention Measure, Acceptability of Intervention Measure and Intervention Appropriateness Measure. Qualitative data from semi-structured interviews and focus groups will also be collected, with the goal of understanding the feasibility of using BBMs and their impact on clinical workflows.
Results: This interim analysis will review available quantitative and qualitative data from clinician surveys and interviews. Clinician acceptability and appropriateness, and perceived barriers and facilitators for the implementation of confirmatory BBMs will be reported.
Conclusions: This study will identify both barriers to and enablers of adoption for the use of confirmatory BBMs in routine care, and provide insights into how barriers can be overcome, with the aim of simplifying the AD patient care pathway.

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SHIFT 01-410

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

AN ALZHEIMER'S DISEASE DIAGNOSTIC METABOLITE

Paul Cox, Sandra Banack
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Aims: In order to rapidly diagnose, facilitate earlier therapeutic interventions, and monitor clinical trials, we here report a stable biomarker from blood samples to characterize early-stage Alzheimer's disease (AD). Currently, in addition to cognitive evaluations, the presence of two proteins or protein fragments, derived from beta-amyloid 42 and phosphorylated-tau in patient samples, are being used for AD diagnosis. Unfortunately, these proteins are not independent of the targets for AD drugs currently being developed. Having an unrelated molecule which can both diagnosis AD and follow disease progression will accelerate research and drug discovery.
Methods: We analyzed blood plasma collected in K2EDTA tubes from early-stage AD patients, late stage AD patients, and blood plasma collected from healthy controls. Following a TCA precipitation step, we measured the concentrations of blood metabolites with two different analytical platforms, Amino Acid Analyzer and Tandem Mass-Spectrometer.
Results: We report a new blood biomarker which completely separates blood sapmles from early-stage AD patients, as well a late-stage AD patients from healthy donor blood plasma. We found that plasma concentrations of a phospholipid metabolite, 2-aminoethyl dihydrogen phosphate, normalized by taurine concentrations, distinguish blood samples of AD patients from blood samples of controls with high accuracy. Increasing disease severity correlates with increased concentrations of the metabolite.
Conclusions: We developed a diagnostic biomarker which is not related to AD protein misfolds and protein fragments. Current laboratory analyses suggests that concentrations of this new biomarker have not only diagnostic value, but also increases with disease progression, and therefore may have prognostic value.

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SHIFT 01-411

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

SALIVARY LACTOFERRIN LEVELS IN DOWN SYNDROME: A CASE-CONTROL STUDY

Desiree Antequera[1], Lucia Sande[2], Eliane Garcia[2], Deborah Romualdi[1], Laura Carrero[1], Cristina Municio[1], Pedro Diz[2], Eva Carro[1]
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Aims: Individuals with Down Syndrome (DS) have a high age-dependent risk of developing Alzheimer's disease (AD). Low lactoferrin levels, one of the main antimicrobial proteins present in saliva, has been associated with AD in the general population. The main objective was to evaluate whether salivary lactoferrin levels change across the life span of individuals with DS.
Methods: Samples were collected to analyzed salivary lactoferrin levels in children and adults with DS attending special educational or occupational therapy centers in Santiago de Compostela, Lugo, and Madrid (Spain) . Salivary lactoferrin and total protein concentration were measured.
Results: Median of salivary lactoferrin were higher among DS individual versus controls, in parallel to salivary total protein. There were no differences in the ratio of lactoferrin to total protein in saliva between DS and control groups. Only DS individuals had higher median salivary lactoferrin levels in the age group under 45 years. Salivary levels of lactoferrin increased with aging in healthy control subjects. However, these results changed when salivary concentrations of lactoferrin were normalized to the total protein concentration. Meanwhile non-significant differences were detected for the ratio salivary lactoferrin levels to total salivary protein between DS and control groups under 45 years, those levels were lower in DS subjects over 45 years old compared with the age-matched control group. Moreover, the ratio of salivary lactoferrin levels to total protein in DS subjects was associated with cognitive decline being lower in demented group comparing with mild and moderate cognitive impairment groups.
Conclusions: Salivary lactoferrin was dysregulated in DS, with significant lower ratio of salivary lactoferrin levels to total salivary proteins in individuals with DS over 45 years old, a population with a gradually increasing risk of AD.

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SHIFT 01-412

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

MODELING THE DYNAMICS OF PROTEINS IN BLOOD AND CEREBROSPINAL FLUID IN HUMAN IN VIVO

Pierre Giroux[1], Jérôme Vialaret[2], Jana Kindermans[3], Audrey Gabelle[4], Luc Bauchet[5], Christophe Hirtz[5], Sylvain Lehmann[2,3,5,6,7], Jacques Colinge[1]
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Aims: The analysis of protein dynamics or turnover in patients has the potential to reveal altered protein recycling, such as in Alzheimer's disease, and to provide informative data regarding drug efficacy or certain biological processes.
Methods: CSF and plasma samples were collected over 36 hours following an intravenous infusion of the isotopic tracer 13C6-Leucine. Preparation involved protein depletion, digestion, and LC-MS analysis to measure protein turnover and tracer incorporation. A compartment mathematical model calculated protein synthesis rates, correcting for intensity variations and noise. An automated pipeline further identified and validated protein dynamics, employing bootstrapping for confidence estimation.
Results: We report an accurate 3-biological compartment model able to simultaneously account for the protein dynamics observed in blood plasma and the CSF including a hidden CNS compartment. We successfully applied this model to 69 proteins of a single individual displaying similar or very different dynamics in plasma and CSF. This study puts a strong emphasis on the methods and tools needed to develop this type of model. We also propose a novel modeling approach to capture population protein dynamics using Bayesian methods. Using two datasets, we demonstrate that we can accurately capture protein turnover within a cohort and account for inter-individual variability.
Conclusions: The 3-biological compartment model we proposed displayed excellent numerical properties for parameter estimation, it was accurate, and it remains physiologically reasonable. This model combined with Bayesian parameter estimation could precisely capture the dynamics of all the 69 proteins and their different dynamics. This study has established a new type of mathematical model for the protein turnover community, which we believe should greatly facilitate the description and comparison of natural and pathological protein turnover at the most relevant scale, the population.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

MODELING THE SIMULTANEOUS DYNAMICS OF PROTEINS IN BLOOD PLASMA AND THE CEREBROSPINAL FLUID IN HUMAN IN VIVO

Pierre Giroux[1], Jérôme Vialaret[2,3,4], Jana Kindermans[5], Audrey Gabelle[6,7,8], Luc Bauchet[9], Christophe Hirtz[2,3], Sylvain Lehmann[2,3,4,5,9], Jacques Colinge[1]
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Aims: The analysis of protein dynamics or turnover in patients has the potential to reveal altered protein recycling, such as in Alzheimer's disease, and to provide informative data regarding drug efficacy or certain biological processes.
Methods: CSF and plasma samples were collected over 36 hours following an intravenous infusion of the isotopic tracer 13C6-Leucine. Preparation involved protein depletion, digestion, and LC-MS analysis to measure protein turnover and tracer incorporation. A compartment mathematical model calculated protein synthesis rates, correcting for intensity variations and noise. An automated pipeline further identified and validated protein dynamics, employing bootstrapping for confidence estimation.
Results: We report an accurate 3-biological compartment model able to simultaneously account for the protein dynamics observed in blood plasma and the CSF including a hidden CNS compartment. We successfully applied this model to 69 proteins of a single individual displaying similar or very different dynamics in plasma and CSF. This study puts a strong emphasis on the methods and tools needed to develop this type of model. We also propose a novel modeling approach to capture population protein dynamics using Bayesian methods. Using two datasets, we demonstrate that we can accurately capture protein turnover within a cohort and account for inter-individual variability.
Conclusions: The 3-biological compartment model we proposed displayed excellent numerical properties for parameter estimation, it was accurate, and it remains physiologically reasonable. This model combined with Bayesian parameter estimation could precisely capture the dynamics of all the 69 proteins and their different dynamics. This study has established a new type of mathematical model for the protein turnover community, which we believe should greatly facilitate the description and comparison of natural and pathological protein turnover at the most relevant scale, the population.

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SHIFT 01-414

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

APPLICATION OF THE 2024 REVISED CRITERIA FOR DIAGNOSIS AND STAGING OF ALZHEIMER'S DISEASE IN THE ALBION COHORT.

Iliana Gkelmpesi[1], Ioannis Foukarakis[1], Xenia Androni[1], Thalia Aggelopoulou[1], Georgios Velonakis[1], Efstratios Karavasilis[1], Foteini Christidi[1], Georgina Angelopoulou[1], Eva Ntanasi[1], Eirini Mamalaki[1], Angeliki Tsapanou[2], Mary Yannakoulia[3], Kostas Patas[4], Stylianos Chatzipanagiotou[4], Christopher Papandreou[5,6], Nikolaos Scarmeas[1,2]
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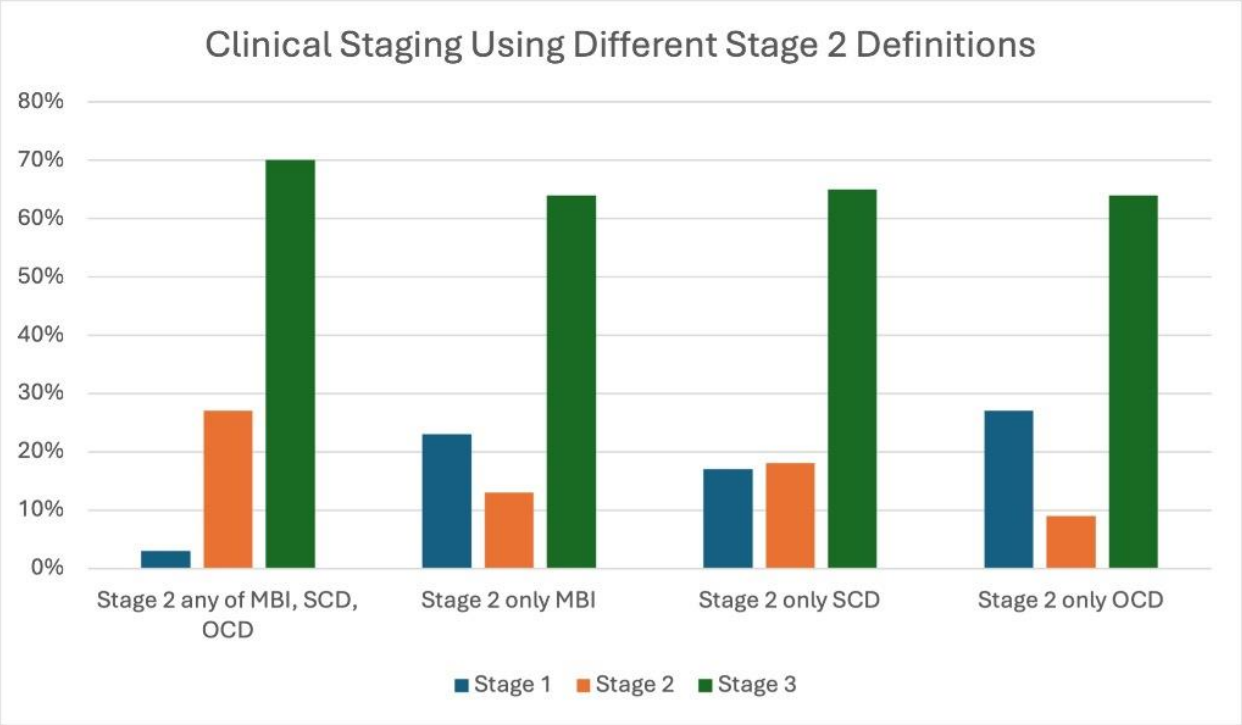
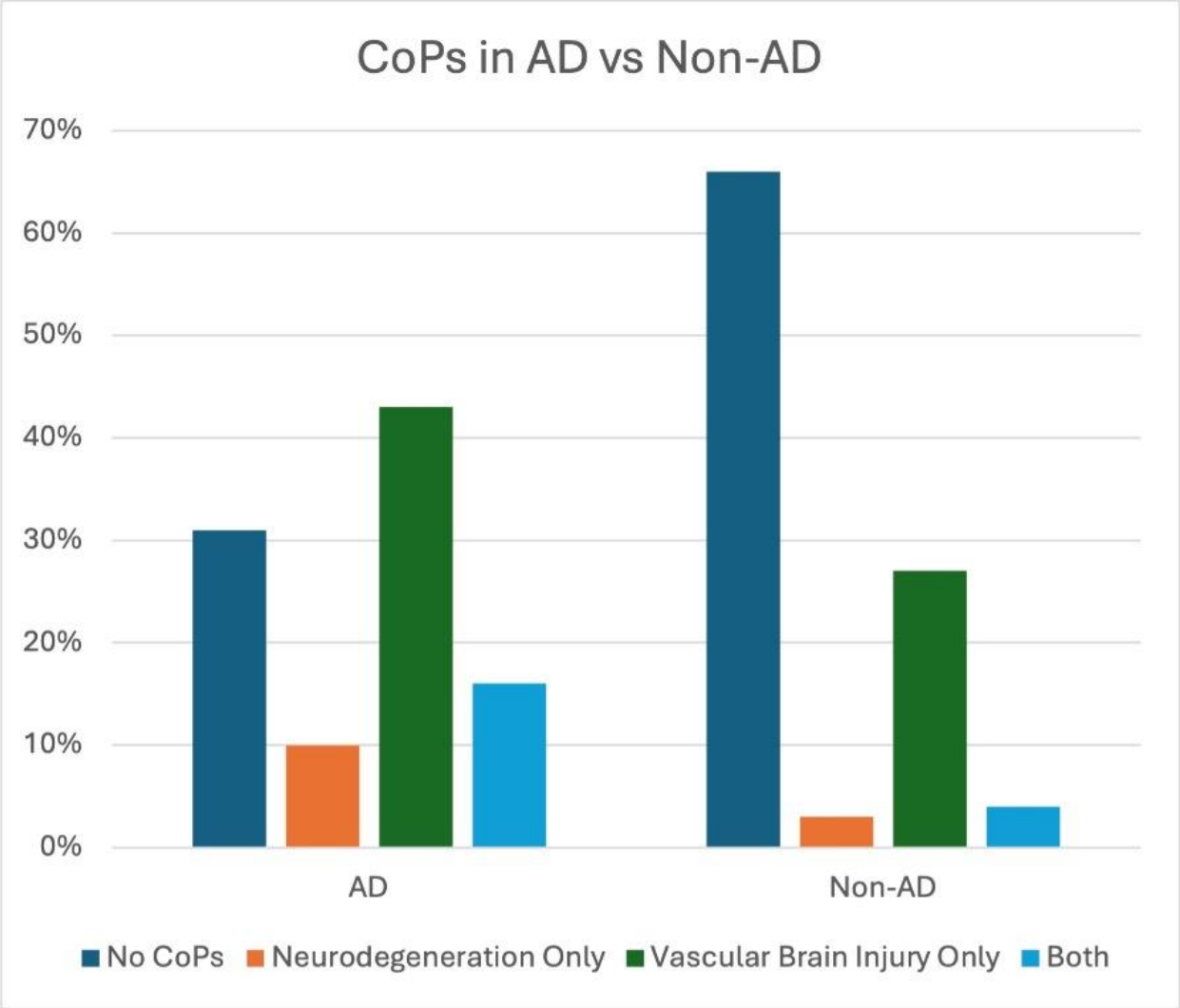
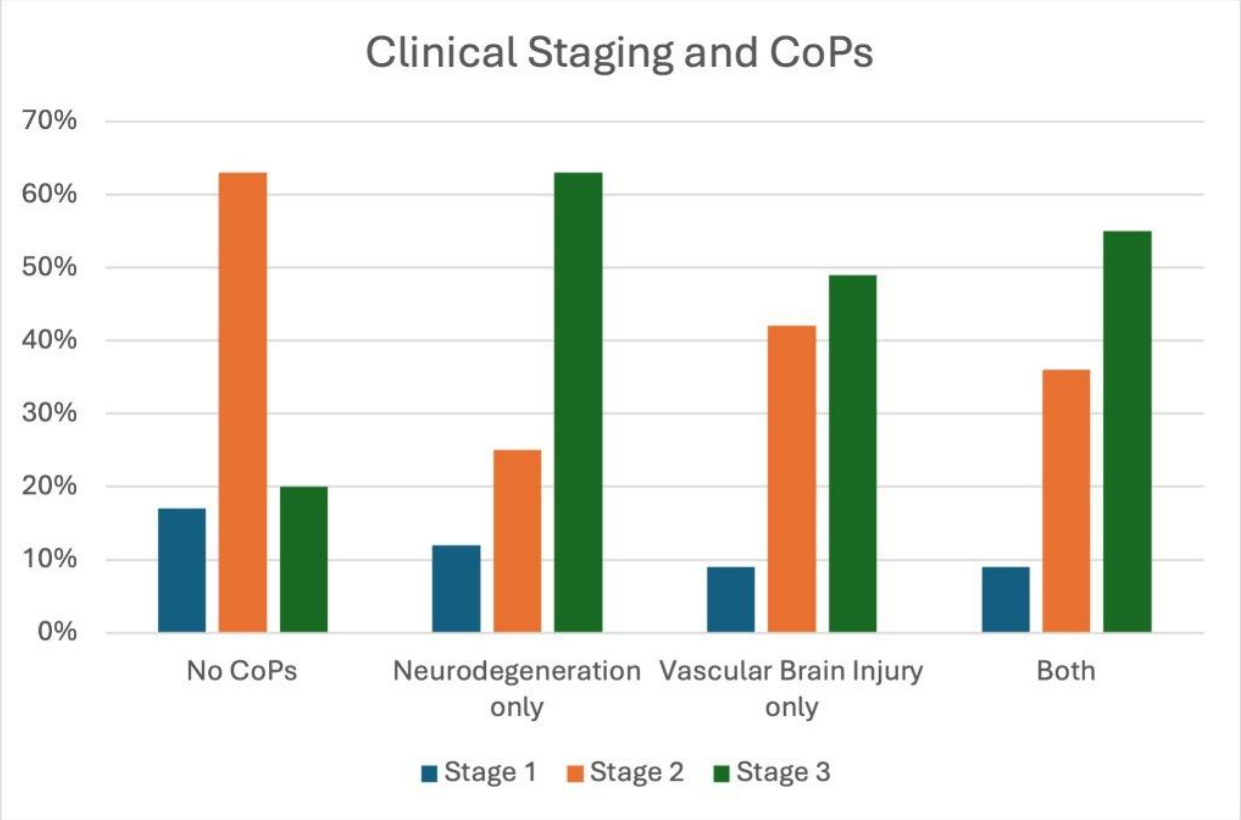
Aims: Objectives: We assessed the 2024 Alzheimer's Association criteria in a prospective cohort of non-demented adults aged ≥40.
Methods: Methods: We evaluated 242 individuals from the Aiginition Longitudinal Biomarker Investigation (ALBION) study through clinical and biomarker assessments, including neuropsychological testing, MRI, lumbar puncture, actigraphy, EEG, and dietary recalls. Alzheimer's disease (AD) biological diagnosis relied on CSF tTau/Aβ42>0.28 or pTau/Aβ42≥0.023. Stage 2 classification required any of the following: Mild Behavioral Impairment (MBI), Subjective Cognitive Decline (SCD), Objective Cognitive Decline (OCD). OCD was defined as a z-score decline between two neuropsychological assessments in the lowest tertile. The Scheltens' scale for neurodegeneration (ages <75: ≥2 abnormal, ≥75: ≥3 abnormal) and the Fazekas scale for vascular brain injury (≥2 abnormal) were used to evaluate CoPs. Although the criteria were designed for biologically AD individuals, we compared distributions of clinical staging to non-AD subjects.
Results: Results: In the AD group, the distribution was: stage 1: 7%, stage 2: 28%, stage 3: 65%. Alternative definitions of Stage 2 based on MBI, SCD, or OCD separately showed distributions of 23/13/64%, 17/18/65%, and 27/9/64%. In the non-AD group, clinical staging was 20/54/26% (p ≤0.001). For ≤65y.o. AD patients, staging was 15/23/62%, while for >65y.o., 5/29/66% (p <0.001). AD patients showed 9.5% neurodegeneration and 43% vascular brain injury; non-AD showed 3% and 27%, respectively (p≤0.001). Older individuals (p≤0.001) and males (p=0.024) had higher CoPs. Higher CoPs correlated with increasing stage 3 and decreasing stage 2 proportion (p=0.010).
Conclusions: Conclusions: The alternative definitions of stage 2 influence the overall clinical staging. For

non-AD participants, there are fewer individuals in stage 3 and more in stage 1. AD subjects have more CoPs than non-AD. Older age and higher CoP counts correlate with advanced clinical staging.




CoPs in AD vs Non-AD
70%
60%
50%
40%
30%
20%
10%
0%
AD
Non-AD
No CoPs
Neurodegeneration Only
Vascular Brain Injury Only
Both


Clinical Staging and CoPs
70%
60%
50%
40%
30%
20%
10%
0%
No CoPs
Neurodegeneration only
Vascular Brain Injury only
Both
Stage 1
Stage 2
Stage 3

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SHIFT 01-415

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

CHOROID PLEXUS AS A CENTRAL NEURO-IMMUNOMODULATORY HUB IN THE PATHOGENESIS OF ALZHEIMER'S DISEASE

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Aims: The choroid plexus (ChP), located within the brain's ventricles, is primarily responsible for producing cerebrospinal fluid (CSF) and maintaining central nervous system homeostasis. ChP also plays an essential immunological role through the blood-CSF barrier, which protects the brain from toxins and modulates inflammatory response. In Alzheimer's disease (AD), the ChP undergoes significant morphological and functional changes that disrupt CSF production and composition. Additionally, it may contribute to the accumulation of pathogenic proteins, including amyloid beta (Aβ) and toxic tau oligomers, key players in AD pathogenesis. Our research aims to elucidate whether Aβ and tau aggregates produced in degenerating brain regions could activate the inflammatory cascade via the choroid plexus hub of immune cells followed by propagation of pathological aggregates into other brain regions.
Methods: We examined the ChP in transgenic rodent models of AD, including APP^{SAA} knock-in and P301S tau-overexpressing PS19 mice, in comparison to wild-type. We assessed ChP morphology, blood-CSF barrier integrity, and immune cell recruitment.
Results: Our studies reveal significant alterations in ChP morphology as AD progresses. The pathological changes of ChP involve the reduction in epithelial cell density, disruption of tight junctions, and compromised blood-CSF barrier function. Further analysis also indicates the recruitment of peripheral immune cells in the ChP stroma, which likely amplify neuroinflammation and facilitate the accumulation of Aβ and tau within the brain parenchyma.
Conclusions: Our findings highlight the choroid plexus as a key player in the pathology of AD. Further investigation into its dysfunction may provide new insights into disease mechanisms and therapeutic targets. Strategies aimed at improving ChP function may offer promising area for future Alzheimer's research and treatment development.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

PERFORMANCE OF PLASMA ABETA BIOMARKERS IN PREDICTING AMYLOID POSITIVITY AND CLINICAL PROGRESSION

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[1]Shimadzu Corporation, Kyoto, Japan, [2]Oita University, Faculty of Medicine, Oita, Japan, [3]Eisai Co. Ltd., Tokyo, Japan

Aims: Studies have reported that plasma APP669–711/Aβ1–42 ratio, Aβ1–40/Aβ1–42 ratio, and a combination of these two biomarkers (a composite biomarker) correlate with amyloid PET results. In our phase 1 study, these biomarkers demonstrated strong predictive performance for identifying individuals with elevated brain amyloid among older adults with mild cognitive impairment, recruited from a community-based cohort. Here, we validate performance within a prospective cohort as part of a phase 2 investigation and explore the utility of plasma Aβ biomarkers in predicting clinical progression.
Methods: Plasma Aβ biomarkers were measured with immunoprecipitation-mass spectrometry (IP-MS) in the two studies. Amyloid positivity was assessed using ^{11}C-PiB PET based on a threshold of a standardized uptake value ratio (SUVR) of 1.2. The longitudinal analysis was conducted using data of the phase 1 study with a follow-up of up to 8 years.
Results: In the phase 2 study, plasma Aβ composite biomarker had high area under the curve (AUC) values of 0.920 for discriminating between amyloid PET positive and negative. The composite biomarker was correlated highly with PiB-PET SUVR. Next, we analyzed effects of plasma Aβ biomarkers in predicting cognitive decline using the longitudinal data obtained in the phase 1 study. The higher plasma Aβ composite biomarker at baseline significantly correlated with an annualized change of MMSE score, showing a Spearman's rank correlation coefficient of -0.575 (95% CI: -0.725 to -0.349, $P<0.001$).
Conclusions: Plasma Aβ composite biomarker measured using IP-MS demonstrated high performance of AUC for predicting amyloid positivity in the prospective phase 2 study. Moreover, our results suggested that the Aβ composite biomarker may be useful in the detection of individuals with the risk of faster cognitive decline.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

THE RELATIONSHIP BETWEEN OSTEOPOROSIS AND THE SHORTENING OF TELOMERE LENGTH IN DEMENTIA PATIENTS.

Min-Ju Kim[1], Myung-Hoon Han[1], Seong-Ho Koh[1], Hyunhee Park[1], Mina Hwang[1], Eun Ji Lee[1], Jeong-Min Baek[1], Yejin Ryu[1], Seon Ju Lee[1], Hyuk Sung Kwon[1], Hyun-Jung Yu[2]
[1]Hanyang University, Seoul, Korea, Republic of, [2]Department of Neurology, Seongnam, Korea, Republic of

Aims: The Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE) cohort study, initiated in 2014, aims to explore the relationship between LTL and osteoporosis while distinguishing dementia risk factors in Alzheimer's Disease (AD).
Methods: In this study, 233 participants from the KBASE cohort with osteoporosis and LTL data were observed over at least two years.
Results: A significant decrease in LTL was noted over this period, with lower LTL values found in participants with osteoporosis. This suggests a link between osteoporosis and accelerated LTL shortening. While LTL decreased with age, those with osteoporosis experienced an approximately 8% greater decline over two years. This may be due to inflammation accelerating telomere shortening, with oxidative stress potentially further exacerbating this process. The study's limitations include the absence of T-score data and the inability to conduct long-term follow-ups, as it was designed to predict Alzheimer's Disease. Therefore, further research is needed to validate the association between osteoporosis and LTL, with long-term observational studies warranted.
Conclusions: the study identified a significant association between osteoporosis and accelerated LTL shortening in dementia patients within a longitudinal cohort.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

CSF PROTEOMIC CHANGES ASSOCIATED WITH AGGREGATING BETA AMYLOID AND TAU PROTEINS IN ALZHEIMER'S DISEASE.

Rajaraman Krishnan[1], Bailin Zhang[2], Mikhail Levit[2], Pavithra Krishnaswami[2], Sofia Kinton[1], S. Pablo Sardi[3], Emanuele De Rinaldis[3], Charlotte Teunissen[4], Henrik Zetterberg[5], Rejko Krüger[6], Kaj Blennow[7], Gwendlyn Kollmorgen[8], Dag Aarsland[9,10], Annika Spottke[11,12], Wiesje M. Van Der Flier[13], Betty Tijms[14,15], Giovanni Frisoni[16,17], Stephanie Vos[18], Pieter Visser[19,20], Thomas Gasser[21,22], Frank Jessen[12,23], Afina Lemstra[15], Jakub Hort[24], Zuzana Nedelská[25], Tormod Fladby[26], Kathrin Brockmann[27], Claire Chevalier[16], Marianna Rizzo[18], Sara Fernandes[6], Olga Borejko[9], Simon Dujardin[1], Julia Bonner[1], Ping-Chieh Pao[1], Michele Hu[28,29], Thomas Klockgether[11], Preeti Bais[2]
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Oxford, Oxford Parkinson's Disease Centre and Division of Neurology, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom, [29]University of Oxford, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom

Aims: Amyloid plaques and tau neurofibrillary tangles are the histopathological hallmarks in Alzheimer's disease (AD). It is hypothesized that misfolding of abeta and tau trigger inflammation, perturb blood brain barrier integrity and drive neuronal loss. Several aspects of how aggregates drive the severity and progression of the disease remain unclear. We examine the biomarkers associated with Alzheimer's disease.

Methods: We partnered with the EPND-biomarker consortia to analyze over 300 human CSF samples from AD, Parkinson's Disease (PD), Lewy Body Dementia (DLB) and control patients. Abeta 1-40,Abeta 1-42, pTau181, tau were measured and a proteomic profiling of over 3000 proteins using the O-link platform was carried out for all the samples.

Results: Approximately 10% of the measured CSF proteins showed significant differences ($p<0.05$) in AD (~250 proteins) and PD (~220 proteins) samples relative to controls. Only 3% CSF proteins (~ 70 proteins) showed changes in DLB samples. Further, CSF samples from AD patients could be stratified into A+T+, A+T- groups based on the pTau181 levels. CSF samples with elevated ptau181 showed altered levels of proteins associated with complement cascade, cytokine-cytokine receptor interactions, cell adhesion and vesicular transport associated proteins.

Conclusions: AD patient samples were stratified into A+T+, A+T- groups to identify biomarkers associated with Aβ and/or tau aggregation. Proteins associated with innate immune response and synaptic loss were dramatically altered[MR1] . These findings will be critical for guiding the selection of therapeutic approaches for neurodegenerative diseases as well as the assessment of their efficacy.

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SHIFT 01-419

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

EXPLORING PAIN, ANXIETY AND ADVERSE EFFECTS ASSOCIATED WITH LUMBAR PUNCTURE IN OLDER ADULTS: A PROSPECTIVE LONGITUDINAL STUDY IN A MEMORY CLINIC POPULATION

Hadrien M Lalive, Alice Accorroni, Dylan Donayre, Umberto Nencha, Chen Wang, Giovanni Frisoni, Aurelien Lathuilière
Memory Center, Department of Rehabilitation and Geriatrics, Geneva University Hospital and University of Geneva, Geneva, Switzerland

Aims: Lumbar puncture (LP) is a common procedure in memory clinics for assessing Alzheimer's disease (AD) biomarkers in older adults and it is generally regarded by physicians as safe and well-tolerated. However, patient discomfort before, during and after LP may be underreported. This study aims to longitudinally evaluate pain, anxiety and adverse events (AEs) associated with LP in older adults and to investigate their association with patients' perceptions, clinical characteristics, and AD cerebrospinal fluid (CSF) biomarker levels.
Methods: We are conducting a prospective observational study at the Memory Clinic of the Geneva University Hospital from January 2024 to January 2025, enrolling over 100 consecutive patients undergoing their first LP as part of clinical cognitive assessment. Pain, anxiety and AEs are assessed using structured surveys and the Beck Anxiety Inventory at multiple time points: pre-procedure, immediately post-procedure, one hour post-procedure, and 24 to 72 hours later. Data on patient perceptions of LP, clinical characteristics and AD CSF biomarker levels are also collected.
Results: Data collection is ongoing. At the time of AD/PD 2025 conference, we will show results regarding patterns of pain, anxiety and AEs related to LP and demographic, cognitive and clinical predictors of worse tolerance. Longitudinal analysis will track changes in AEs, pain and anxiety over time to assess patient tolerance. Multivariate analyses will further investigate associations between these variables and identify predictors of poor tolerance.
Conclusions: The results of this study will allow to understand patient perceptions, especially as LP is increasingly performed to evaluate eligibility for disease-modifying therapy in cognitively impaired adults. Modifiable risk factors may be targeted by future protocol adjustments to reduce discomfort and anxiety, while recognizing unmodifiable factors may help identify patients at higher risk of poor tolerance.

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SHIFT 01-420

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

SOLUBLE SORLA IN CSF, A NOVEL BIOMARKER TO EXPLORE DISRUPTED TRAFFICKING OF SORLA PROTEIN IN ALZHEIMER DISEASE

Magalie Lecourtois[1], Romain Castelot[2], Aline Zarea[3], David Wallon[3], Anne Rovelet-Lecrux[1], Catherine Schramm[1], Muriel Quillard-Muraine[4], Anne Beaume[5], Frederic Blanc[6], Oliver Bousiges[6], Julien Dumurgier[7], Maïté Formaglio[8], Gwenaël Le Guyader[5], Sylvain Lehmann[9,10,11], Cecilia Marelli[12], Matthieu Martinet[13], Leonor Noguiera[14], Pariente Jeremie[15], Isabelle Quadrio[16], Adeline Rollin-Sillaire[17], Susanna Schraen[17], Gael Nicolas[3]
[1]InsermU1245, Rouen, France, [2]InsermU1245, ROUEN, France, [3]Univ Rouen Normandie, Normandie Univ, Inserm U1245 and CHU Rouen, Department of Genetics and CNRMAJ, Rouen, France, [4]CHU Rouen, Department of General Biochemistry and Univ Rouen Normandie, Rouen, France, [5]Service de Génétique, CHU Poitiers, POITIERS, France, [6]University Hospital of Strasbourg, Laboratory Of Biochemistry And Molecular Biology, strasbourg, France, [7]Assistance publique hôpitaux de paris, GHU Paris.nord, Cognitive Neurology Center, Fernand Widal Hospital, Paris, France, [8]BIORAN Team, Lyon Neuroscience Research Center, CNRS UMR 5292, INSERM U1028, Lyon 1 University, Bron, France. CMRR Lyon, Department of Neurology, University Hospital of Lyon, Hospices Civils de Lyon, Lyon, France, [9]Montpellier university, Montpellier, France, [10]CHU Montpellier, PPC Clinical Proteomics Plateform, Montpellier, France, [11]Plateforme de Protéomique Clinique, Irmb - Chu De Montpellier - Hôpital Saint Eloi, Montpellier, France, [12]Service de Neurologie, Hopital Gui de Chauliac, CHU de Montpellier, Montpellier, France., Montpellier, France, [13]AP-HP Nord, Cognitive Neurology Center Hôpital Lariboisière-Fernand Widal, Université Paris Cité, 200 rue du Faubourg Saint-Denis,, Paris, France, [14]Laboratory of Cell Biology and Cytology, Toulouse University Hospital, Toulouse, France, [15]Neurology Department, Hôpital Pierre-Paul Riquet, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; Toulouse NeuroImaging Center (ToNIC), INSERM-University of Toulouse Paul Sabatier, Toulouse, France., Toulouse, France, [16]Centre de Recherche en Neurosciences de Lyon, Inserm U1028 - Cnrs Umr5292 Groupement Hospitalier Est, Lyon, France, [17]CHU Lille, Memory Center, CNRMAJ 59000 Lille, France, Lille, France

Aims: The SorLA protein is a major player in Alzheimer's disease (AD) pathophysiology. SorLA deficiency results in increased Aβ peptide levels, and thus a higher risk of AD. SorLA can be subject to proteolytic shedding at the cell surface, leading to the release of the soluble ectodomain of the protein (sSorLA) in the extracellular space. ~25% of rare *SORL1* missense variants found in AD patients alter SorLA trafficking, resulting in reduced delivery of SorLA to the plasma membrane and thus a loss of function. Here, we determined if CSF levels of sSORLA in AD patients can be used as a novel biomarker to explore disrupted trafficking of SorLA protein in AD.

Methods: 151 participants were categorized into 5 study groups: controls without any neurodegenerative disease, patients suffering from FTLD, AD patients not carrying a *SORL1* rare variant, AD patients carrying *SORL1* trafficking-defective variants or a protein-truncating variant (PTV) ($AD^{SORL1\ TD}$), and AD patients carrying a *SORL1* variant with no evidence of trafficking defect. Thirty-three unique rare variants of *SORL1* were included for this study: 3 PTVs, 13 missense trafficking-defective variants, and 17 variants with no detectable effect on SorLA trafficking. We measured amounts of cleaved sSorLA by western blot.

Results: We found significantly decreased levels of sSorLA in $AD^{SORL1\ TD}$, compared to all other groups. According to ROC curve analysis, levels of sSorLA showed good performances to distinguish $AD^{SORL1\ TD}$ patients from other AD patients (AUC=0.89 [95%CI: 0.81-0.97]).

Conclusions: Our results suggest that differential levels of sSorLA in CSF could be used as a novel marker to explore disrupted trafficking of SorLA protein in Alzheimer disease. This could help solve some proportion of variants of uncertain significance in *SORL1*.

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SHIFT 01-422

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / FUNCTIONAL MRI
2-3 April 2025

FMRI-BASED BRAIN ENTROPY AS AN EARLY DIAGNOSTIC BIOMARKER FOR ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is a leading cause of dementia, typically diagnosed in later stages when symptoms are severe. This has led to increased interest in identifying early biomarkers for AD. Brain entropy (BEN), has emerged as a promising tool for understanding AD. Research indicates that while BEN increases with normal aging and MCI, it decreases along the AD continuum. This study aims to explore BEN across various stages of cognitive decline, including SCD, MCI, and AD.
Methods: The study used a dataset from a Hungarian research center, including 60 HC, 14 SCD, 20 MCI, and 29 AD participants. After fMRI preprocessing, Brain Entropy (BE) maps were calculated, and mean BE was determined for 132 regions of interest (ROI). A Multivariate Analysis of Variance (MANOVA) was used to assess group differences across the ROIs, followed by post hoc analysis with Tukey's HSD and Univariate ANOVA with Bonferroni correction to examine specific group and ROI effects.
Results: No significant differences were observed between HC, SCD, and MCI groups. However, a significant difference was found between the AD group and all other groups ($p < 0.001$ for comparisons with HC, SCD, and MCI). Additionally, many brain regions showed significant differences after univariate ANOVA.
Conclusions: Our findings align with previous literature, demonstrating that BE maps can effectively distinguish AD. However, the absence of significant differences between HC, SCD, MCI suggests that BE mapping may not be suitable for identifying AD in its early stages. Future work will focus on examining group-specific patterns of hyperexcitability, as detected through EEG data. Additionally, we aim to incorporate data from the ADNI dataset to validate our findings and conduct a longitudinal analysis of BE.

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SHIFT 01-425

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2-3 April 2025

SPATIAL RELATIONSHIP BETWEEN HYPERPOLARIZED [1-13C]PYRUVATE MRI AND METABOLIC PET IN THE HUMAN BRAIN

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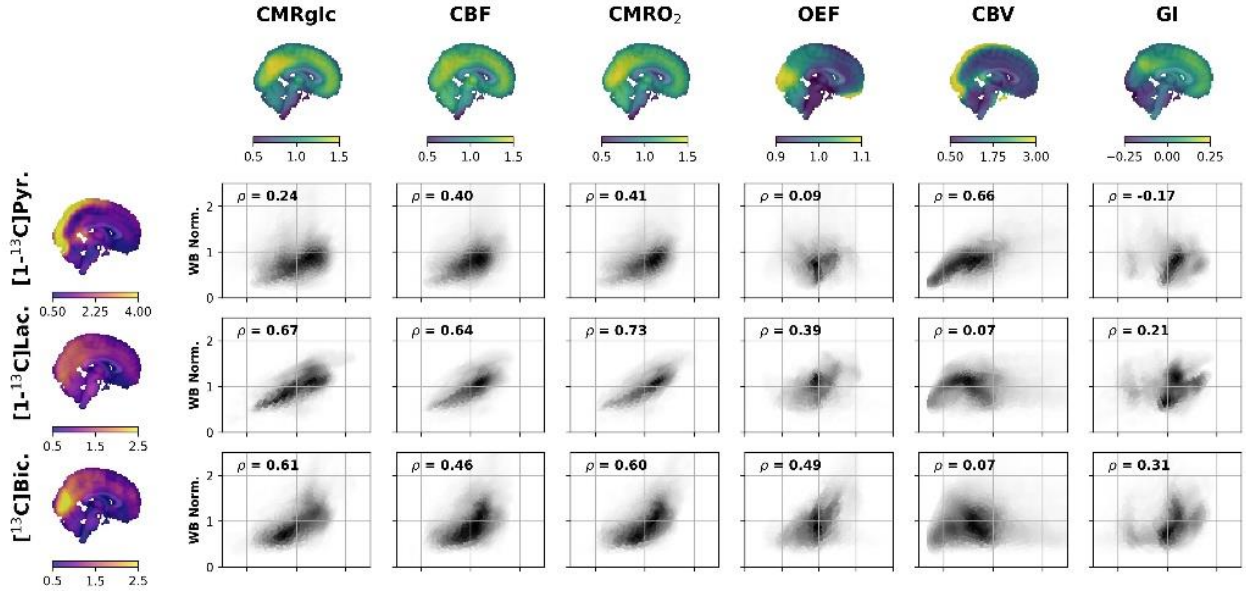
Aims: [^{18}F]fluorodeoxyglucose (FDG) positron emission tomography (PET) is a well-established biomarker of metabolic decline in Alzheimer's disease (AD). However, the radiation associated with PET poses challenges for longitudinal studies. Hyperpolarized (HP) ^{13}C magnetic resonance imaging (MRI) with [1-^{13}C]pyruvate is an emerging technique that can measure the production of [1-^{13}C]lactate and [^{13}C]bicarbonate without any radiation. It is not clear, though, how the HP ^{13}C MRI signal relates to traditional metabolic PET. We address this gap by comparing the spatial distribution of HP ^{13}C MRI with multi-tracer PET in healthy adults.
Methods: Regional cerebral blood flow (CBF), glucose consumption (CMRglc), oxygen consumption ($CMRO_2$), blood volume (CBV), and aerobic glycolysis (GI) was measured in a previous study of 33 young adults[1]. HP ^{13}C images of [1-^{13}C]pyruvate, [1-^{13}C]lactate, and [^{13}C]bicarbonate were taken from a published study of 37 cognitively normal adults[2].
Results: The topopgraphy of HP ^{13}C lactate and bicarbonate production correlated most strongly with CMRglc and $CMRO_2$ ($\rho \geq 0.6$), whereas [1-^{13}C]pyruvate correlated best with CBV ($\rho = 0.66$; **Figure 1**). None of the HP images correlated with GI ($|\rho| \leq 0.31$). **Figure 1:** Comparison of PET and HP ^{13}C MRI.



Conclusions: Although HP [1-^{13}C]lactate production is thought to reflect glycolysis, we found that both [1-^{13}C]lactate and [^{13}C]bicarbonate correlated best with overall measures of cerebral energy metabolism. We

are planning to test HP ^{13}C MRI as an AD biomarker based on these results. **References** 1. Vaishnavi, S. N. *et al*. Regional aerobic glycolysis in the human brain. *Proc Natl Acad Sci U S A* **107**, 17757–17762 (2010). 2. Uthayakumar, B. *et al*. Age-associated change in pyruvate metabolism investigated with hyperpolarized 13C-MRI of the human brain. *Hum Brain Mapp* **44**, 4052–4063 (2023).

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SHIFT 01-426

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2-3 April 2025

COMPARISON OF PENTAMERIC FORMYL THIOPHENE ACETIC ACID (PFTAA) STAINING IN HUMANS AND ANIMAL MODELS OF DISEASE

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Aims: Histological detection of amyloids in human and mouse brain tissue is complex. Fibril structures and aggregation lead to a reduction of relevant epitopes for primary antibody detection and some amyloids remain undetected in histology samples because of the lack of antibody binding. Binding sites may become internalized within fibrillary aggregates, others become truncated, modified (e.g. phosphorylation, acetylation), and standard histological tissue processing affect binding sites, especially fixation procedures. pFTAA was published to stain diverse amyloids and prions. While commercially available, pFTAA is sparsely used in clinical or preclinical detection. It has many advantages compared to Thioflavin S or Congo including no binding on natural beta-sheet structures, higher sensitivity and specificity, stronger signal, high stability and no toxicity (in vivo tracker).
Methods: Histological sections from standard blocks (FFPE and cryo) in human diseased patients and mouse models to AD, PD, Tauopathy and ALS (SODG93A, rNLS8, APP/PS1, rTg4510, hPFF and mPFF, Line61) were stained with pFTAA and pathological co-markers and imaged on a Zeiss slide scanner.
Results: pFTAA reliably and specifically detected Abeta plaques, neurofibrillary tangles, pTDP-43 and SOD1 aggregates, and human and mouse fibrillary alpha-synuclein inclusions in animal model and human tissue. The amount of specific amyloids varied across the models with some models showing little to no formation of significant amounts of mature amyloids, such as the Line61 or rNLS8 mice.
Conclusions: pFTAA could be the easiest to use and most universal detector for the majority kind of fibrillary amyloid aggregates. Staining is clear and distinct in samples prepared using standard methods. Here we show the detection both of single and mixed human pathology and compare this to prominent preclinical models of amyloid diseases.

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SHIFT 01-427

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2-3 April 2025

MULTIMODAL MACHINE LEARNING FOR ASSESSMENT OF AMYLOID-BETA AND TAU PET POSITIVITY STATUS.

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Aims: To develop and validate a data-driven approach for identifying amyloid-beta and tau PET positive cases using multimodal standard of care data.
Methods: We developed a machine learning approach that can process multimodal features, including demographics, medical history, physical and neurological exam findings, neuropsychological assessments, APOE-e4 allele status, plasma and cerebrospinal fluid biomarkers, and neuroimaging, to identify persons who are likely to be positive on amyloid-beta and/or tau PET imaging. We processed data from 12,187 participants obtained from multiple cohorts and trained a CatBoost model via supervised learning. For amyloid-beta positivity as the output label, we used a pre-defined threshold of 24 centiloids. In a separate model that used tau PET positivity in a meta-temporal region as the output label, we identified a threshold of 1.40 standardized uptake value ratio using a two-component Gaussian mixture model applied to the training set. Overall, 10,354 participants were used for model training and 1833 participants were used for testing.
Results: On the testing dataset, our CatBoost model achieved an area under the receiver operating characteristic curve of 0.85 for predicting amyloid-beta positivity and 0.86 for predicting tau PET positivity. Additionally, our model demonstrated accuracies of 0.74 and 0.72 for amyloid-beta and tau PET status predictions, respectively.
Conclusions: Our approach provides a cost-effective means by which to assess amyloid-beta and tau PET statuses without requiring participants to undergo expensive PET imaging. Such tools can be invaluable in real-world settings to increase efficiency in participant selection for drug trials that target amyloid-beta and tau pathologies, either individually or in combination.

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SHIFT 01-428

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2-3 April 2025

THINNER RETINAL LAYERS ARE ASSOCIATED WITH CEREBRAL GRAY MATTER, WHITE MATTER HYPERINTENSITY AND METABOLISM CHANGES IN EARLY-ONSET ALZHEIMER'S DISEASE.

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Aims: Neurodegeneration plays a significant role in Alzheimer's Disease (AD) pathology. Studies have shown that retinal neurodegeneration in AD reflects cerebral changes; however, retinal neurodegeneration is associated with gray matter structural changes via voxel-based morphometry (VBM) and cerebral metabolism in AD. We investigated the associations of retinal structural thickness with gray matter volume using VBM analysis and metabolism in early-onset AD (EOAD).
Methods: Optical coherence tomography (OCT) was used to image and measure the retinal structural thickness of 48 participants. Fifteen subjects had early-onset AD (EOAD) and 23 were cognitively normal controls. The OCT tool generated the peripapillary retinal nerve fiber layer (pRNFL) and ganglion cell complex (GCC) thicknesses. EOAD patients underwent magnetic resonance imaging (MRI) and positron emission tomography (PET). VBM, SPM 12 and the Lesion Segmentation Toolbox were applied to MRI images.
Results: EOAD patients showed thinner pRNFL and GCC than controls. Thinner retinal structural thickness in EOAD was significantly associated with voxel-wise gray matter volumes and cerebral metabolism changes involved in visual and cognitive function. Thinner pRNFL thickness was associated with increased WMH volume in EOAD. pRNFL thickness was reduced in EOAD patients who were Apolipoprotein E carriers than non-carriers.
Conclusions: Our study suggests that retinal neurodegeneration changes identified using OCT are associated with gray matter volume and cerebral metabolism changes involved in cognitive and visual impairments in patients with EOAD.Our study suggests that retinal neurodegeneration changes identified using OCT are associated with gray matter volume and cerebral metabolism changes involved in cognitive and visual impairments in patients with EOAD.

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SHIFT 01-429

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
2-3 April 2025

ASSOCIATION OF LONG-TERM BMI CHANGE WITH ALZHEIMER'S NEUROIMAGING BIOMARKERS IN NON-DEMENTED OLDER ADULTS

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Aims: This study aims to investigate how BMI at different life stages and BMI change after midlife are associated with AD-related biomarkers in late life.
Methods: A total of 268 non-demented (193 cognitive normal and 75 mild cognitive impairment) older adults from 55 to 90 years of age were enrolled from the Korean Brain Aging Study for Early Diagnosis and Prediction of Alzheimer's Disease (KBASE). Current or late-life BMI was calculated using the measured height and body weight. Midlife BMI was calculated using self-recall based midlife body weight and height. All participant received [^{18}F] fludeoxyglucose (FDG)-PET, [11C] Pittsburgh compound B (PiB) PET, and [18F] AV-1451 PET. Multiple linear regression analyses were conducted to assess the association between midlife and late-life BMI, BMI change patterns, and AD-related biomarkers, including cerebral glucose metabolism (AD-CM), beta-amyloid (Aβ), and tau deposition.
Results: Higher midlife BMI was significantly associated with reduced AD-CM (β = -0.001, p = 0.005), suggesting impaired cerebral glucose metabolism in regions typically affected by AD. No significant association was found between late-life BMI and AD-CM, nor between BMI in either life period and Aβ or tau deposition. BMI change patterns from midlife to late life showed that a decline in BMI was significantly associated with reduced AD-CM compared to an increase in BMI (β = 0.030, p = 0.022) . No significant associations were observed between BMI change patterns and Aβ or tau deposition.
Conclusions: The findings indicate that higher midlife BMI is linked to impaired brain glucose metabolism,

potentially increasing the risk of AD, while late-life weight loss may be indicative of underlying neurodegenerative processes. These results underscore the importance of managing BMI across the lifespan to prevent or mitigate Alzheimer's disease.

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SHIFT 01-437

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2-3 April 2025

IDENTIFYING A SIGNATURE OF INFLAMMATORY BLOOD PROTEINS PREDICTING DEMENTIA

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Aims: Inflammation, driven by systemic mediators, plays a key role in dementia. However, the link between dementia risk and circulating inflammatory proteins before the onset of dementia remains unknown. We aimed to investigate the individual and collective associations between circulating inflammatory proteins and incident dementia. We further explored whether these associations were independent of the *APOE-ε4* genotype and polygenic risk (PGS) for Alzheimer's disease (AD). Lastly, we examined the associations between dementia-related proteins and protein-scores with brain image-derived endophenotypes.
Methods: We leveraged proteomics data from 44,150 participants from the UK Biobank. Cox proportional-hazard regression was used to model associations between 728 proteins and incident dementia, in three separately adjusted models and elastic-net regularisation for feature selection. Formal mediation analyses were applied following the Baron and Kenny criteria. Linear regression models were used to investigate associations between dementia-related proteins and protein-scores, and 124 image-derived brain endophenotypes in 4,106 participants.
Results: We identified up to 31 individually associated proteins in Cox models ($P_{Bonferroni} < 0.05$). A signature of 14 proteins best predicted the risk of dementia (C-index =0.84) with a higher predictive power than a model excluding proteins (C-index=0.67). Mediation analysis suggested that some proteins may mediate the effects of the *APOE-ε4* genotype. Five signature proteins were significantly associated with AD-PGS, but these associations were driven by the *APOE-ε4* genotype. Lastly, we found associations between brain volume endophenotypes and nine signature proteins, with three proteins negatively associated with up to 38/124 endophenotypes and positively associated with incident dementia.
Conclusions: Our findings underscore the critical role of inflammation in dementia and highlight the importance of identifying inflammatory biomarkers for early dementia detection. Early identification of these proteins will ultimately enhance recruitment for clinical trials and support personalized therapeutic interventions.

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SHIFT 01-438

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2-3 April 2025

INDIVIDUALISED RISK PREDICTION FOR DEMENTIA: DERIVING ACTIONABLE INFORMATION FROM MULTIMODAL HEALTH DATA

Sara Calhas[1], Yue Liu[1], Sheena Waters[1], Oleg Blyuss[2], Charles Marshall[1], Petroula Proitsi[1]
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Aims: Dementia diagnosis is complex and typically occurs when symptoms emerge, which may be too late as brain damage may have occurred. The increasing availability of multimodal data and powerful machine learning algorithms opens new avenues for detecting individualised dementia risk in the preclinical stage. This research aims to identify cost-effective, non-invasive dementia risk signatures, such as blood-based biomarkers for dementia risk prediction. To the best of the author's knowledge, this is the first study to integrate proteomics, metabolomics, genetic markers, and baseline clinical variables for preclinical dementia risk prediction.
Methods: The project used data from the UK Biobank. Participants with baseline proteomic and metabolomic data were included, comprising 872 dementia cases and 29,006 controls, with a follow-up period of 15.2-years. A total of 3,241 omics were explored. The primary focus was on machine learning to predict all-cause dementia. SVMs, Random Forest, and XGBoost algorithms were tested, with XGBoost selected to predict all-cause dementia at three thresholds: overall dementia prediction, dementia occurring 5 to 10 years from baseline, and dementia occurring more than 10 years from baseline.
Results: XGBoost emerged as the top classifier, demonstrating strong predictive power with ROC AUC scores of 0.85 or above for overall dementia prediction, as well as for predicting dementia 5 to 10 years and more than 10 years from baseline. The project offered new insights into promising plasma biomarkers for the preclinical and early diagnosis of dementia. Previously identified blood-based biomarkers were validated, and new biomarkers were discovered.
Conclusions: This work provided novel insights into specific proteins crucial for assessing individualised risk prediction for dementia and early diagnosis. The study confirmed machine learning as a viable method to help realise the benefits of preclinical dementia risk prediction.

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SHIFT 01-439

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2-3 April 2025

NEURODEGENE 2.0: ADVANCING GENETIC RISK ASSESSMENT, PATIENT STRATIFICATION AND PERSONALIZED THERAPIES FOR NEURODEGENERATIVE DISEASES

Miguel Casanova[1], Nicolas Scalzitti[2], Seval Kul[2], Dany Mukesha[2], Lucas Pham-Van[2], Çetin Kocaefe[2,3], Stéphanie Boutillier[1], Hüseyin Firat[1]
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Aims: As the prevalence of neurodegenerative diseases (NDs) rises, there is an increasing need for tools offering early diagnosis and prognosis. Expanding on previous work, we present NeuroDeGene 2.0, an enhanced genetic panel designed for comprehensive screening, patient stratification, and risk prediction across multiple NDs. The tool aims to aid differential diagnosis, support clinical trial enrichment, and contribute to developing personalized therapies.
Methods: We expanded our genetic panel to include 15,533 coding and non-coding variants associated with 19 NDs, including Alzheimer's disease (AD) and Parkinson's disease (PD). We sequenced 964 whole blood samples from cohorts such as ADDIA (ClinicalTrials.gov NCT03030586) and ADDKIT on the NovaSeq X platform. Our approach integrates AI-driven Polygenic Risk Scores (aiPRS) to assess individual genetic risk and machine learning models for patient stratification and disease classification.
Results: In AD, the expanded panel confirms the strong association of *APOE* variants with disease risk, while highlighting additional variants with either increased or decreased association with dementia. The larger dataset, enhanced by a comprehensive variant selection, enables more precise patient stratification, revealing distinct genetic profiles within the AD population. Preliminary results from our machine learning models indicate high classification performance, with anticipated improvements in sensitivity, specificity, and AUC.
Conclusions: NeuroDeGene 2.0, powered by the latest sequencing technology, represents a significant advancement in precision medicine for NDs. Its broader genetic coverage offers enhanced insights into the genetic underpinnings of neurodegenerative diseases. It holds promise as a clinically applicable diagnostic tool while supporting the development of new disease-modifying therapies, particularly those targeting amyloid plaques, and aiding clinical trial designs for early-stage dementia populations. The potential for integration with other biomarkers, such as transcriptomics and imaging, further enhances its clinical utility.

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SHIFT 01-440

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2-3 April 2025

NEUROPSYCHOLOGICAL PROFILE AND ITS RELATIONSHIP WITH BRAIN ATROPHY IN PATIENTS WITH EARLY-ONSET ALZHEIMER'S DISEASE

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Aims: The aim of this study is to examine the cognitive profile of patients with early-onset Alzheimer's disease (EOAD) during the predementia stage, with the goal of defining a phenotype and identifying the most sensitive neuropsychological tests for early detection. Additionally, the study investigates the relationship between cognitive status and brain structural integrity.
Methods: A total of 26 participants, including 13 EOAD patients and 13 healthy controls (HC) matched for age, gender, and education level, underwent a comprehensive neuropsychological assessment. In addition, EOAD patients performed a structural magnetic resonance imaging (MRI) to quantify global and regional brain volumes and cortical thickness. Cognitive performance was compared between groups, and correlated with MRI measures.
Results: Patients exhibited poorer cognitive performance compared to the HC, with language, attention, and visuospatial function being the most affected cognitive domains. The most sensitive tests, which showed a high proportion of failures in the patient group, were the *Stroop Test*, the *Mini Linguistic State Examination*, and the *Clock Drawing Test*. In addition, the cognitive performance was associated with global measures suggestive of cerebral atrophy, such as increased lateral and third ventricular enlargement.
Conclusions: According to these results, language, processing speed, and visuospatial deficits might be critical signs for the precise and early identification of EOAD patients.

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SHIFT 01-441

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2-3 April 2025

BIOPHYSICAL METHODOLOGIES FOR THE QC OF ABCAM RABBIT MONOCLONAL ANTIBODIES AND PROTEINS

Will Howat, Yingwu Xu, Hiaji Zhuang, Fiona Tooke, Julie Ayton, Caroline Wickramasinghe
Abcam, Research And Development, Cambridge, United Kingdom

Aims: Abcam aims to have the highest quality of validated Rabbit Monoclonal antibodies (RabMAb) to the neuroscience field, particularly Alzhemiers Disease and Parkinson's Disease and to use up-to-date methodologies to measure this quality.
Methods: As a measurement of quality, Abcam RabMAb's® are tested in a variety of applications that are relevant to the neuroscience field and with materials that can confirm specificity and sensitivity. In addition to these application tests we have supplemented these methods with biophysical methodologies of LC-MS and HPLC to measure identity, purity and aggregation.
Results: Utilising these core biophysical processes, we have >9,000 RUO recombinant rabbit monoclonal antibodies characterised to date. This work show a high pass rate for these tests, but also demonstrates examples of low purity, proteolytic cleavage and examples of ligh or heavy chain modifications, such as sulfation, glycosylation and C-terminal lysines that will be apparent in all antibody samples and are subsequently repaired in Abcam RabMAb's®.
Conclusions: The addition of these QC methods provides additional confidence for the researcher in the quality of the products, giving a reliable and consistent measurement of production to provide reproducibility to our customers and highlights the potential issues in all antibodies regardless of vendor.

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SHIFT 01-442

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
2-3 April 2025

ASSOCIATIONS BETWEEN DECLARATIVE MEMORY AND OLFACTORY IDENTIFICATION IN OLDER ADULTS AT RISK FOR ALZHEIMER'S DISEASE: PRELIMINARY RESULTS FROM THE CIMA-Q COHORT

Benoit Jobin[1,2], Johannes Frasnelli[3], Benjamin Boller[1,2], Consortium For The Early Identification Of Alzheimer's Disease – Quebec (Cima-Q)[4]
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Aims: Olfactory identification is impaired early in Alzheimer's disease (AD), including in patients with mild cognitive impairment (MCI). This early sensory impairment could result from several factors such as early cognitive damages. The aim of this study was to examine the relationship between declarative memory and olfactory identification functioning in a cohort of older adults at risk of developing AD.
Methods: We included 64 cognitively unimpaired (CU) participants (mean age: 76.15, SD: 5.84) and 45 patients with MCI (mean age: 80.08, SD: 5.86) from the Consortium for the Early Identification of Alzheimer's Disease-Quebec (CIMA-Q). Olfactory assessment was completed using the University of Pennsylvania Smell Identification Test (UPSIT). Episodic memory was assessed using the Logical Memory subtests of the Wechsler Memory Scale, semantic memory was assessed using the Boston Naming Test (BNT) and the Animal Fluency Test. We fit a regularized regression model with the least absolute shrinkage and selection operator for variable selection (LASSO), trained on 80% of the data and tested on the remaining 20%. Candidates for predicting UPSIT score included immediate/delayed recalls, BNT, semantic fluency, age, sex, education.
Results: Olfactory identification score was significantly lower in the MCI group compared to CU participants (p=.003) and was significantly correlated with MoCA score (r=.36, p<.001), immediate (r=.31, p=.001) and delayed (r=.29, p=.002) recalls, and with the BNT (r=.31, p<.001) and semantic fluency (r=.26, p=.008) scores. After regularization, only the BNT remained in the model for predicting UPSIT score, however with a poor predictive value (rmse=6.89).
Conclusions: While olfactory identification was associated with declarative memory functioning, this relationship had a poor predictive value in explaining olfactory identification performance.

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SHIFT 01-443

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - AMYLOID
2-3 April 2025

COMPARATIVE ANALYSIS OF ARTIFICIAL INTELLIGENCE-POWERED QUANTITATIVE SOFTWARE FOR BRAIN AMYLOID PET IMAGING

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Aims: The aim of this study was to evaluate the parameters of brain amyloid PET with two different software.
Methods: This study was retrospectively performed and 29 healthy subjects were enrolled. All subjects underwent a 10-minute PET/CT scan 90 minutes after an intravenous injection of 185 MBq of ^{18}F-flutemetamol. Two commercially available software (BTXbrain, Brightonix Imaging Inc., Seoul, Korea; SCALE PET, Neurophet Inc., Seoul, Korea) for brain amyloid PET analysis in Korea were used. BTXbrain is a software that can analyze only PET data. SCALE PET can analyze PET/MR (3D T1), PET/CT and PET data. We analyzed the total SUVR (T-SUVR) in the brain with each method and the reference region was the whole cerebellum. We used PET/MR data for SCALE PET and PET data for BTXbrain to obtain and compare centroid values. The Friedman test was used to assess the difference between the T-SUVRs of each method, and post hoc comparisons were performed using the Wilcoxon signed-rank test. The Wilcoxon signed-rank test was also used to compare centiloid values.
Results: The age of the enrolled subjects (10 male and 19 female) was 61.9±5.3 years and the mean MMSE score was 29.1±0.9 (range 27-30). The values of T-SUVR of BTXbrain and SCALE PET (PET/MR, PET/CT, and PET) were 0.917±0.043, 0.969±0.042, 1.070±0.082, and 1.012±0.047, and a significant difference was observed (p=0.000). Each value was significantly different from the others on post hoc analysis (all p values were 0.000). There was no significant difference between the centiloid values of the two software (p value = 0.496).
Conclusions: T-SUVR is significantly different between software and data used, while centiloid value is not. It seems that the use of centiloid value is better for brain amyloid PET analysis.

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SHIFT 01-444

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - AMYLOID
2-3 April 2025

CLINICAL IMPLICATIONS OF ARTIFICIAL INTELLIGENCE-BASED IMAGE ANALYSIS IN BRAIN AMYLOID PET

Byung Wook Choi[1], Hae Won Kim[2]
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Aims: This study aimed to evaluate the clinical implications of artificial intelligence (AI)-based analysis of brain amyloid PET scans in patients with suspected Alzheimer's disease (AD).
Methods: A total of 69 subjects were included in this retrospective study. All subjects underwent a 10-minute PET/CT scan 90 minutes after an intravenous injection of 185 MBq ^{18}F-flutemetamol. Brain PET analysis was performed using commercially available AI-based software (SCALE PET, Neurophet Inc., Seoul, Korea) with PET/MR (3D T1) data. Centiloid scale, global SUVR (G-SUVR), and SUVR values of frontal, parietal, temporal, precuneus, cingulate, and striatum, which are AD-specific regions, were obtained. The whole cerebellum was selected as the reference region. Amyloid PET scans were classified as positive and negative by visual analysis. Area under the curve analysis of each value was used to evaluate the diagnostic accuracy of AD pathology and the concordance of visual analysis.
Results: The age of the enrolled subjects (25 male and 44 female) was 67.6±7.1 years. Among the patients, 24 were diagnosed with Alzheimer's continuum, and 21 had a positive scan on visual analysis. The values of AUC of centiloid scale, G-SUVR, frontal, parietal, temporal, precuneus, cingulate, and striatum were 0.830, 0.830, 0.845, 0.826, 0.852, 0.871, 0.820 and 0.820 for diagnostic accuracy of AD, and 0.999, 0.999, 0.997, 0.997, 0.999, 0.999, 0.997, and 0.970 for predicting a positive visual scan, respectively. There was no significant difference in the comparison of the AUC values of the six regions with highest diagnostic accuracy and visual assessment. There were strong positive correlations between results of visual analysis and quantitative values (all p values< 0.001).
Conclusions: Clinical diagnosis and visual assessment of brain amyloid PET could be assisted by AI-based image analysis.

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SHIFT 01-445

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - AMYLOID
2-3 April 2025

A NEWLY DEVELOPED BLOOD-BRAIN BARRIER-PENETRANT TETRAZINE ENABLES ANTIBODY-BASED BRAIN PRETARGETED PET IMAGING

Tobias Gustavsson[1], Thomas Kustermann[2], Lars Hvass[3], Vladimir Shalgunov[1], Anne Skovsbo Clausen[3], Sophie Stotz[1], Thomas Wünsche[1], Sara Lopes Van Den Broek[1], Gitte Moos Knudsen[4], Blanca Aldana[1], Jens Niewoehner[2], Luca Gobbi[2], Michael Honer[2], Umberto Battisti[1], Andreas Kjær[3], Matthias Herth[1]
[1]University of Copenhagen, Department Of Drug Design And Pharmacology, Copenhagen, Denmark, [2]Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Roche Pharma Research And Early Development, Neurosciences And Rare Diseases, Basel, Switzerland, [3]Cluster for Molecular Imaging, Department Of Biomedical Sciences, University Of Copenhagen, Copenhagen ø, Denmark, [4]Copenhagen University Hospital, Neurobiology Research Unit And Center For Integrated Molecular Brain Imaging, Copenhagen, Denmark

Aims: In this study, we evaluate whether a newly developed blood-brain barrier (BBB) penetrable tetrazine (BBB-Tz) with rapid trans-cyclooctene (TCO) ligation kinetics can be used for brain pretargeted PET imaging. The BBB-Tz was tested in 5xFAD mice, an amyloid-beta (Aβ) mouse model, using a TCO-modified bispecific construct (TCO-BS-mAb) of the Aβ-targeting antibody mAb31 connected to a single-chain Fab fragment of the BBB-penetrating antibody 8D3.
Methods: The BS-mAb was TCO-functionalized and TCO load was quantified by radio-SDS-PAGE. Affinity for Aβ and mouse transferrin receptor (mTfR) and antibody integrity were assessed by ELISA and size-exclusion HPLC. Five months old female 5xFAD (n=2) and aged-matched WT (n=2) mice received TCO-BS-mAb (40 nmol/kg) intravenously. After 72h, [18F]BBB-Tz (8 MBq/mouse, 20 nmol/kg) was administered intravenously, and mice underwent dynamic PET scanning for 90 minutes. Brain uptake was quantified as standardized uptake value (SUV). Next, brains were extracted, sectioned, and co-stained with thioflavin S and anti-human secondary antibody to visualize Aβ and TCO-BS-mAb, respectively. Tracer distribution was examined by ex vivo autoradiography.
Results: TCO-functionalized BS-mAb (10 TCOs/BS-mAb) displayed minor affinity alterations towards Aβ and mTfR with no change in antibody integrity. SUV time-activity curves (80–90 minutes timeframe) showed a 27% increase in cortical and a 39% increase in hippocampal retention of [18F]BBB-Tz in 5xFAD mice compared to WT mice. Co-staining revealed abundant TCO-BS-mAb binding to Aβ plaques in 5xFAD mice brain sections. Autoradiography supported PET findings, showing elevated tracer retention in the cortical and hippocampal areas in brain sections from 5xFAD mice.
Conclusions: Our newly developed BBB-Tz shows significant promise for brain pretargeting by effectively crossing the BBB, ligating with an Aβ-targeting TCO-BS-mAb, and allowing visualization of Aβ pathology in an Aβ mouse model by in vivo PET imaging.

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SHIFT 01-446

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - AMYLOID
2-3 April 2025

AGE GROUP-SPECIFIC PREDICTORS OF AMYLOID POSITIVITY IN COGNITIVELY UNIMPAIRED INDIVIDUALS

Byung H. Lee[1], Bo-Hyun Kim[2], Sua Kim[1], Daeun Shin[1,2], Jun Pyo Kim[1,2], Sang Won Seo[1,2]
[1]Samsung Medical Center, Neurology, Seoul, Korea, Republic of, [2]Samsung Medical Center, Alzheimer's Disease Convergence Research Center, Seoul, Korea, Republic of

Aims: Amyloid beta plaques, the pathology of Alzheimer's disease (AD), are detectable in cognitively unimpaired (CU) individuals. AD can be classified into the early-onset or late-onset based on the age at onset. This study aimed to investigate factors predicting amyloid positivity (AP) in CU across age groups.
Methods: A total of 723 participants aged ≥50 years were retrospectively enrolled. All participants were classified as CU based on neuropsychological assessments and completed the short form of the Geriatric Depression Scale (SGDS), APOE genotyping, and amyloid PET imaging. Participants were divided into three age groups: ≤64 (N=138), 65–74 (N=330), and ≥75 years old (N=264).
Results: The prevalence of AP increased with age (11.8%, 17.9%, and 24.2% in the ≤64, 65–74, and ≥75 age groups). Logistic regression analyses were performed to predict AP using demographic factors, APOE genotype, SGDS score, Mini-Mental State Examination (MMSE) score, and z-scores of verbal and visual delayed recalls. In the entire sample, APOE genotype, age, MMSE, and the z-score of verbal delayed recall were significant predictors of AP. In the ≤64 age group, only higher depression scores were associated with a lower likelihood of AP. For the 65–74 age group, APOE ε4 carrier, older age, and higher education level predicted AP. In the ≥75 age group, APOE genotype and MMSE scores were significantly associated with AP.
Conclusions: In individuals aged ≤64 depressive symptoms may indicate causes unrelated to AD pathology. APOE ε4 status may be a strong predictor around the typical age of onset for clinical symptoms of AD, and cognitive function may serve as a predictor of AP in more older age. This implies that the prediction of AP should incorporate different factors depending on the age range.

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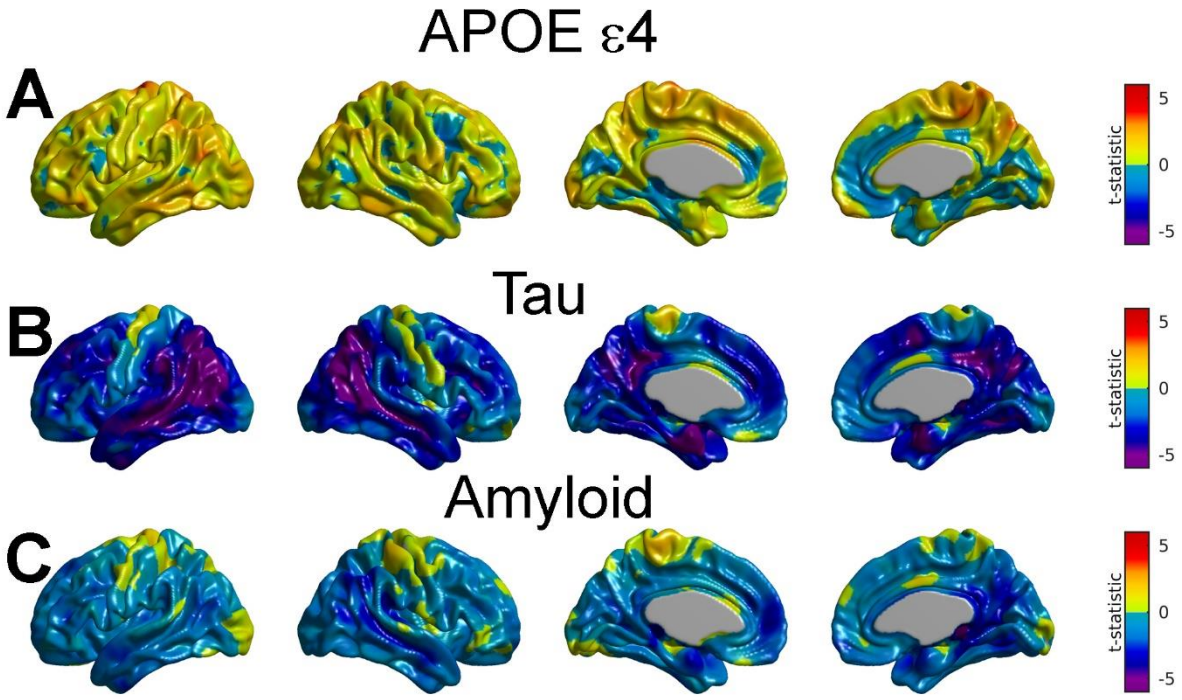
SHIFT 01-447

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
2-3 April 2025

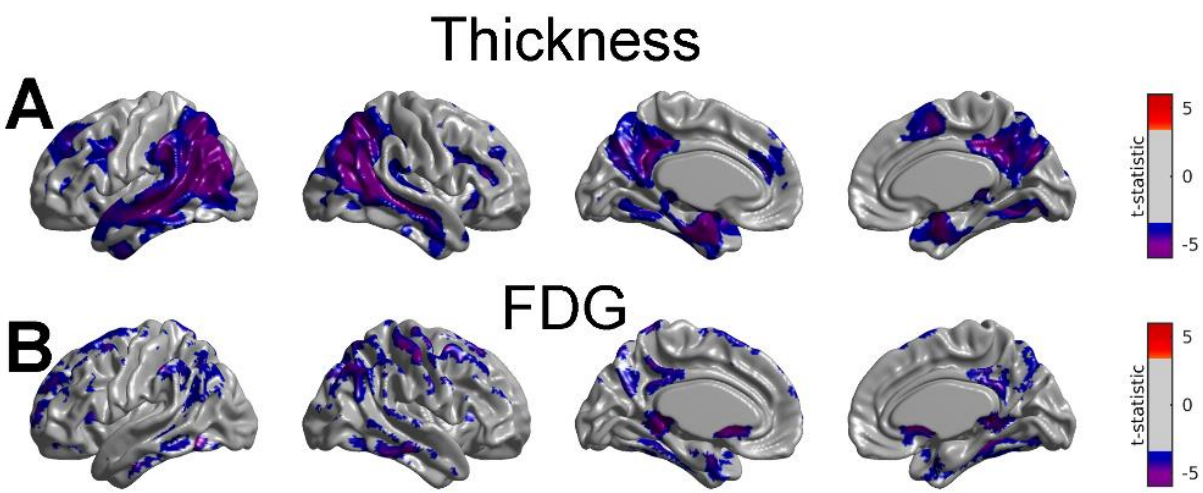
TAU IS ASSOCIATED WITH CORTICAL THICKNESS REDUCTION IN MCI INDEPENDENTLY OF BETA-AMYLOID AND APOE E4 GENOTYPE

Felix Carbonell, Carolann Mcnicoll, Alex Zijdenbos, Barry Bedell
Biospective Inc., Montreal, Canada

Aims: It has been shown that spatially distributed scores from Tau and Amyloid PET images are significantly correlated with glucose metabolism in MCI [1, 2]. We hypothesize that Tau PET scores have a strong association with cortical thinning independently of the effects of beta-amyloid and APOE e4 genotype.
Methods: Our cross-sectional statistical analysis was applied to Tau, Amyloid, and FDGPET images, as well as cortical thickness maps, of MCI subjects from the ADNI study. We employed a Singular Value Decomposition (SVD) approach to the cross-correlation matrix between Tau PET images and cortical thickness maps. The resulting SVD-based individual scores were used to fit vertexwise models for assessing the effect of the SVD-based tau, beta-amyloid scores, and APOE ε4 status on the cortical thickness.
Results: The first SVD component accounted for 27.59% of the total co-variability between cortical thickness and tau. Figures 1A, 1B, and 1C show the t-statistic maps for the effects of APOE e4, SVD-based tau scores, and beta-amyloid on cortical thickness, respectively. Figure 2A and 2B show the FDR-thresholded t-maps for the effects of the tau scores on cortical thickness and FDG,



respectively. Fig



ure 1. Figure 2.

Conclusions: We determined that only the distributed tau scores showed extended areas of statistical significance with cortical thickness. More importantly, such a relationship seems to be stronger than the corresponding Tau-FDG association. Our results suggest that tau is associated with reduced cortical thickness in MCI independently of beta-amyloid burden, reflecting direct implication of tau in neurodegeneration. References [1] Carbonell et al., J. Alzheimer Dis.,73: 543–557, 2020. [2] Carbonell et al., bioRxiv, 2024 (https://doi.org/10.1101/2024.01.23.576866)

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SHIFT 01-451

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2-3 April 2025

"UNDERSTANDING THE IMPACT OF RACE ON WHITE MATTER HYPERINTENSITIES IN ALZHEIMER'S DISEASE: FINDINGS FROM THE ADNI STUDY

Victor Ekuta[1], Jordan Ahn[2], Yorghos Tripodis[3], Roy Hamilton[4]
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Aims: Background: White matter hyperintensities (WMH) are markers of small vessel disease associated with cognitive decline and Alzheimer's disease (AD). African Americans (AAs) are disproportionately affected by cerebrovascular risk factors, but their representation in WMH research remains limited. **Objective**: This study examined the relationship between race, cognitive status, and WMH burden among African American (AA) and non-Hispanic White (NHW) participants, aiming to identify potential racial differences in WMH burden.
Methods: Data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) were analyzed, including 1,649 participants: 682 cognitively normal (CN), 584 with mild cognitive impairment (MCI), and 383 with AD. Of these, 124 participants (7.5%) were African American: CN (70, 10.26%), MCI (39, 6.68%), and AD (15, 3.92%). Linear mixed effects models were employed to assess the influence of race, cognitive status, and demographic factors on total WMH burden.
Results: Preliminary analyses revealed that factors such as time since MRI, age, intracranial volume, and MRI acquisition type significantly predicted total WMH across cognitive states. Time since the first MRI scan, age, and intracranial volume were positively correlated with increased total WMH volume, with the strongest associations seen in the dementia subgroup. MRI acquisition type (FLAIR) was negatively associated with WMH, suggesting that newer MRI techniques are more sensitive in detecting WMH. Higher education levels were associated with decreased WMH burden, indicating a potential protective effect. However, after controlling for other factors, race did not independently predict WMH burden.
Conclusions: These findings suggest that while race was not an independent predictor of WMH burden, other demographic and clinical factors such as age, education, and MRI methods significantly influenced WMH volumes. Further research is needed to explore protective factors against WMH accumulation, particularly in racially diverse populations.

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SHIFT 01-452

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2-3 April 2025

SEX DIFFERENCES IN ALZHEIMER DEMENTIA - RELATED NEURODEGENERATION TRAJECTORIES.

Vladimir Fonov[1], Joseph Therriault[2], Nesrine Rahmouni[2], Stijn Servaes[2], Jenna Stevenson[2], Nina Poltronetti[1], Pedro Rosa-Neto[3]
[1]McGill University, Mcconnell Brain Imaging Centre, Montreal Neurological Institute, Montreal, Canada, [2]McGill University, Neurology And Neurosurgery, Montreal, Canada, [3]McGill Research Centre for Studies in Aging, Translational Neuroimaging Laboratory, Montreal, Canada

Aims: Alzheimer's Dementia (AD) affects females twice as often as males, making it crucial to understand sex-based differences in disease progression for effective interventions.
Methods: We used anatomical MRI scans from publicly available databases: (N Scans,N subjects, age range) : ADNI1,2,3 (8739, 2131, 50-97y), AIBL (1243, 668, 55-97y), NKI (2306, 1326, 6-85y), OASIS 1,2,3 (3212, 1802, 18-97y), UK Biobank (47396, 42912, 44-83y) and TRIAD (914,20-91y) and processed them with AssemblyNET. We split all scans into two groups: CN subjects that remained stable and CN and MCI subjects that progressed to AD dementia.
In the progressor group, the average age of AD diagnosis was 75.77 in females and 77.63 in males. We modeled healthy aging trajectories for each brain structure from ages 21 to 98 using a non-linear mixed effects model, identified the time delay (or advance) relative to clinical AD diagnosis when volumes diverged from normative, and calculated the sex differences in these delays.
Results: We identified several regions that deviated from the normal trajectory before AD dementia onset including well-known hippocampus, parahippocampal gyrus, temporal pole and entorhinal regions. More interestingly, we identified 7 regions changing earlier in males compared to females, and 24 regions changing earlier in females compared to males (Table 1, Figs 1-3). The largest difference was found in the precuneus, where deviation from normal controls occurred roughly 4 years before diagnosis in males, and 7.7 years after for females.

Table 1: Male - Female onset difference

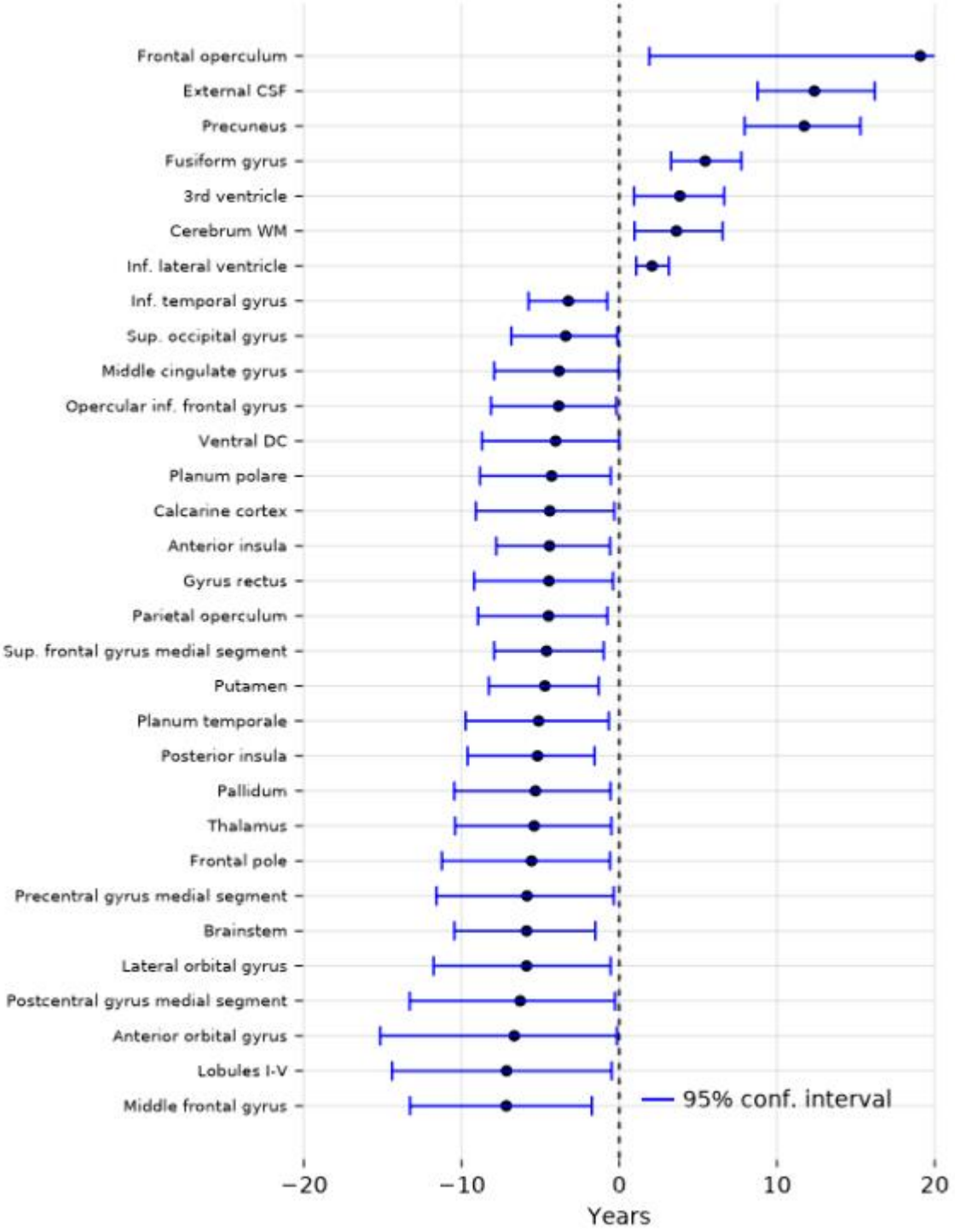


Figure 1: Males neuregeneration onset advance w.r.t AD DX

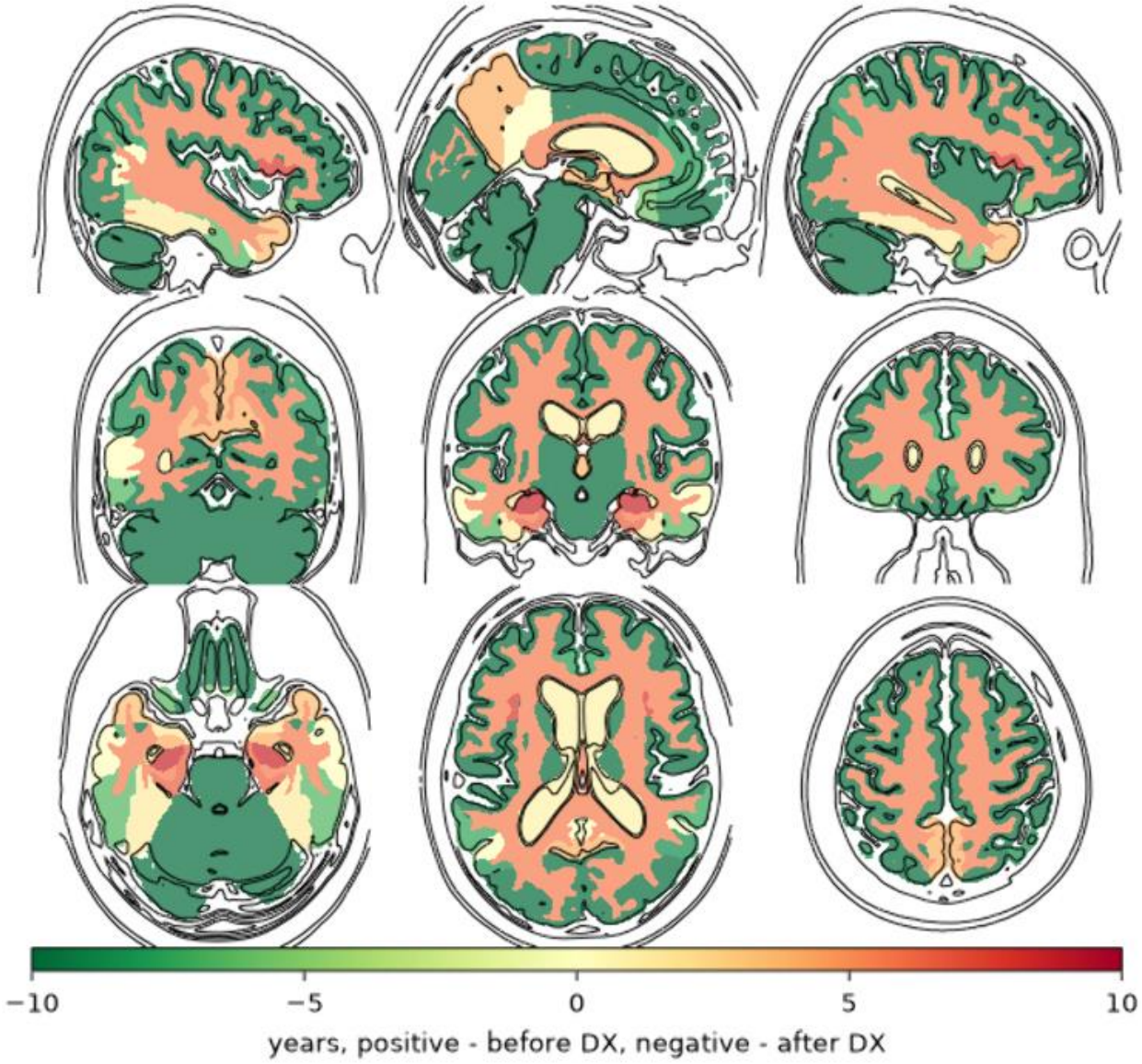


Figure 2:Females neuregeneration onset advance w.r.t AD DX

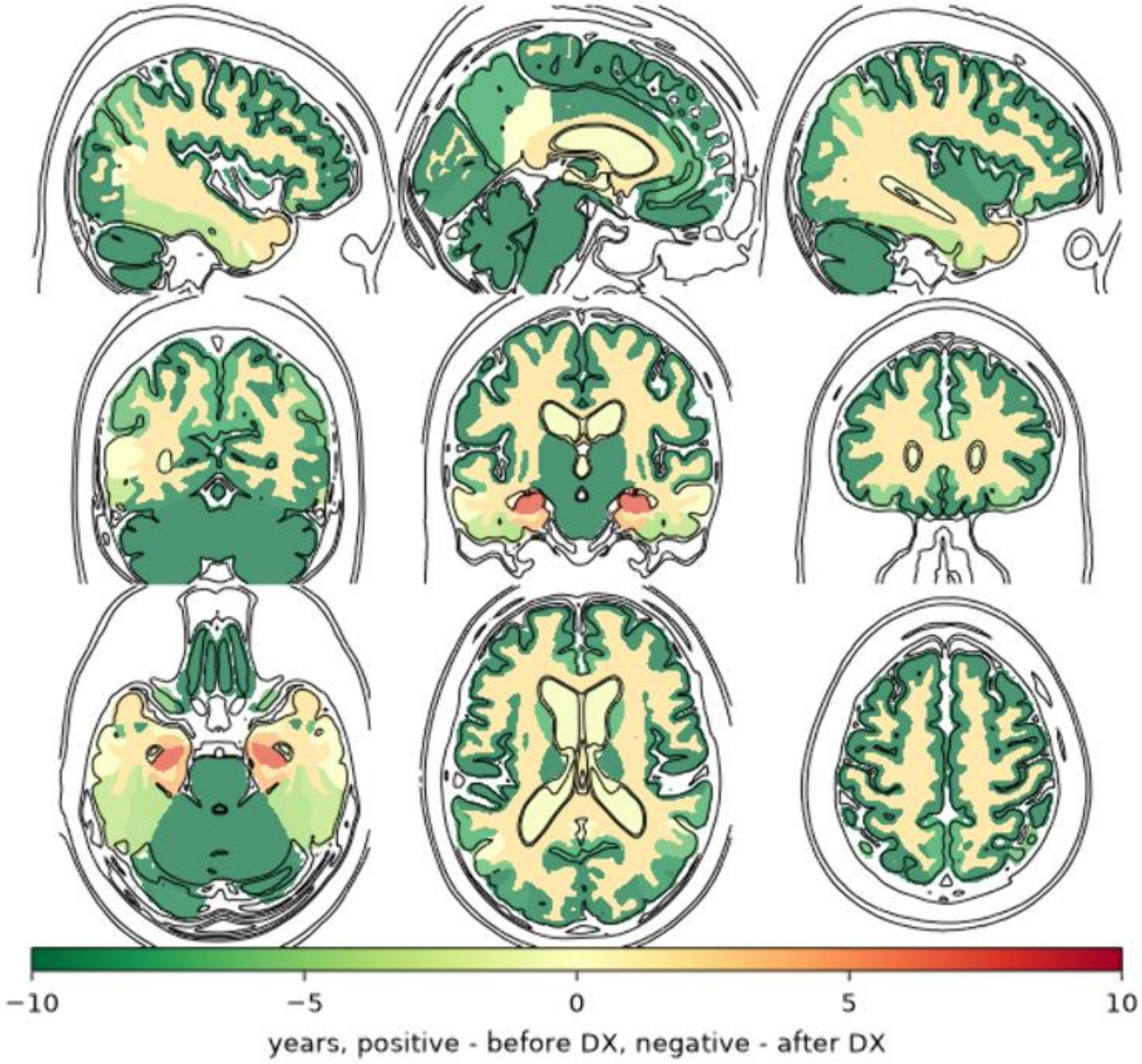
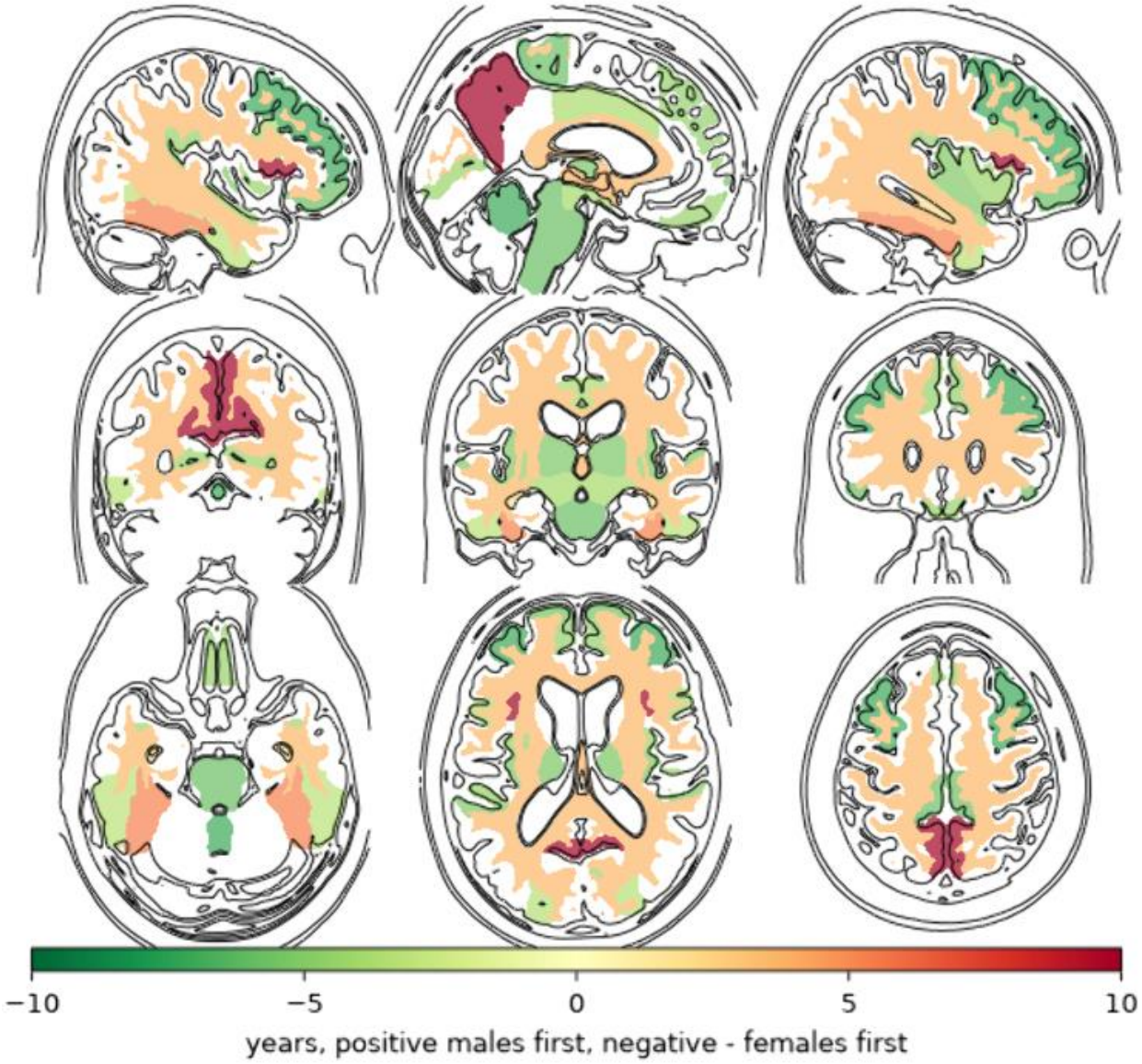


Figure 3: Males - Females neuregeneration onset difference



Conclusions: We have identified 31 anatomical regions showing significant differences in neurodegeneration progression between males and females, providing evidence for faster brain changes in females after AD dementia onset (more green regions, Fig. 3), perhaps due to a sex-specific vulnerability to AD pathology.

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SHIFT 01-453

Poster on Board - Shift 01
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
2-3 April 2025

CORTICAL MAGNETIC SUSCEPTIBILITY DIFFERENCES BY APOE GENOTYPE REVEALED USING X - SEPARATION METHOD

Jae Woo Kim[1], Eun Seon Jeong[2], Jungwon Hwang[1], Yangsean Choi[2], Jae-Sung Lim[1], Jae-Hong Lee[1]
[1]Asan Medical Center, Neurology, Seoul, Korea, Republic of, [2]Asan Medical Center, Radiology, Seoul, Korea, Republic of

Aims: The apolipoprotein E (APOE) gene influences amyloid clearance, cerebral vessel integrity, and lipid metabolism in the brain. The χ-separation method is based on magnetic susceptibility source separation, thereby reflecting paramagnetic (ferritin) and diamagnetic (myelin or lipid) content in the brain, which may be related to neurodegeneration in the brain. We aimed to determine whether regional cortical susceptibility differences by *APOE* genotype could be distinguished using χ-separation.
Methods: We conducted a case-control study of patients aged 18 years or older who underwent *APOE* genotyping and MRI as part of the differential diagnosis of cognitive impairment from May 2023 to August 2024. Patients were divided into *APOE* ε3ε3, ε3ε4, and ε4ε4, age-matched to the ε4ε4 group. Multi-echo gradient recalled echo images were processed via χ-separation method to generate paramagnetic (χ_{para}) and diamagnetic (χ_{dia}) susceptibility maps. Mean susceptibility values were acquired from frontal, temporal, parietal, occipital, and cingulate cortical regions. Perivascular space (PVS) and choroid plexus volumes (CPV) were also acquired as fractions of the total intracranial volume. Group differences were compared using one-way ANOVA.
Results: A total of 91 patients were enrolled (ε3ε3, n=32; ε3ε4, n=27; and ε4ε4, n=32). The mean age was 72±7 years [56 females (61.5%)]; no significant differences were found in age and sex among the groups. The PVS and CPV fractions showed no significant group differences. The ε4ε4 group had significantly higher mean χ_{dia} values in the temporal, occipital, and frontal regions, and higher mean χ_{para} values in the temporal and occipital regions (all, p <0.05).
Conclusions: The χ-separation method may detect subtle differences in the intracerebral substances associated with *APOE* genotype. Further research is needed to understand the biological significance of this regional predilection.

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SHIFT 01-455

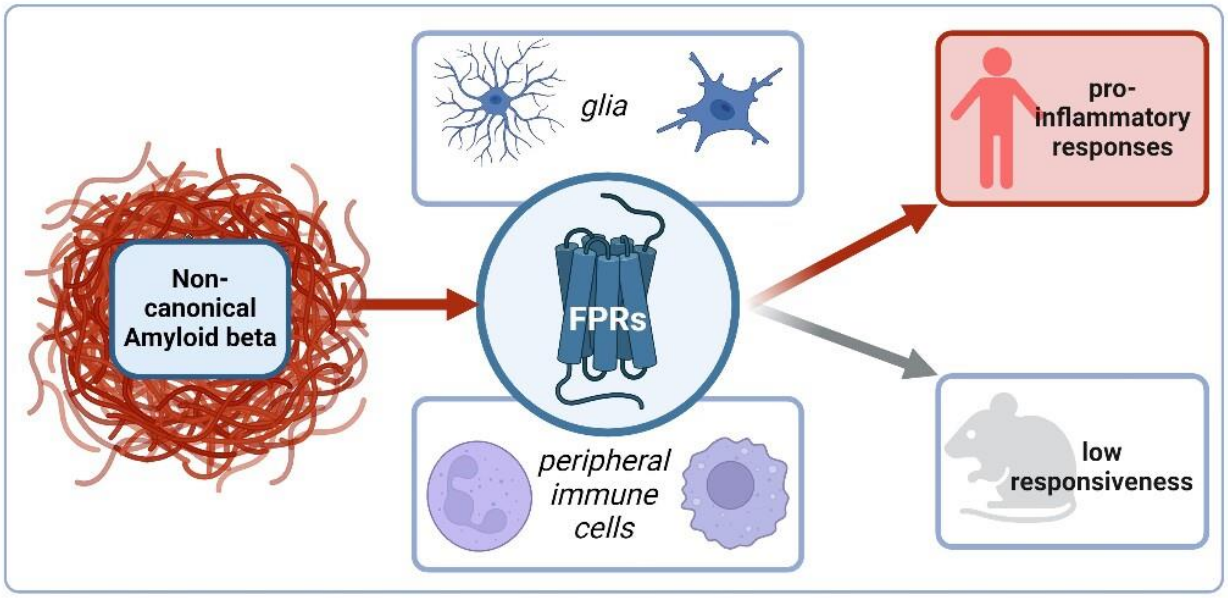
Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
2-3 April 2025

OF MICE AND MEN: HUMAN BUT NOT MOUSE FORMYL PEPTIDE RECEPTORS DRIVE THE PRO-INFLAMMATORY RESPONSES OF NEUTROPHILS TOWARDS AMYLOID BETA

Lukas Busch, Bernd Bufe
University of Applied Sciences Kaiserslautern, Department Of Informatics And Microsystems Technology, Zweibrücken, Germany

Aims: Alzheimer's disease (AD), the most common neurodegenerative disorder, affects over 10% of elderly populations. However, its research is compromised by several challenges. First, while amyloid beta (Aβ) peptides drive disease progression, most research only focuses on Aβ1-42, leaving >100 Aβ species unexplored. Second, suitable research models are sparse, especially since AD involves multiple cell types, including peripheral immune cells, whose roles remain unclear. Humanized mouse models offer partial solutions but are criticized for their limited transferability to human AD pathology. In this study, we investigated and compared the molecular basis of Aβ detection by human and mouse formyl peptide receptors (FPRs) to gain further insight into non-canonical Aβ and the comparability between species.
Methods: ►Calcium Imaging ►MAPK-Signaling-Assays ►Chemotaxis-Assays ►NETosis-Assays
Results: By challenging FPRs with various physiological Aβ peptides, we found significant differences between human and mouse FPR responses. Screening systematically fragmented peptides derived from the whole Aβ domain identified species- and subtype-specific activation motifs for each FPR. Comparing immune cell models revealed distinct signaling patterns between human and mouse FPRs, with mouse models showing either absent or diminished responses. In validation experiments with primary isolated human and mouse neutrophils, N-truncated Aβ and the FPR1-specific motif triggered strong signaling and pro-inflammatory responses in human cells, but only minimal activity in mice.
Conclusions: Our study demonstrates species-specific differences in FPR-mediated responses to Aβ peptides, particularly in FPR1-driven pro-inflammatory activity. This highlights a potential new role for FPRs

and N-truncated Aβ peptides in AD while emphasizing particular limitations of mouse models in AD research.



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SHIFT 01-456

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
2-3 April 2025

ENHANCED DELIVERY OF ANTI-PYROGLUTAMATE AMYLOID-BETA ANTIBODY, ALIA-1758, ACROSS THE BLOOD-BRAIN BARRIER VIA TFR-MEDIATED TRANSCYTOSIS

Danijela Dukovski, Alycia Shoultz, Keith Canada, Jessica Mcdonald, Berkley Lynch, Antonella Pirone, Magnus Ivarsson, John Dunlop, James Ryan
Aliada Therapeutics, Biology, Boston, United States of America

Aims: Aliada Therapeutics, Inc. has developed ALIA-1758, a modified human IgG1 bispecific antibody with high affinity binding to 3-pyroglutamate (3pE) Aβ peptide and a genetically fused scFv domain that binds transferrin receptor (TfR) enabling BBB transcytosis, as a potential Aβ plaque-reducing therapy for patients with Alzheimer's Disease (AD).
Methods: TfR-mediated internalization of Aβ peptides and aggregates was tested in THP-1 and iPSC microglia. To demonstrate that internalization was TfR-dependent, TfR-ectodomain was included in experiments. iPSC-derived microglia were used to demonstrate Aβ aggregate clearance by effector-negative ALIA-1758. Brain exposure and target engagement of ALIA-1758 were evaluated in hTfR knock-in (KI) mice and human TfR KI mice expressing the Arctic, Iberian, and Swedish APP mutations (hTfR*APP NL-G-F), respectively, as well as in human AD brain slices by ICH.
Results: ALIA-1758 showed dose-dependent internalization of 3pE Aβ peptides in THP1 cells. Incubation with TfR ectodomain blocked internalization of Aβ peptides, thereby demonstrating TfR -dependent endocytosis. 3pE Aβ aggregates were internalized in IPSC-microglia by effector negative ALIA-1758 and microglia activation was not observed (measured by cytokine release). PK studies showed ~16 fold greater exposure in the brain samples of ALIA-1758-treated hTFR KI mice compared to the hIgG1 3pE antibody without TfR binding domain. Target engagement in NL-G-F mouse as well as human AD brain slices was demonstrated.
Conclusions: These preclinical results demonstrate that ALIA-1758 utilizes the TfR scFV to cross the BBB and, with limited immune activation, clears Aβ plaques via receptor-mediated-endocytosis. Based on the available preclinical data, ALIA-1758 could be an effective AD therapeutic with Aβ plaque-reducing efficacy achieved at lower dosage levels than conventional anti-Aβ antibody therapeutics. ALIA-1758 is currently being assessed in a Phase 1 clinical trial enrolling healthy participants (NCT06406348).

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SHIFT 01-457

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
2-3 April 2025

LECANEMAB BINDS TO TRANSGENIC MOUSE MODEL-DERIVED AMYLOID-BETA FIBRIL STRUCTURES RESEMBLING ALZHEIMER´S DISEASE TYPE-I, TYPE-II AND ARCTIC FOLDS

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Aims: Lecanemab, an FDA-approved monoclonal antibody targeting Alzheimer's disease, was previously reported to have high affinity for intermediate-sized amyloid-beta aggregates. Subsequently, it was observed by immunogold labelling that lecanemab can also bind to human type-I amyloid-beta fibrils. To determine whether lecanemab binds to amyloid-beta fibril structures other than type-I, we analysed the binding capacity of lecanemab to various structurally defined amyloid-beta fibril preparations from six different Alzheimer's disease mouse models.
Methods: Lecanemab binding was analysed by immunogold-EM on the same ex-vivo amyloid-beta fibril preparations whose structures were previously solved by cryo-EM (Zielinski, M. et al. 2023, Nat Neurosci 26, 2073, doi 10.1038/s41593-023-01484-4).
Results: Lecanemab binds to amyloid-beta fibrils from several Alzheimer's disease tg-mice whose structures resemble the type-I, type-II and Arctic folds found in Alzheimer's patients, all of which share a flexible, unstructured N-terminus. Lecanemab is therefore expected to be active against all common familial and sporadic AD cases containing these folds.
Lecanemab binding ability is unaffected by and tolerates the Arctic E22G mutation, at least in type-I or Arctic folds.
Weak, if any, lecanemab binding was observed to amyloid-beta fibrils from tg-SwDI mice, whose structures DI1, DI2 and DI3 all share structured, fixed N-termini.
Since the fixed N-termini of tg-SwDI DI1 fibrils and human meningeal amyloid-beta40 fibrils derived from CAA-affected brain are identical, most likely preventing lecanemab binding, treatment with lecanemab may be less or ineffective against CAA, but may explain the reported beneficial low ARIA-E frequency with lecanemab.
Conclusions: Our results demonstrate at individual fibril folds level high-affine lecanemab binding to amyloid-beta fibril structures that all share flexible, nonstructured N-termini, which may be a prerequisite for lecanemab´s binding capability, as only negligible binding was observed to fibril structures with fixed N-termini.

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SHIFT 01-458

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
2-3 April 2025

SCREENING CANDIDATE DRUGGABLE GENES FOR ALZHEIMER'S DISEASE USING MENDELIAN RANDOMIZATION

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Aims: Alzheimer's disease (AD) is characterized by a neuropathological cascade that begins with β-amyloid (Aβ) deposition. The recent success of disease-modifying drugs targeting Aβ has shown that modulating amyloidopathy can yield clinical benefits, underscoring the need for additional drugs affecting amyloid pathology. This study aims to identify novel drug targets by performing Mendelian Randomization (MR) analysis on expression quantitative trait loci (eQTL) of the druggable genome in relation to Aβ accumulation.
Methods: MR analysis was conducted to examine the causal relationships between blood and brain eQTLs of the druggable genome and Aβ accumulation, using the Summary-data-based Mendelian Randomization (SMR) method. Blood eQTL data were obtained from eQTLGen, while brain eQTLs were sourced from BrainMeta and PsychENCODE. The Aβ PET GWAS data included 11,816 non-Hispanic white participants across 13 cohorts. To enhance the reliability of the MR results, a colocalization analysis was performed. Additionally, MR analysis was conducted using blood and brain protein quantitative trait loci (pQTLs) as instrumental variables to validate the MR findings.
Results: The SMR and colocalization analyses revealed a causal association between druggable genome and Aβ accumulation. In the blood eQTL data, only the APH1B was identified, whereas three genes (ACE, APH1B, CR1) were identified in the brain eQTL data. The SMR analysis using pQTL data as exposure also showed causal associations for ACE and CR1 with Aβ. Among these genes, only ACE was negatively associated with Aβ PET uptake.
Conclusions: Our results identified potential target genes for AD treatment. Notably, the protective effect of ACE against amyloid pathology suggests that alternative medications to ACE inhibitors might be preferred for blood pressure management in the context of AD. Our findings highlight the potential of MR in facilitating drug repurposing for AD.

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SHIFT 01-459

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-INFLAMMATORY
2-3 April 2025

HYDROXYTYROSOL OF OLIVE OIL PREVENTS OXYSTEROL-INDUCED NEUROINFLAMMATION IN ALZHEIMER'S DISEASE THROUGH SIRTUIN-1 INDUCTION

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Aims: Growing experimental evidence suggests that the Mediterranean diet reduces risk of dementia. Of note, olive oil contains the potent polyphenol hydroxytyrosol (HXT) currently considered a bioactive compound able to improve cognitive function. Since little data are available regarding HXT anti-inflammatory effects in Alzheimer's disease (AD), the aim of our study focused on the ability of HXT in preventing neuroinflammation induced by an oxysterol mixture, cholesterol oxidation products, whose composition represent oxysterol amounts previously quantified in severe AD brain samples, using human neuroblastoma SK-N-BE cells. Among the potential involved molecular mechanisms, we have analyzed the neuroprotective effect of sirtuin 1 (SIRT1), a deacetylase enzyme. The SIRT1-dependent anti-inflammatory pathway through which HXT might act was investigated.
Methods: Inflammatory mediator and SIRT1 gene expression and protein levels were analyzed by quantitative RT-PCR and Bio-plex®/Luminex® technology or Western blotting, respectively. NFκB p65 translocation and TLR4 levels were observed by the LSM 800 confocal laser microscope.
Results: Our results show an increase of expression and synthesis of IL-1β, IL-6, IL-8, TNFα, IFNγ, and MCP-1 inflammatory mediators induced by oxysterols; this increase was markedly prevented by HXT cell pre-treatment. It was also demonstrated that oxysterols trigger neuroinflammation via TLR4-mediated NFκB activation. Moreover, mRNA overexpression and protein up-regulation of SIRT1 induced by HXT was observed. Through SIRT1 induction, HXT was able to inhibit the oxysterol-induced TLR4 up-regulation and the consequent NFκB p65 translocation; using sirtinol, a specific SIRT1 inhibitor, the anti-inflammatory effects of HXT were not observed.
Conclusions: Data show HXT's ability to mitigate oxysterol-induced neuroinflammation via SIRT1/TLR4/NFκB pathway, suggesting HXT as a potential nutraceutical. It offers promise for preventing neuroinflammation and, consequently, amyloid β and tau accumulation to counteract the neurodegeneration in AD.

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SHIFT 01-460

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-INFLAMMATORY
2-3 April 2025

EFFEROCYTOSIS-DRIVEN NEUROINFLAMMATION REDUCTION BY NOVEL GAS6 FUSION PROTEIN (GAIA) IN ANTI-AB IMMUNOTHERAPIES

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Aims: Amyloid-beta (Aβ) immunotherapy has emerged as a promising approach for treating Alzheimer's disease (AD). Recent FDA approvals of antibody therapeutics like Lecanemab and Donanemab have demonstrated significant reductions in Aβ burden and deceleration of cognitive decline, reinforcing Aβ as a viable therapeutic target. However, these therapies are associated with adverse reactions, including antibody-induced inflammation, amyloid-related imaging abnormalities (ARIA), and cerebral microbleeding [1]. The GAIA platform introduces a novel chimeric protein that leverages Tyro3, Axl, and MerTK (TAM) receptors to mediate efferocytosis-driven phagocytosis without triggering inflammatory responses, aiming to address the limitations of current Aβ immunotherapies [2]. This study applies the GAIA platform to Aβ antibodies (GAIA-Aβ) to evaluate their efficacy and pharmacokinetics for therapeutic potential.
Methods: We engineered GAIA-Aβ chimeric proteins featuring two functional domains: Aβ-specific fragments fused with an engineered GAS6 domain for TAM receptor binding. Specific binding to oligomeric Aβ (oAβ) and TAM receptors was confirmed using ELISA assays. TAM receptor-mediated phagocytosis and oAβ clearance were assessed using HMC3 (human microglial cells lacking Fcγ receptors). Anti-inflammatory responses were evaluated in induced pluripotent stem cell (iPSC)-derived monocytes. Pharmacokinetic properties and in vivo efficacy of GAIA-Aβ were studied.
Results: GAIA-Aβ exhibited specific binding to oAβ and activated TAM receptors in a dose-dependent manner. Phagocytosis assays demonstrated effective clearance of oAβ, while a reduction in inflammatory cytokines indicated successful efferocytosis-mediated activity. Pharmacokinetic analysis revealed that GAIA-Aβ possesses properties comparable to those of existing monoclonal antibody therapeutics.
Conclusions: GAIA-Aβ effectively clear amyloid plaques and induce anti-inflammatory responses, with favorable pharmacokinetic profiles. These findings suggest that GAIA-Aβ may offer comparable therapeutic benefits in reducing Aβ burden while improving safety profiles by mitigating issues like vascular damage and ARIA associated with current immunotherapies.

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SHIFT 01-461

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-OXIDANTS
2-3 April 2025

POLYPHENOLIC PREPARATION FROM FRUITS USEFUL FOR NUTRITIONAL SUPPORT OF ALZHEIMER'S DISEASE TREATMENT

Dominik Szwajgier[1], Ewa Baranowska-Wójcik[1], Wirginia Kukuła-Koch[2], Katarzyna Krzos[3], Marta Ziaja-Sołtys[4]
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Aims: To create a polyphenolic preparation useful for the nutritional support of Alzheimer's disease treatment.
Methods: Twenty fruits were screened, of which 7 (peach *Prunus persica,* apricot *P. armeniaca*, chokeberry *Aronia melanocarpa*, blueberry *Vaccinium corymbosum,* cranberry *V. oxycoccus*, raspberry *Rubus idaeus* and wild strawberry *Fragaria vesca*) were chosen to create a polyphenolic preparation (after enzyme-assisted extraction, ultrafiltration and concentration). The composition of the preparation was studied by LC-MS and gelatin edible jellies were produced. Jellies as well as liquid preparation were „digested" in a static *in vitro* gastro-intestinal model to analyze anticholinesterase, anti-inflammatory and other biological activities. Freeze dried fruits were enclosed in hard DRcaps capsules (commercial form).
Results: The preparation showed strong anticholinesterase activities due to the presence of 26 individual polyphenols, covering total anthocyanins (53.3 mg cyanidin-3-glucoside/g), total condensed tannins (3.75 mg catechin/g), total flavonoids (1.5 mg quercetin/g), total flavanols (0.42 mg catechin/g). During „digestions" of liquid preparation, the levels of flavanoids were gradually increasing and other polyphenolic classes were decreasing beginning from the *duodenum* phase. The anticholinesterase activities were decreasing with the course of the „digestion", as compared with the undigested preparation. CUPRAC activities were increasing with the course of „digestion", FRAP and linoleic acid oxidation markers were increased with the course of „digestions", while HORAC and B-carotene bleaching tests were unchanged. Increased ability to inhibit GPx, decreased ability to inhibit SOD, GR and CAT and no effect on COX-2 activity with the course of „digestion" were observed. At every stage of „digestion", the entrapment of the preparation in jellies delayed the release of polyphenols during "digestions".
Conclusions: A new polyphenolic preparation possessing strong anticholinesterase, anti-inflammatory and antioxidant activities was created for the nutritional support of Alzheimer's disease treatment.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-OXIDANTS
2-3 April 2025

TITLE: TITLE: SIMVASTATIN AMELIORATED AB1-42-INDUCED NEURONAL INJURY BY REGULATING NRF2/KEAP1 ANTI-OXIDATIVE PATHWAY AND INDUCING AUTOPHAGY ACTIVATION

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Aims: In Alzheimer's disease, neurons experience autophagy dysfunction and oxidative stress that contribute to extracellular neurotoxic amyloid-β (Aβ) peptide accumulation. Chemical modulators that modulate autophagy and regulate oxidative stress are potential drugs for AD therapies. This study aimed to investigate the effect of Simvastatin (SV) on oxidative stress and autophagy dysfunction by $A\beta_{1-42}$ -induced in primary neurons and explore its regulations of the PI3K/Akt pathway.
Methods: Mouse primary cortical neurons were incubated with $A\beta_{1-42}$ (50, 1000, 1000 nM) and treated with SV for 24 h. The neuroprotective effect of SV and its mechanism were 24 observed on cell viability, anti-oxidative stress, autophagy and PI3K/Akt/Nrf2/Keap1-related protein expression.
Results: 5 μM SV increased Bcl-2 levels and decreased the expression of Bax by PI3K/Akt pathway activation, suggesting that SV prevented $A\beta_{1-42}$ induced neurotoxicity. Meanwhile, SV reduced the $A\beta_{1-42}$ induced up-regulation of intracellular ROS production through Nrf2/Keap1 anti-oxidative pathway. Further, SV increased the LC3BII/LC3BI ratio and decreased p62 levels, pointing to an increase in autophagic flux, which was activated by unclear translocated Nrf2. Additionally, SV-induced autophagy activation could not be reversed by PI3K inhibitor LY294002.
Conclusions: Our results suggest that SV ameliorated $A\beta_{1-42}$ -induced neuronal injury via both Nrf2/Keap1 activated anti-oxidative stress effect and autophagy activation.

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SHIFT 01-463

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-OXIDANTS
2-3 April 2025

HEMOGLOBIN AS A PEROXIDASE AND DRUG TARGET FOR ALZHEIMER'S DISEASE

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Aims: In the brains of Alzheimer's disease (AD) patients, levels of reactive oxygen species (ROS) are significantly elevated compared to those in healthy aging brains. Hydrogen peroxide (H_2O_2), a prominent ROS, contributes to oxidative stress and is produced by various metabolic pathways in AD. Hemoglobin (Hb), widely known for its role in oxygen transport in red blood cells, is also present in the brain, though its function there remains largely unclear. In this study, we demonstrate that Hb, found in astrocytes of neurodegenerative animal models and human patients, exhibits substantial antioxidant properties through its peroxidase activity, which breaks down H_2O_2. We aimed to develop a small molecule enhancer amplifies this activity, reducing abnormal H_2O_2 levels and alleviating H_2O_2-induced neurodegeneration.
Methods: We synthesized a series of novel compounds to counteract the harmful effects of H_2O_2-production in AD by enhancing the peroxidase activity of Hb. These compounds were evaluated using an optimized *in vitro* assay system. The enhancement in peroxidase decomposing activity was tested also in primary cultured astrocytes using H_2O_2-sensors DCFDA and oROS-G. Reduction of H_2O_2 concentration, neuroprotective effects, and memory impairment recovery were tested in both APP/PS1 mouse models and focal DTR-expressing astrocytes in APP/PS1 mice (fGID). Gene silencing of Hbβ validated the effects of these compounds also shown in culture and animal models.
Results: We developed KDS12025, a small molecule capable of crossing the blood-brain barrier (BBB) that enhances the peroxidase activity of hemoglobin (Hb) at low concentrations by 100 times. KDS12025 decreases H_2O_2 levels in astrocytes, offers neuroprotective benefits, and improves memory deficits in AD models.
Conclusions: Our findings identify Hb as a novel therapeutic target for AD, with KDS12025 effectively enhancing Hb's peroxidase activity to reduce H2O2 levels.

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SHIFT 01-464

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / APOE & LIPOPROTEIN-BASED
2-3 April 2025

ANTI-APOE4 ANTIBODY AMELIORATES COGNITIVE IMPAIRMENTS AND SYNAPSE LOSS IN APOE4/TAU-P301S MICE

Min-Seok Kim[1], Ha-Lim Song[1], Na-Young Kim[1], Yeon-Seon Mun[1], Jung-Su Shin[1], Mi-Hyang Cho[1], Jun-Sub Kim[1], Dong-Hou Kim[2], Seung-Yong Yoon[1,2]
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Aims: Apolipoprotein (ApoE) is a protein encoded by APOE gene that plays an important role in lipid transport in the body. Among the three isotypes (2, 3, and 4), APOE4 is the strongest genetic risk factor for late-onset Alzheimer's disease, while APOE2 is thought to be protective against Alzheimer's disease. APOE4 contributes to metabolic and neuropathological changes during brain aging showing strong correlation with phosphorylated tau load and amyloid deposition. The purpose of this study was to determine whether targeting of apoE4 by anti-apoE4 antibody restores pathologic changes mediated by apoE4 isoform and tauopathy.
Methods: We utilized Tau-P301S transgenic mice model crossed with APOE4-knockin mice expressing human APOE4 (ApoE4/Tau-P301S) to assess the effect of anti-ApoE4 antibody, ADEL-Y04: its delivery to the brain, target binding, reduction of tau pathology, and restoration of cognitive functions.
Results: ADEL-Y04 specifically recognized human ApoE4. Peripherally injected ADEL-Y04 bound to brain ApoE4, and mice injected with ADEL-Y04 showed improvements in cognitive function tests. Loss of synapse and pathological tau accumulation were inhibited by the antibody.
Conclusions: These results support the targeting of ApoE4 as a potential therapeutic approach for Alzheimer's disease. Our finding suggests that modulation of ApoE4 improved APOE4-mediated tau pathology and memory impairment, contributing to the evidence for ApoE4 targeting by peripheral injection of anti-ApoE4 antibodies. Currently humanization of ADEL-Y04 is complete, and open for future IND-enabling studies. Further, avenues to enhance the brain penetration by means of brain penetrating peptides is being incorporated to the antibody for study.

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SHIFT 01-465

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ASO AND RNAI
2-3 April 2025

DISCOVERY OF A NOVEL C3-TARGETING AND CNS ACTIVE SIRNA AS A POTENTIAL THERAPEUTIC FOR ALZHEIMER'S DISEASE

Tara Barbour[1], Yan Li[1], Fay Touti[1], Salome Funes[1], Elisabeth Lonie[1], Anshu Jain[1], Andrew Carvalho[1], Zhouning Zhang[1], Maggie Mohr[2], Sole Gatto[3], Sijin Guo[4], Matthew Poulin[5], Anke Geick[6], Soham Mandal[6], Kate Lane[1], Lukas Scheibler[1], David Eyerman[1]
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Aims: Complement dysregulation plays a key role in neuroinflammation and synaptic loss in neurodegenerative disorders, including Alzheimer's disease (AD). The third component, C3, is an attractive therapeutic target due to its pivotal role in all known complement activation pathways. C3 mRNA is elevated in post-mortem AD brains, which correlates with Braak staging, and C3 protein is elevated in CSF of living patients. Here, we present the discovery of a novel siRNA for selective silencing of CNS C3.
Methods: siRNAs were synthesized with various modification patterns and RNAi activity was evaluated *in vitro*. Potential off-target liabilities were investigated *in silico* and immunostimulatory potential was assessed *in vitro* in PBMCs. Pharmacology, tolerability, and distribution of an intrathecally dosed lead siRNA (synthesized with a delivery conjugate) were evaluated in NHP studies at multiple dose levels. C3 mRNA levels were determined in tissues by RT-qPCR at various timepoints post-dose. C3 protein in CSF, tissue, and plasma were evaluated by MesoScale Discovery assay. Tissue, CSF, and plasma siRNA concentrations were determined by LC-MS/MS.
Results: Highly potent siRNAs were identified through *in vitro* screening. A lead siRNA was selected based on potency, potential off-target profile, and immune-stimulatory potential. Following dosing, C3 protein levels were rapidly reduced in NHP CSF vs baseline and prolonged suppression was observed. C3 mRNA and protein levels were significantly reduced in several Alzheimer's relevant brain regions at study terminus. siRNA was detected in all brain regions evaluated. No adverse test article-related findings were observed in exploratory histopathology of CNS tissues.
Conclusions: Here we describe a novel C3-targeting siRNA, demonstrating potent and durable silencing of C3 in NHP CNS. This compound represents a putative therapeutic for clinical testing against cognitive decline in AD.

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SHIFT 01-466

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ASO AND RNAI
2-3 April 2025

BRAIN-DELIVERY OF SIRNAS USING ENGINEERED NANOBODIES THAT CROSS THE BBB FOR ALZHEIMER'S DISEASE APPLICATIONS

Charline Chalbot[1], Angélique Bôle[1], Anne Bernard[1], Pascaline Lecorché[2], Guillaume Jacquot[2], Simone Mastrogiacomo[1], Michel Khrestchatisky[1]
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Aims: Oligonucleotide-based treatments represent a promising strategy for AD and other neurodegenerative diseases, offering highly-specific regulation of genetic risk factors. Nevertheless, effective delivery of therapeutics into the brain is hindered by the blood-brain barrier (BBB). We developed a nanobody-based construct that efficiently shuttles siRNAs across the BBB and in this study a nanobody-siRNA conjugate was used to target AD risk factors in the CNS.
Methods: siRNAs are synthesized via DNA/RNA synthesizer applying stabilization schemes and functional groups required for chemical conjugation to the engineered nanobody. The siRNA-nanobody conjugates are characterized through chromatography (SEC-HPLC) and mass spectrometry (LC-MS) and assessed in vitro in N2a and HEK293 cells. In vivo evaluation is performed via intracerebroventricular (ICV) and systemic injection in wild type (WT) mice. Knockdown (KD) activity is assessed at the mRNA level through RT-qPCR and in situhybridization, and at protein level through Western Blot.
Results: We developed siRNAs targeting both mouse and human mRNAs encoding AD risk factors. Optimized siRNAs synthesis resulted in purity grade that ranges between 80% and 90%. In vitro, siRNAs demonstrated KD efficiency with potent IC50 in both murine N2A and human HEK293 cells. We are currently corroborating these results at the protein level by western blot. Following in vivo validation by ICV administration in WT mice, nanobody-siRNA conjugates with optimal BBB-crossing potential will be evaluated by systemic administration.
Conclusions: We demonstrated that our chemically stabilized siRNAs induce KD of mRNAs encoding neurodegenerative disease risk factors and some of these factors can be down regulated in vitro and in vivo when shuttled into cells with nanobodies targeting an endocytic receptor. Therefore, our siRNA-nanobody technology holds high potential as novel treatment for AD and other neurodegenerative conditions.

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β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ASO AND RNAI
2-3 April 2025

ARTIFICIAL MIRNA MEDIATED REDUCTION OF SNCA FOR THE TREATMENT OF SYNUCLEINOPATHIES

Bradford Elmer, Johanna Flyer-Adams, Thanga Mahendran, Erik Wischhof, Jeffrey Ardinger, Christian Mueller, Shyam Ramachandran
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Aims: Multiple lines of evidence implicate α-synuclein (αSyn) as a causal factor in synucleinopathies like Parkinson's disease. Adeno-associated viruses (AAVs) are well-validated gene delivery vectors enabling durable expression in the brain. Here, we assessed the therapeutic potential for reduction of endogenous *SNCA* and screened optimized therapeutic RNAi constructs relevant for clinical translation to PD.
Methods: AAV-amiRNAs were administered to wild-type mice to reduce endogenous *Snca* mRNA in the PFF mouse model of synucleinopathy. Arificial miRNAs targeting *SNCA* were designed as single hairpin amiRNAs, or polycistronic variants to enhance potency in HeLa cells or in mice expressing the full human *SNCA* gene (BAChSyn mice, MJFF). Processsing and expression of the guide and passenger strands of candidates was evaluated using next-gen sequencing and RT-dPCR.
Results: A 50% decrease in endogenous *Snca* mRNA levels was sufficient to mitigate the spread of PFF-induced αSyn pathology and prevent the loss of dopaminergic neurons in the substantia nigra. To support clinical translation, human-specific amiRNA sequences were designed and screened in vitro and in vivo for guide strand expression, processing and *SNCA* reduction with four candidates selected for further optimization. Novel polycistronic amiRNA expression formats were evaluated in order to enhance the potency of our candidate guide sequences, resulting in up to 10-fold increases in amiRNA guide expression and significantly enhanced human *SNCA* reduction in vivo.
Conclusions: Partial reduction of Snca was able to completely prevent the spead of aSyn pathology in the PFF model of synucleinopathy. To support clinical translation we designed and optimized expression formats for human-specific amiRNAs, selecting several candidates with desirable in vitro and in vivo characterics, supporting the continued development of αSyn lowering therapeutics as a safe and efficacious approach for treating patients with synucleinopathies

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SHIFT 01-468

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
2-3 April 2025

PRE-CLINICAL AMYLOID PRECURSOR PROTEIN-TARGETED GENE EDITING FOR ALZHEIMER'S DISEASE

Linting Geng[1], Martin Chan[1], Zihua Jiang[2], Zhixiong Zhou[1], Hua Lu[1], Jinlan Yang[1], Chao Zhang[1], Qian Zhang[1], Zongli Zheng[2]
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Aims: Alzheimer's disease (AD)—one of the most prevalent neurodegenerative disorders—is characterized by the deposition of amyloid-beta (Aβ). Gene editing by the CRISPR/Cas9 system has been evaluated as a therapeutic strategy in neurodegeneration diseases. We developed engineered protein delivery vehicles (ePDVs) for the delivery of gene-editing Cas9 and single-guide RNA (sgRNA) ribonucleoprotein (RNP) complexes that are highly effective, transient and safe. We assessed the performance of the ePDVs delivered CRISPR-cas9 to knockdown the amyloid precursor protein (APP) gene both *in vitro* and *in vivo* as a potential therapy for AD.
Methods: We packaged sgRNA and Cas9 protein into ePDVs and evaluated them *in vitro* in human neuroblast and astrocytoma cell lines, as well as *in vivo* by stereotactic intracerebroventricular (ICV) and intracisternal magna (ICM) injection into transgenic mice and non-human primates (NHPs). Genomic DNA was isolated from cell line lysates and various brain regions and analyzed by high-throughput sequencing. The APP in cerebrospinal fluid (CSF) was measured using ELISA kits.
Results: Through engineering, we developed an optimal ePDV design offering an 80% editing efficiency and over 70% decline in supernatant APP level in vitro. ePDV administered via ICV and ICM could reach multiple brain regions of both mice and NHP, including cortex, thalamus, hippocampus, hypothalamus and spinal cord. Additionally, ePDVs demonstrated robust editing in vivo, achieving bulk tissue editing efficiency up to 4% in postnatal day 0 (P0) mice following ICV injection and 20% in NHP following ICM injection. Preliminary toxicology studies suggested that ePDV was well tolerated following direct injection into the brain.
Conclusions: Our ePDVs can deliver gene-editing cargo to nervous system of mice and NHP, demonstrating their therapeutic potential in gene-editing for AD.

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SHIFT 01-469

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
2-3 April 2025

MIR-132 GENE THERAPY IN ALZHEIMER'S DISEASE

Boutheyna Khelaifia[1], Claudia Goupil[1], Dana Mika[2], Brittney Armitage-Brown[2], Nadia Fortin[1], Steve Lacroix[1], Douglas Munoz[2], Sébastien Hébert[1]
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Aims: Accumulating evidence suggests that multi-target drugs will be required to completely restore neuronal dysfunction and cognitive loss in AD. This could be feasible using microRNAs (miRNAs) by simultaneously targeting key disease genes and phenotypes. Neuronal microRNA-132 (miR-132) is the most strongly downregulated during AD progression and has been shown to rescue disease phenotypes (Amyloid, Tau, cognition) in mice and cells. The study aims to advance the preclinical development of a miR-132 mimic (miR-132m, a double-stranded RNA oligonucleotide) for AD gene replacement therapy. Specifically, we performed pharmacokinetics (PK) and biosafety studies following miR-132m delivered to the central nervous system (CNS) of mice and non-human primates (NHPs).
Methods: C57Bl6 mice and naïve cynomolgus monkeys were injected with fluorescent miR-132m into the cisterna magna. Samples of CSF and blood were collected, and animals were euthanized at various time points post-injection for CNS tissue dissection. miR-132m and other microRNAs associated with neuroinflammation, and degeneration were quantified by qRT-PCR, while miR-132m distribution was observed using confocal microscopy. Additionally, a biosafety study was conducted in monkeys treated with unmodified miR-132m via continuous intrathecal infusion over 30 days, with blood tests performed throughout.
Results: We observed a significant increase in miR-132m levels in the CSF and CNS tissues, while other microRNAs remained stable, and no toxicity was detected, indicating its safety and efficacy.
Conclusions: These results suggest that the direct injection of miR-132m into the CSF is effective and well-tolerated by the organism. Further studies are underway to assess the cellular distribution and genes targeted by miR-132m in the CNS. These findings will be used in developing Phase I clinical trials in humans.

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SHIFT 01-471

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

ENRUPATINIB, A BRAIN-PENETRANT CSF-1R INHIBITOR, REDUCES NEUROINFLAMMATION AND ENHANCES COGNITIVE FUNCTION IN ANIMAL MODELS OF ALZHEIMER'S DISEASE

Hung-Kai Chen[1], Wahyu Tamayanti[2], Agnes Ariyanti[2], Jun-Ru Lin[2], Uni Lin[2], Tsung Han Hsieh[2], Cheng-Ru Wu[2], Yenni Chang[2], Chuan-Yao Wang[2], Chia-Wei Huang[2], Hao-Yuan Cheng[2], Hui-Chin Huang[2], Jin-Wu Tsai[2]
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Aims: Microglial activation is a hallmark of Alzheimer's disease (AD). Chronic activation of microglia causes neuroinflammation, leading to neuronal injuries and cognitive impairment. Therefore, targeting activated microglia via modulating CSF-1R signaling represents an attractive therapeutic strategy. Enrupatinib (a.k.a. EI-1071) is a highly selective CSF-1R inhibitor with BBB-permeability, currently in a phase II trial for AD. The goal of this study is to assess the pharmacological effects of enrupatinib in AD mouse models.
Methods: Wildtype or 5xFAD mice were dosed with enrupatinib (0, 150, or 300 mg/kg/day) for 28 days. Brain slices were analyzed to reveal the numbers and distribution of microglia in the context of amyloid plaques. Brain tissues were collected for analyzing the expression profiles. Iba1+ microglial cells were analyzed in single-cell RNA sequencing (scRNA-seq).
Results: Enrupatinib decreased the plaque-associated microglia and reduced the number of fragmented neurons in brains of 5XFAD mice, suggesting that enrupatinib effectively slowed down AD-associated pathological progression. Furthermore, treatments of enrupatinib attenuated memory impairment in AD mice as revealed by the novel object recognition (NOR) and Y-maze tests.
The expression of genes associated with M1-type and disease-associated microglia was reduced in brain tissues of enrupatinib-treated mice, suggesting a trend toward reduced amyloid plaque burden. Overall expression of Csf1r, Trem2 and Tyrobp reduced, but not that of Iba1, indicating differences in sensitivity to enrupatinib exist among microglial sub-populations.
RNA sequencing of brain tissues revealed downregulation of inflammation-related pathways in both 5xFAD and J20 models after enrupatinib intervention. This is further supported by the results from scRNA-seq of sorted microglia, which showed a reduction in pro-inflammatory microglia in enrupatinib treated 5xFAD mice was evident.
Conclusions: Enrupatinib is effective in reducing neuroinflammation and attenuating memory impairment, which holds therapeutic potential for AD.

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SHIFT 01-472

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

ELIGIBILITY FOR LECANEMAB TREATMENT IN KOREA: BASED ON REAL WORLD DATA FROM MEMORY CLINICS OF MULTI-CENTERS

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Aims: We investigated how many patients could be administered Lecanemab based on the United States Appropriate Use Recommendations to Korean patients with early Alzheimer's disease (AD).
Methods: We retrospectively enrolled 6,132 patients with amnestic mild cognitive impairment (MCI) or mild stage of probable AD dementia (ADD) in 13 hospitals from June 2023 to May 2024. Among 6,132 candidates, 2,058 patients underwent amyloid PET. One thousand one hundred and ninety-nine (58.3%) were amyloid-positive on PET. We exclude 732 patients who did not underwent brain MRI within 1 year of baseline. Finally, 467 patients were included in the present study.
Results: Two hundreds and twenty-nine (49.0%) met the inclusion and exclusion criteria. Regarding the inclusion criteria, 460 (98.5%) patients were diagnosed with MCI and mild ADD, 295 (63.2%) had MMSE 22-30, and 454 (97.2%) were between 50 and 90 years. In the exclusion criteria, 16 (3.4%) patients had any condition of non-AD MCI or dementia. In brain MRI, 36 (7.7%), 10 (2.1%), 17 (3.6%), 36 (7.7%), 3 (0.6%), 37 (7.9%), 0 (0%), or 5 (1.1%) patients had 4 microhemorrhages, macrohemorrhage, superficial siderosis, >2 lacunes or a major vascular territory stroke, vasogenic edema, severe white matter hyperintensities, amyloid beta-related angiitis, or cerebral amyloid angiopathy-related inflammation, respectively. Seven (1.5%) patients had recent history of stroke or seizures, 36 (7.7%) had MRI evidence of a non-AD dementia, 5 (1.1%) had immunologic disease or systemic immunologic treatments, 2 (0.4%) had a bleeding disorder, 6 (1.3%) took anticoagulants, and 7 (1.5%) had unstable medical conditions.
Conclusions: Strict inclusion and exclusion criteria are likely to limit the population for which lecanemab can be used. In older adults with lower educational attainment, the MMSE criteria should be reconsidered, especially for MCI.

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SHIFT 01-473

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

TARGETED PROTEIN DEGRADATION OF AMYLOID AGGREGATES RESULTS IN ENHANCED CLEARANCE AND LIMITED INFLAMMATION

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Aims: Objectives: Alzheimer's disease (AD) is the most common dementia, characterized by pathological accumulation of aggregated β-amyloid (Aβ), accompanied by damaging chronic inflammation. Reducing amyloid burden on disease pathogenesis has met with limited clinical success, possibly due to insufficient clearance, as well as dose limiting toxicity driven by Fc mediated inflammatory responses. Active immunization with anti-Aβ monoclonal antibodies mediates reduction in Aβ aggregates via Fc Receptor (FcR) internalization by CNS resident immune cells including macrophages, microglia and astrocytes. However, Fc mediated uptake of Aβ results in neuroinflammation, as well as activation of the classical complement system, which may lead to dose limiting ARIA. Novel methods by which Aβ aggregates can be cleared through non-Fc mediated uptake would enable similar Aβ clearance, without detrimental downstream effects by FcR internalization.
Methods: Methods: We generated engineered bispecific antibody-based PROTACs (EpiTACs) with reduced Fc-effector function. The EpiTACs were designed with one arm targeting aggregated Aβ, and another arm binding to an internalizing receptor on the surface of phagocytic cells. These EpiTACs were used to treat primary human macrophages and microglia in the presence of various forms of aggregated Aβ to measure phagocytosis and subsequent downstream cellular activation.
Results: Results: Our data indicates that the EpiTACs are capable of binding to both Aβ and phagocytic cells. Compared to traditional Aβ/Fc binding constructs, EpiTACs resulted in enhanced internalization and degradation of Aβ in vitro via the targeted degrading receptor, resulting in diminished unwanted inflammation, while increasing Aβ internalization and degradation.
Conclusions: Conclusion: EpiTAC mediated clearance of Aβ represents a potential novel mechanism to enhance clearance of Aβ while minimizing dose limiting toxicity, allowing for increased dosing concentration and frequency and a superior efficacy profile.

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SHIFT 01-474

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

COMPARISON OF BINDING SPECIFICITY OF ANTI-AMYLOID-BETA ANTIBODIES IN SERIAL SECTIONS OF APPNL-F/NL-F;APOE4 MOUSE BRAINS

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Aims: Immunotherapy is the leading treatment strategy for Alzheimer's disease (AD), with the FDA approving anti-amyloid-beta (Aβ) monoclonal antibodies (mAbs), lecanemab and donanemab, for early-stage AD. In clinical studies, 12-35% of AD patients develop Amyloid Related Imaging Abnormalities (ARIA). The ARIA-H subtype, characterized by microbleeds and hemosiderin deposition, is hypothesized to be caused by direct binding of anti-Aβ antibodies to cerebral amyloid angiopathy (CAA) deposits. Since CAA deposits are heterogeneous and composed of various forms of Aβ (fibrils, protofibrils, oligomers), differences in mAbs' affinities for these species may underlie ARIA prevalence variability. Antibodies that target CAA more aggressively may lead to higher ARIA incidences. Here, we examined the binding profile of three anti-Aβ mAbs for vascular and parenchymal amyloid.
Methods: Immunoreactivity of recombinant lecanemab (r-lecanemab), recombinant murine lecanemab precursor (r-mAb158), and sabirnetug (ACU193) mAbs was quantitatively characterized in serial sections from briefly fixed 20-month-old APPNL-F/NL-F;ApoE4fl/fl mice. Sections were double-labeled with fluorescent amyloid-specific dye, Amylo-Glo. A dilution series ranging from 0.2 to 2.0 µg/ml was used to evaluate changes in binding preference based on concentration. Brain regions with varying profiles of vascular and parenchymal amyloid were examined.
Results: At the highest concentration, all three mAbs consistently labeled parenchymal plaques in the cerebral cortex. Variations in plaque morphology selectivity were observed, with some antibodies preferentially staining diffuse over core plaques. A broad range of vascular amyloid staining was also noted, including colocalized with Amylo-Glo, adjacent regions, and Amylo-Glo-negative leptomeninges.
Conclusions: The observed differences in binding affinities suggest that antibody selectivity may play a role in ARIA prevalence. High-magnification analyses will further clarify these differences, potentially revealing whether antibodies linked to higher ARIA show increased binding to vascular amyloid and how binding profiles vary with concentration. Funding_1R01NS136122-01_CAL.

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Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

3D WHOLE-BRAIN IMAGING OF PARENCHYMAL/VASCULAR AMYLOID PLAQUE ARCHITECTURE DURING DISEASE PROGRESSION IN A TRANSGENIC MOUSE MODEL OF ALZHEIMER'S DISEASE

Henrik Hansen[1], Lea Larsen[1], Frederikke Sørensen[1], Laura Griffin[2], Marta Vega[1], Ditte Thorbek[1], Yasir Gallero-Salas[1], Jacob Hecksher-Sørensen[1]
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Aims: Alzheimer's disease (AD) is histologically defined by accumulation of beta-amyloid (Aβ) plaques in the brain. Age and gender are important factors in AD pathology. Also, cerebral amyloid angiopathy (CAA) is recognized as contributing to AD progression. To develop more effective interventions, preclinical studies should therefore consider these factors in the evaluation of drug candidates. Using light sheet fluorescence microscopy (LSFM) coupled with AI-image analysis, we compared age-dependent changes in parenchymal and vascular plaque architecture in female and male transgenic AD mice.
Methods: Intact brains from 15, 30 and 42-week-old female and male APP/PS1 transgenic (ARTE10, n=5-6 per group) and 30-week-old male wild-type (C57BL/6, n=6) mice were co-stained for amyloid plaques (anti-human Aβ) and vasculature (anti-mouse CD31+podocalyxin), cleared and scanned on a LSFM. Deep-learning image analysis enabled whole-brain segmentation, mapping and counting of parenchymal and vasculature-associated plaques using a custom mouse brain atlas comprising more than 400 regions.
Results: ARTE10 mice showed age- and sex-dependent differences in whole-brain amyloid plaque architecture. Whereas both female and male ARTE10 mice demonstrated age-dependent increases in plaque load within the cortex, hippocampus and neighbouring areas, amyloidosis progressed at a faster rate in female ARTE10 mice. In both sexes, parenchymal plaques were detected at 15-weeks of age while vascular plaque deposition was most consistently observed at 30- and 42-weeks of age, suggesting delayed manifestation of CAA in the model.
Conclusions: We set a framework for using high-throughput, quantitative 3D whole-brain imaging of plaque load in an industry-standard transgenic APP/PS1 mouse model of AD. Our study emphasizes the importance of considering sex and age as critical factors when designing intervention studies for profiling drug candidates with potential plaque-clearing efficacy in mouse models of AD and CAA.

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SHIFT 01-476

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

INHIBITION OF TREM1 ATTENUATES MAJOR PATHOLOGICAL FEATURES IN ALZHEIMER'S DISEASE MOUSE MODEL.

June-Hyun Jeong, Yoonhee Kim, Kyusik Ahn, Jaehoon Song, Inhee Mook-Jung
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Aims: TREM1 amplifies pro-inflammatory innate immune responses. In our AD mouse model ($ADLP^{APT}$), we observed elevated TREM1 levels in the brain, blood, and gut. Although the TREM1 inhibitor cannot cross the blood-brain barrier, we investigated whether its systemic administration, targeting TREM1 in the peripheral, such as in the blood and gut, can reduce brain pathology.
Methods: $ADLP^{APT}$ mice received daily intraperitoneal TREM1 inhibitor injections for six weeks. Behavioral assessments (open field test, Y-maze, novel object recognition, and contextual fear conditioning) were performed post-treatment. Brain, gut, and blood samples were analyzed via FACS, ELISA, IHC, and/or western blotting to assess Alzheimer's markers, including amyloid-beta, tau, gliosis, and neuronal cell death.
Results: The $ADLP^{APT}$ mice treated with the TREM1 inhibitor exhibited improvements in cognitive function and locomotion in behavioral tests. We confirmed that TREM1 levels in the brain, gut, and blood of the mice were reduced by the drug, as determined by ELISA and FACS. Furthermore, we observed the treated mice showed alleviation of AD pathological markers such as amyloid-beta, tau, gliosis, and neuronal cell death by ELISA, immunofluorescence, or western blotting.
Conclusions: While TREM2, which plays a protective role in microglia, has been primarily studied in AD, our findings underscore its functional counterpart, TREM1. We discovered that inhibiting TREM1 attenuates important clinical features in our mouse model. We previously found that the $ADLP^{APT}$ mice experience gut leakage and microbiota dysbiosis, potentially influenced by brain protein aggregates. Our results suggest that reducing systemic inflammation with a TREM1 inhibitor can not only alleviate peripheral organ damage but also improve brain pathology, highlighting a potential therapeutic approach for AD.

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SHIFT 01-477

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

IMMUNOTHERAPY TARGETING PLASMA ASM IS PROTECTIVE IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Acid sphingomyelinase (ASM) has been implicated in neurodegenerative disease pathology, including Alzheimer's disease (AD). However, the specific role of plasma ASM in promoting these pathologies is poorly understood.
Methods: We explore plasma ASM as a circulating factor that accelerates neuropathological features in AD by exposing young APP/PS1 mice to the blood of mice overexpressing ASM, through parabiotic surgery.
Results: Elevated plasma ASM was found to enhance several neuropathological features in the young APP/PS1 mice by mediating the differentiation of blood-derived, pathogenic Th17 cells. Antibody-based immunotherapy targeting plasma ASM showed efficient inhibition of ASM activity in the blood of APP/PS1 mice and, interestingly, led to prophylactic effects on neuropathological features by suppressing pathogenic Th17 cells.
Conclusions: Our data reveals new insights into the potential pathogenic mechanisms underlying AD and highlights ASM-targeting immunotherapy as a potential strategy for further investigation.

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SHIFT 01-478

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

SELECTIVE TARGETING OF UNCOMPLEXED, FREE BETA-2 MICROGLOBULIN VIA ANTIBODY

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Aims: Beta-2 microglobulin (β2m) is a 12-kDa protein found as light chain of the major histocompatibility complex class I (MHC-I). Dissociated from the heavy chain, it exists as free-β2m serving as a potential marker of renal function, inflammation, amyloidosis, and malignancy. Recent studies have identified β2m as a pro-aging factor, associated with impaired cognitive function, and increased in the blood and cerebrospinal fluid of patients with Alzheimer's disease. As β2m in MHC-I is found in almost all nucleated cells, targeting via antibodies poses potential risk in targeting functional MHC-I affecting the immune system. ADEL-Y03 specifically targets free-β2m and this study aimed to investigate the effects of targeting free-β2m in the context of neurodegeneration.
Methods: Monoclonal antibody against free-β2m was developed by obtaining hybridoma clones from mice injected with β2m fragments of the interacting region between MHC-I heavy chain and β2m. One of the clones, ADEL-Y03, was selected for subsequent studies. In vivo effects of ADEL-Y03 was studied in β2m-induced cognitive deficit model and 5xFAD amyloid model mice.
Results: ADEL-Y03 exhibits high affinity and specificity to free-β2m, but not to β2m in the MHC-I. Stereotaxically injected ADEL-Y03 rescued β2m-induced cognitive deficit in wild-type mice. In addition, intraperitoneal injection of ADEL-Y03 reduced free-β2m levels in the brain and plasma of 5xFAD mice, which showed decreased beta-amyloid and inflammation. In vitro studies revealed role of free-β2m on AD pathology which effects were ameliorated by ADEL-Y03.
Conclusions: Our results contribute to the evidence that β2m is involved in neurodegeneration and that targeting β2m may be a potential therapeutic option. Selective targeting of free-β2m using ADEL-Y03 may be a promising approach without unwanted downregulation of immune functions of MHC-I. Currently humanization of ADEL-Y03 is complete for further IND-enabling studies.

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SHIFT 01-479

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

USING HUMAN IPSC-DERIVED MICROGLIA WITH TREM2 OR APOE MUTATIONS TO IDENTIFY ALZHEIMER'S DISEASE PHENOTYPES

Coby Carlson, Michelle Curtis, Sarah Burton, Christie Savic, Madelyn Donegan, Rebecca Fiene, Simon Hilcove, Scott Schachtele
FUJIFILM Cellular Dynamics, Madison, United States of America

Aims: Microglia dysfunction has been implicated as a key player in Alzheimer's Disease (AD) neurodegeneration. Genome-wide association studies have implicated mutations in the triggering receptor expressed on myeloid cells 2 (TREM2) gene as well as allelic variants of Apolipoprotein E (APOE) as contributing to AD progression or protection. TREM2 is a receptor involved in phagocytosis and reactive oxygen species release. TREM2 mutations (i.e., R47H) and functional TREM2 knockouts, can help elucidate the role of TREM2 signaling microglia. The APOE gene is involved in cholesterol transport and composition of the three main alleles (e.g., epsilon(E)2, E3, E4) is related to AD risk. For example, inheriting 2x APOE E4 alleles means increased risk and earlier onset of AD, while 2x APOE E2 alleles has been associated with reduced risk. In this study, we investigated the functional role of TREM2 and APOE in human induced pluripotent stem cells (iPSC)-derived microglia.
Methods: Patient-derived (TREM2 R47H or ApoE E4/E4) and engineered (TREM2 heterozygous and homozygous knockouts) iPSC donors were differentiated into microglia. This disease panel of cells was utilized in phenotypic screening assays, including cytokine release, phagocytosis, and mitochondrial bioenergetics.
Results: All cells showed characteristic marker expression (Iba1, Pu.1) and expected microglia morphology. Functional assays revealed differing rates of phagocytosis and substrate preferences, altered amounts of cytokine secretion (i.e., IL-6 and IL-1beta), and separate oxygen consumption rates in metabolic assays compared to apparently healthy normal (AHN) controls.
Conclusions: These data demonstrate that human iPSC-derived microglia are useful cell models for evaluating mechanisms of AD pathology. The impact of TREM2 and APOE variants can be demonstrated across multiple phenotypic assays. This study highlights the importance of implementing human cells with AD-relevant mutations into drug discovery workflows.

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SHIFT 01-480

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

TARGETING MICROGLIAL ADP RECEPTORS TO MODULATE ALZHEIMER'S DISEASE PROGRESSION: INSIGHTS FROM A NOVEL APP/TAU MOUSE MODEL

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Aims: Microglial cells are essential for maintaining brain homeostasis, contributing to synaptic plasticity and modulating neuronal activity through their interaction with neurons. Disruptions in microglia-neuron communication have been linked to neurodegenerative diseases, such as Alzheimer's disease (AD). This research aimed to investigate the role of microglial ADP receptors - activated by ATP released from distressed neurons - in AD pathogenesis, examining their potential effects on neuronal activity and disease progression.
Methods: To determine the role of microglial ADP receptor activity on AD progression, we used a novel APP/Tau transgenic mouse model that recapitulates key features of AD pathology. Mice at early and advanced disease stages were chronically treated with an ADP receptor antagonist, and the effects on cognitive and motor functions were assessed. Biochemical and histological analyses were conducted to examine changes in protein markers related to neurodegeneration and neuroinflammation following treatment.
Results: Chronic ADP receptor blockade led to moderate spatial memory and motor coordination improvements in APP/Tau mice. Biochemical and histological analyses revealed significant alterations in the expression of microglial, neuronal, astrocytic, synaptic and inflammatory markers associated with AD pathology, with some changes mitigated by the antagonist.
Conclusions: These findings suggest that ADP receptor signalling in microglia contributes to AD pathogenesis and that inhibiting this pathway can partially restore both functional and molecular deficits in APP/Tau mice. Thus, targeting microglial ADP receptors could represent a potential therapeutic strategy for AD, though further research is needed to clarify the therapeutic efficacy and underlying mechanisms of ADP receptor modulation in AD.

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SHIFT 01-481

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

EFFECTS OF CD22 LOSS IN AN ALZHEIMER'S DISEASE MOUSE MODEL

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Aims: CD22 is a canonical B-cell receptor that negatively regulates B-cell receptor signaling. In the murine CNS, CD22 is mainly expressed in microglia and found to be upregulated in aged mice and in neurodegeneration. Functionally, it was shown that microglial CD22 negatively regulates phagocytosis of myelin, oligomeric Aβ and α-synuclein fibrils. Based on these data, we hypothesized that levels of CD22 may influence AD pathology.
Methods: First, we quantified *Cd22* expression in microglia of APPPS1 mice, an AD-like mouse model with Aβ deposition and progressive neuroinflammation. To determine the effect of CD22 on AD pathology, we employed mice with a constitutive Cd22 knockout, which were crossed to APPPS1 mice. At the beginning of amyloid beta pathology and at a later stage, when Aβ plaque pathology has reached a plateau, APPPS1.CD22$^{-/-}$ mice were compared to APPPS1 mice.
Results: We could confirm the microglia-specific localization of *Cd22* and found a specific upregulation in microglia surrounding Aβ plaques. Aβ40 and Aβ42 as well as neuroinflammation in the brains of APPPS1.CD22$^{-/-}$ and APPPS1 mice were measured by electrochemiluminescence and immunohistochemistry. Next, the proteomic signature of microglia isolated from APPPS1.CD22$^{-/-}$ and APPPS1 mice was investigated by high-throughput mass spectrometry. 6038 proteins as well as differently regulated signaling pathways could be detected and the impact of CD22 on these pathways was confirmed using primary wild type and CD22$^{-/-}$ microglia.
Conclusions: Our data reveal the molecular mechanism of CD22 signaling in murine microglia in response to AD pathology.

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SHIFT 01-482

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / NEUROTRANSMITTERS & RECEPTOR-BASED, GLP-1 RECEPTOR-BASED
2-3 April 2025

MECHANISM OF SEMAGLUTIDE (OZEMPIC) IN ALZHEIMER'S DISEASE AS ASSESSED BY SHOTGUN PROTEOMICS

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Aims: Semaglutide is a glucagon like peptide 1 agonist which is effective in obesitas and diabetes type 2. Recently, Semaglutide has also been studied for its efficacy in Alzheimer's Disease. Although preclinical and clinical data seem positive, little is known about its central mechanism of action in AD. Shotgun proteomics uses a high-resolution mass-spectrometer in combination with liquid chromatography to measure thousands of proteins within a single sample. This method allows unbiased study of biomarkers and sheds light on mechanistic cascades, induced by drug administration or during development of certain pathology. In the current study we evaluated the effects of semaglutide administration on protein expression in mouse brain with the aim to shed additional light on the mechanism of action in the treatment of Alzheimer's disease.
Methods: In this study we administered Semaglutide or vehicle to mice. Three hours after administration, brains were harvested and dissected into different brain regions. Tissue was processed and proteins were extracted and digested prior to analysis. The samples were analysed using a nanoLC and Exploris Orbitrap 480 HRAM mass-spectrometer and proteins were quantified using specialized software.
Results: Semaglutide induced differentially expressed proteins in plasma and brain compared to vehicle treated mice. The differentially expressed proteins are correlated to concurrent genes and to different underlying mechanistic pathways, like pathways involved in Alzheimer's disease, mTor signalling and other neurodegenerative pathways next to the expected energy and metabolism related pathways. The mechanistic indications are further explored for their contribution in the treatment of AD and other neurodegenerative disorders.
Conclusions: Using stringent criteria for rating biomarkers in mechanistic research, multiple mechanistic events can be identified that might be relevant to the therapeutic effects of Semaglutide in AD.

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SHIFT 01-483

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / NEUROTRANSMITTERS & RECEPTOR-BASED, GLP-1 RECEPTOR-BASED
2-3 April 2025

INVESTIGATING THE FUNCTIONAL INTERACTION BETWEEN CELLULAR PRION PROTEIN AND AMYLOID-BETA

Md Abdullah Kafi[1], Mario Passalacqua[1], Viviana Villa[1], Stefano Thellung[2], Raffaella Grimaldi[1], Pietro Baldelli[1], Tullio Florio[2], Roberta Ricciarelli[1]
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Aims: Accumulation of amyloid-beta (Aβ) and the misfolded counterpart of cellular prion protein (PrP^C) is a hallmark of Alzheimer's disease (AD) and prion diseases, respectively. Recent findings have revealed that PrP^C acts as a receptor for Aβ peptides on the neuronal surface, though the functional significance of this interaction remains unclear. Given the critical roles of Aβ and PrP^C in neurodegenerative processes, our objective was to investigate the relationship between these proteins and the pathophysiological implications of their interaction.
Methods: Using the N2a cell line as a model system, we employed siRNA to knock down PrP^C expression and performed stable transfection and pharmacological treatments to increase Aβ production. The expression levels and subcellular localization of both proteins were assessed with ELISA, Western blotting, and confocal microscopy techniques. Additionally, excitatory glutamatergic synapses were analyzed in primary hippocampal neurons from mice.
Results: Our data demonstrate that PrP^C is responsible for the uptake of Aβ into neuronal cells. Furthermore, we provide evidence that pharmacologically induced Aβ production significantly increases the density of excitatory glutamatergic synapses, a response that depends on the interaction between Aβ and PrP^C.
Conclusions: These findings suggest that the Aβ-PrP^C interaction plays a critical role in modulating synaptic function and potentially contributes to the pathophysiology of neurodegenerative diseases. Further investigation in this direction could reveal new therapeutic targets for AD, including the potential to modulate this pathway pharmacologically to mitigate disease progression and improve synaptic function.

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SHIFT 01-484

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE
2-3 April 2025

PSYCHEDELIC-INDUCED NEUROPLASTICITY: DOI AND PSILOCYBIN SHOW PROMISE IN ALLEVIATING COGNITIVE DEFICITS AND STEREOTYPIC BEHAVIORS

Emile Andriambeloson, Cindy Duchemin-Neveu, Louise Peter, Etienne Poiraud, Bertrand Huyard, Stéphanie Wagner
Neurofit SAS, ILLKIRCH, France

Aims: Cognitive deficit and repetitive and stereotypic behaviors are hallmark symptoms of Alzheimer's disease (AD), stemming from disrupted synaptic connections and impaired neuronal plasticity. Psychedelics, as "psychoplastogens," have shown potential to promote neuronal plasticity and synaptic rewiring, offering a promising therapeutic approach to counter these behavioral dysfunctions in AD.
Methods: To explore the potential of psychedelics in promoting neuronal plasticity and addressing cognitive issues, we first investigated the ability of 2,5-Dimethoxy-4-iodoamphetamine (DOI) and Psilocin, the primary metabolite of Psilocybin (PSI), to induce neurite outgrowth in neuronal cultures. Then, we assessed their impact on behaviors of mice in the marble burying task, which measures repetitive and stereotypic burying behaviors, and the scopolamine-induced cognitive deficit, which involves working memory and attention.
Results: indicate that DOI enhanced primary neurite number, total neurite length, and branch points in a dose-dependent manner. In contrast, Psilocin increased only branch points and the neurite critical value (radius "r") at a particular dose, without affecting the neurite number and length parameters. This suggests that both compounds enhance neural plasticity through distinct morphological changes in the neurite profiles. Both DOI and PSI reduced in a dose-dependent manner the frenetic marble burying behavior of mice. In scopolamine-treated mice, the dramatic reduction of spontaneous alternation caused by perseverative focus on a single arm visit was attenuated by both DOI and PSI. This suggests that both compounds reduce repetitive and stereotypic behaviors and mitigate cognitive impairment in mice.
Conclusions: In conclusion, although DOI and PSI exhibit distinct morphological neuroplastic effects, they produce similar behavioral outcomes in mice. These findings suggest that the unique profiles of psychedelics may address Alzheimer's symptoms through enhanced synaptic plasticity, supporting their potential as therapeutic agents.

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SHIFT 01-486

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

DO ANTIDIABETIC AGENTS IMPROVE COGNITIVE FUNCTION IN ALZHEIMER'S DISEASE MODELS VIA INSULIN MODULATION OR NEUROINFLAMMATION REDUCTION?

Stéphanie Wagner, Bertrand Huyard, Etienne Poiraud, Fabien Lauga, Charley Pinault, Christelle Albac, Nassima Kadouci, Emile Andriambeloson
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Aims: Growing evidence suggests a pathophysiological link between type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD), with over 80% of AD patients also diagnosed with T2DM or abnormal glycemia. This overlap points to possible shared mechanisms, such as insulin resistance and neuroinflammation, that may be targeted by antidiabetic agents. In this study, we evaluate the cognitive effects of two antidiabetic drugs, semaglutide, a glucagon-like peptide-1 (GLP-1) receptor agonist that acts as an insulin secretagogue, and metformin, an insulin sensitizer, in models of AD.
Methods: Cognitive impairment was induced in rats via intracerebroventricular injections of fibrillated amyloid-beta (Aβ) peptide. Additionally, mice were treated with a non-septic dose of lipopolysaccharide (LPS) to induce brain-inflammation-related cognitive deficits. Following treatment with semaglutide or metformin, cognitive performance was assessed using the passive avoidance test in Aβ-treated rats and the T-maze spontaneous alternation task in LPS-treated mice, measuring memory retention and spatial working memory, respectively.
Results: showed that both semaglutide and metformin significantly alleviated the memory deficits induced by intracerebroventricular injection of amyloid-beta peptide in the passive avoidance test in rats. In mice displaying cognitive impairment in T-maze spontaneous alternation following a single administration of lipopolysaccharide (LPS), semaglutide and metformin markedly restored cognitive performance.
Conclusions: These findings suggest that both semaglutide and metformin, despite their distinct roles as an insulin secretagogue and an insulin sensitizer, exhibit cognitive benefits in models of Alzheimer's-related memory impairment. While it remains to be elucidated whether these benefits arise from modulation of insulin signaling pathways or a direct reduction in neuroinflammation, the observed improvements in memory performance provide compelling support for further exploration of these agents as adjunctive therapies in AD, particularly for patients with concurrent type 2 diabetes mellitus.

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SHIFT 01-487

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

REEVALUATION OF A PATIENT INITIALLY CONSIDERED INELIGIBLE FOR LECANEMAB INFUSIONS

Sandra Cobb, Andy Liu
Duke University, Neurology Memory Disorders Clinic, Durham, United States of America

Aims: Lecanemab, an anti-amyloid therapy, is a new monoclonal antibody drug available to patients with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD). Because of the risk profile of the drug, patients who may be eligible for lecanemab require an extensive workup to ensure they are good candidates for treatment. Some patients may initially be deemed ineligible for lecanemab but later become eligible. The purpose of this poster presentation is to convey the importance of periodic reevaluation of patients who are interested in lecanemab.
Methods: We examined a case of a 71-year old woman with MCI due to AD who was initially deemed ineligible for lecanemab. She was deemed ineligible due to multiple autoimmune conditions, uncontrolled pain from ankylosing spondylitis, and use of adalimumab and methotrexate.
Results: The patient returned to the memory clinic after she had surgery for lumbar spinal fusion and spinal hardware replacement for ankylosing spondylitis. During surgery, she was found to have a fungal infection on her original hardware and was placed on antifungal therapy. After the infection was treated, her back pain and cognitive functioning improved. She was no longer eligible to take immunosuppressant drugs. After reevaluation, she was deemed eligible to start lecanemab therapy if desired.
Conclusions: We initially thought this patient would never be eligible for lecanemab since she had chronic autoimmune conditions and used systemic immunosuppressant drugs. Chronic health conditions are dynamic and require periodic reevaluation. It is important that clinicians continue to monitor patients with AD and periodically reevaluate their candidacy for anti-amyloid therapies.

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SHIFT 01-488

Poster on Board - Shift 01
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2-3 April 2025

CASE REPORT OF DEATH DUE TO COMPLICATIONS OF ARIA IN A PATIENT RECEIVING LECANEMAB

Sandra Cobb, Andy Liu
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Aims: Amyloid-related imaging abnormalities (ARIA) are potential adverse effects of anti-amyloid therapies (ATT) used to slow progression of Alzheimer's disease (AD). Most patients who develop ARIA are asymptomatic and have no lingering effects. However, there is a small subset of patients who develop neurologic symptoms. In rare cases, death may occur. The purpose of this poster presentation is to review a case of patient who died due to complications of ARIA that occurred during treatment with lecanemab.
Methods: We reviewed the case of an 84-year old man with mild dementia APOE4 heterozygote who died after receiving three lecanemab infusions.
Results: The patient reported new onset disorientation, weakness, visual changes, and decreased ability to perform basic tasks 10 days after his third lecanemab infusion. He had mild right upper extremity weakness on exam, and his clock draw was abnormal. His symptoms were improving. The brain MRI showed severe ARIA-E (edema) and ARIA-H (hemorrhage) and moderate superficial siderosis. Lecanemab infusions were canceled. He was hospitalized twice over the next 6 weeks for seizures. He was in status epilepticus during his final hospitalization and seizures were not controlled despite multiple antiepileptic drugs. The patient's family transitioned him to hospice and he died 51 days after symptom onset.
Conclusions: Adverse events can occur when using ATTs. We presented a case of severe ARIA that resulted in death. Patients need to be monitored closely when receiving ATTs. Risks of adverse events, including death, should be communicated clearly with the patient when discussing ATTs.

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SHIFT 01-489

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

EPILEPTIC PRODROMAL ALZHEIMER'S DISEASE: LONG-TERM ANTISEIZURE TREATMENT REDUCES MMSE DECLINE, BUT NOT THE RATE OF CONVERSION TO DEMENTIA.

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Aims: There is growing evidence that antiseizure medications (ASMs) may have the potential to slow the progression of Alzheimer's disease (AD) and, if initiated early, to be disease-modifiers. We aimed to investigate such potential in epileptic AD patients who initiated ASMs at the prodromal stage.
Methods: 28 biomarker-defined epileptic prodromal sporadic AD patients (epADs, mean age = 73.5 [± 8.6]) were followed for a mean of 7 years and retrospectively compared with 43 matched non-epileptic prodromal AD patients (nepADs, mean age = 68.8 [± 8.3]). They were assessed annually for MMSE score, pharmacological burden and functional impairment.
Results: At the last follow-up, epADs had converted to dementia in a similar proportion to nepADs (85.7% vs. 79.1% respectively, p = 0.5), but with a significant delay (4.1 [± 2.7] years vs. 2.8 [± 2.2] years respectively, p = 0.03) and with higher MMSE scores (18.2 ± 7.9 vs. 13.6 ± 9.5 respectively, p = 0.04). The patients (n = 8) with the lowest annual rate of cognitive decline were those who started ASMs earlier, when seizures were treated before the diagnosis of prodromal AD (mean time = 5.5 ± 5 years before cognitive decline; p = 0.03).
Conclusions: This retrospective study confirms that ASMs have the potential to slow cognitive decline in AD if started early, with the optimal window of opportunity being initiation at the preclinical stage. However, such cognitive benefits are overcome during progression, as conversion to dementia at final follow-up was not significantly different between epADs and nepADs. Our results suggest that ASMs alone are not sufficient to achieve a long-term disease-modifying effect in AD, but potentially in combination with other interventions (e.g. neuropathology-targeting agents, management of cardiovascular risk factors).

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SHIFT 01-490

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

DESIGN OF THE COGNIKET-MCI TRIAL: COGNITIVE OUTCOMES OF KETOGENIC MEDIUM CHAIN TRIGLYCERIDES + B-VITAMINS VERSUS PLACEBO IN PATIENTS WITH MCI

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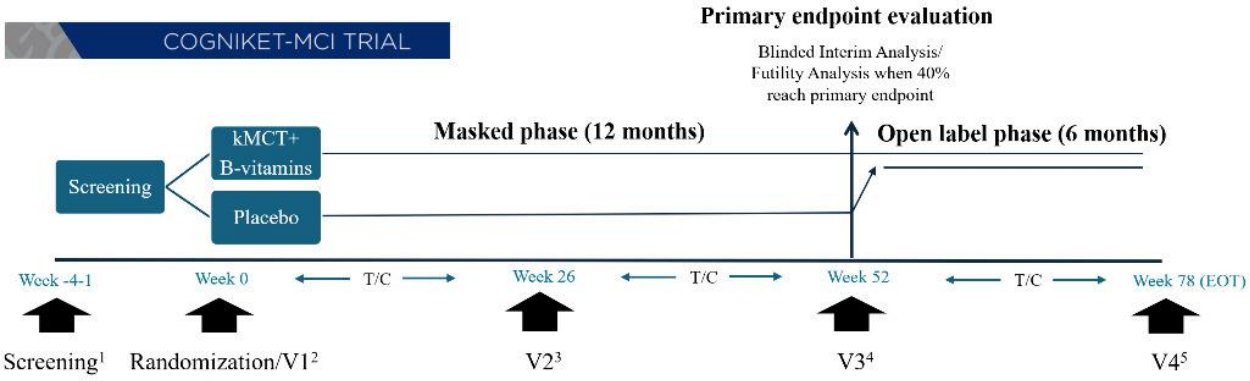
Aims: Impaired brain glucose utilization is an emerging neurometabolic hallmark in mild cognitive impairment (MCI), and consumption of an alternative brain-energy substrate, e.g., ketones derived from ketogenic medium chain triglycerides (kMCT), has been proposed to improve cognitive function. This multi-center, multi-country, randomized controlled trial (RCT) in people with MCI (NCT06347315), assess cognitive effects of consuming a 25 g ketogenic oral nutritional supplement of kMCT (15g) and specific B-vitamins (B3, B6, B9, B12) twice daily.
Methods: This double-blind, placebo-controlled RCT recruits people with MCI with a clinical phenotype compatible with underlying AD, insidious small vessel disease (SVD), or mixed AD/SVD pathologies. Further eligibility criteria are: age ≥ 60 years, independence in ADL, presence of acquired memory complaints >3 months, CDR global score ≤0.5, and absence of depressive/anxiety disorders. Participants are also required to have a trial informant. The first 12 months will be double-blinded, to be followed by a 6-month open-label period (Figure). The primary endpoint evaluate cognitive impact of the blend vs placebo on the Preclinical Alzheimer's Cognitive Composite (PACC) score (z-score). Several other cognitive- or related outcomes are also planned (Figure), including PACC components and CDR. We hypothesize a between-group difference in 0.25 SD units in the z-score at 12 months, which requires recruiting 380 participants for a power of 80% and a one-sided alpha of 0.05, accounting for a pre-planned blinded interim analysis for efficacy/futility, and lost-to-follow-up.



Visit	Rater assessments	Participant questionnaires	Trial informant questionnaires	Laboratory assessments
1: Screening	CERAD-NB, CDR	IADL-Lawton, HADS	N/A	Glucose, HbA1c, Triglycerides
2: V1	PACC, MoCA, CCI	CES-D, PSQI, CFI, EQ-5D	CFI, A-IADL-Q-SV	AD biomarkers, genetics (volountary), HbA1c, glucose, insulin, hematology, kidney, lipids
3: V2 (W26)	PACC, MoCA	CES-D, PSQI	N/A	N/A
4: V3 (W52)	PACC, MoCA, CCI, CDR	CES-D, PSQI, CFI, EQ-5D	CFI, A-IADL-Q-SV	HbA1c, glucose, insulin, hematology, kidney, lipids
5: V4 (W78)	PACC, MoCA, CCI, CDR	CES-D, PSQI, CFI, EQ-5D	CFI, A-IADL-Q-SV	HbA1c, glucose, insulin, hematology, kidney, lipids

Abbreviations: A-IADL-Q-SV, Amsterdam-Instrumental Activity of Daily Living-Questionnaire-Short Version; CCI, Cognitive Complaints Interview; CDR, Clinical Dementia Rating; CERAD-NB, Consortium to Establish a Registry for Alzheimer's Disease neuropsychological battery; CES-D, Center for Epidemiological Studies-Depression; CFI, Cognitive Function Index; EQ-5D, European Quality of Life-5 Dimensions; HADS, Hospital Anxiety and Depression Scale; HbA1c, hemoglobin A1c; IADL, Instrumental Activities of Daily Living; MoCA, Montreal Cognitive Assessment; N/A, not applicable; PACC, Preclinical Alzheimer's Cognitive Composite; PSQI, Pittsburgh Sleep Quality Index; TC, telephone contact; V, Visit; W, Week

Results: First randomization occurred June 7, 2024. The trial involves ~30 sites across Germany, France, Spain, Italy, Switzerland, UK, and USA.

Conclusions: This trial will inform whether a ketogenic oral nutritional supplement of kMCT and specific B-vitamins is superior to placebo in supporting cognitive function in people with MCI. Results are expected in 2027.

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SHIFT 01-491

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

INCREASED RELATIVE THALAMIC CEREBRAL BLOOD FLOW IS ASSOCIATED WITH IMPROVED COGNITION IN SOCIALLY ISOLATED OLDER ADULTS: I-CONECT STUDY

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Aims: A recently completed behavioral intervention study demonstrated efficacy in improving global cognitive function by providing frequent conversational interactions to socially isolated older adults (age 75+). We conducted an exploratory study to assess the impact of social interactions on relative cerebral blood flow (rCBF) measures.
Methods: The Internet-Based Conversational Engagement Clinical Trial (I-CONECT, NCT02871921) provided 30-minute conversational video sessions with trained interviewers four times per week for six months to socially isolated participants. Of 186 randomized participants, 43 underwent 3T MRI ASL at baseline, and 13 had a second MRI due to the COVID-19 pandemic. Multiple voxelwise linear regressions were performed within GM voxels with rCBF z-score as the dependent variable and age, sex and MOCA (global cognitive score) as regressors with cluster size thresholding for multiple comparison corrections. Baseline rCBF z-scores were subtracted from rCBF from the coregistered second visit scan and then coregistered to the MNI template. Multiple voxelwise linear regression was repeated in the same manner using age, sex and change in rCBF between the timepoints as predictors of change in MOCA.
Results: Higher MOCA score was associated with increased rCBF cluster in the left thalamus ($p<.01$). Greater MOCA score improvement over time was associated with increased rCBF cluster in the thalamus, bilaterally ($p<.05$). Participants who underwent social engagement intervention (n=6) showed improved MOCA scores ($p<.0024$) and improved rCBF in the bilateral thalamus ($p=.006$) compared to participants who did not receive the intervention (n=7).
Conclusions: Improved global cognition in socially isolated older adults following regular participation in video conversations may be related to enhanced cognitive reserve secondary to relative increases in blood flow in the thalamus, a structure known to be related to cognitive performance and loneliness in older individuals.

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2-3 April 2025

LANCL-TARGETING THERAPEUTICS DEMONSTRATE NEUROPROTECTIVE PROPERTIES IN STRESSED SH-SY5Y CELLS AND IN A 3D MINI-BRAIN MODEL OF ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) features an accumulation of toxic proteins (e.g. amyloid beta (Aß)), inflammation and loss of neurons in the brain. The LanCL family of proteins can protect tissues, including the brain, from pathological stress. Lateral has identified compounds that interact with LanCL proteins and are effective in animal models of neuropathy, with human proof-of-concept demonstrated in sciatica. We investigated the effects of Lateral's compounds on: (1) the proliferation rate of a human neuroblastoma cell line (SH-SY5Y) exposed to toxic stressors, and (2) a human cell-based 3D model of AD with fluorescently tagged Aß (FL-ADBrain micro-tissues).
Methods: The SH-SY5Y cells were stressed with doses of glutamate, paclitaxel, or hydrogen peroxide titrated to reduce the proliferation rate of the cells by approximately fifty percent. Following a 16 hour treatment with Lateral's test compounds, SH-SY5Y cell viability was measured using a CellTiter-Glo® assay. Transient siRNA knockdown was used to validate the involvement of LanCL1. The FL-ADBrain micro-tissues were treated with Lateral test compound, vehicle or control compound for seven-days. Cell viability was assessed using the Resazurin assay kit, and levels of Aß were quantified using relative total cell fluorescence, comparing pre- and post-treatment.
Results: A dose-dependent restoration of viability to all stressors was observed in the Lateral compound-treated SH-SY5Y cells, but not with control compounds or with vehicle control. siRNA to LanCL1 abrogated the test compound response. In the FL-ADBrain model, Lateral compounds improved cell viability and significantly reduced Aß deposition in a dose-dependent manner.
Conclusions: Lateral's LanCL-targeting compounds represent a promising novel therapeutic approach for promoting neural health in response to acute toxic insults as well as in treating chronic neurodegeneration. Additional studies are underway to further characterise the neuroprotective potential of Lateral's compounds.

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SHIFT 01-493

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

DISCOVERY OF A NOVEL DUAL-ACTION SMALL MOLECULE THAT IMPROVES MULTIPLE ALZHEIMER'S DISEASE PATHOLOGIES

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Aims: The importance of acid sphingomyelinase (ASM) activation has been recognized as a contributor to multiple Alzheimer's disease (AD) pathologies, leading to the concept of using ASM inhibitors for AD treatment.
Methods: Chemical compounds (1,273) were tested in AD fibroblasts with abundance ASM activity. The compounds backbone with 30% inhibition was identified and optimization was performed based on lipophilicity. Further qualification was performed through biochemical and cellular assays, drug ability, and in vivo efficacy.
Results: We found KARI 201 with selectivity ASM inhibition effects, excellent pharmacokinetic properties, and especially brain distribution. Unexpectedly, another role of KARI 201 was revealed as a ghrelin receptor agonist, which has novel therapeutic potential for AD. This dual role of KARI 201 in neurons efficiently rescued multiple pathologies in AD mice, leading to memory function improvement.
Conclusions: Our data highlights the potential clinical application of KARI 201 as innovative and multi-faceted drug for AD treatment.

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SHIFT 01-494

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

BALANCING OMEGA-3 AND OMEGA-6: UNLOCKING DIETARY KEYS TO BRAIN HEALTH IN AGING

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Aims: Dementia, including Alzheimer's disease (AD), poses a major global health challenge with severe socio-economic impacts and no effective treatments. Diet, particularly the balance of polyunsaturated fatty acids (PUFAs) like ω-3 and ω-6, is vital for brain health. While ω-3 PUFAs support cognitive function and reduce AD pathology, the ω-6-rich Western diet (WD) may promote neuroinflammation and impair synaptic function. This study hypothesizes that the high ω-6:ω-3 ratio in WD disrupts brain physiology by driving chronic inflammation and accelerating neurodegeneration.
Methods: In this study, 2-year-old female mice were fed a WD for 8 weeks, followed by 8 weeks on WDs mimicking either a harmful (23:1) or beneficial (1:7) ω-6:ω-3 ratio.
Results: Mice on the WD gained 10–14% more weight than age-matched controls on standard chow, but no behavioral changes were observed, consistent with unaltered brain gross morphology. PET imaging revealed distinct effects of dietary interventions on brain physiology. WD-ω6-fed mice showed increased [$_{18}$F]MNI-1126 uptake in the amygdala and hippocampus, suggesting synaptic alterations, while WD-ω3-fed mice exhibited reduced [^{18}F]DPA-714 signals in the hypothalamus and cortex, indicative of decreased inflammation. Additionally, WD-ω3-fed mice showed elevated [^{18}F]FDG uptake in the hippocampus, reflecting enhanced glucose metabolism. Lipidomic analysis supported these findings, revealing increased docosahexaenoic acid (C-22:6, ω3) in the cortex and hippocampus of WD-ω3-fed mice, demonstrating a positive shift in fatty acid composition. The WD-ω3 diet also upregulated cortical and hippocampal levels of phosphatidic acid and phosphatidylethanolamine, both critical components of synaptic and mitochondrial membranes.
Conclusions: These results demonstrate that variations in the ω-6:ω-3 ratio in WDs during aging significantly influence neuronal activity, fatty acid metabolism, and membrane composition in the brain, underscoring the importance of dietary PUFA balance for brain health and dementia prevention.

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SHIFT 01-495

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

CHOLINERGIC SIGNALLING IS NECESSARY FOR AMYLOID REDUCTION INDUCED BY GAMMA STIMULATION_

Nicolas Lavoie[1], Martin Kahn[1], Cristina Blanco-Duque[1], Hiba Nawaid[1], Ravikiran Raju[1], Alexis Davison[1], Anjanet Loon[1], Cheng-Yi Yang[1], Mitchell Murdock[1], Li-Huei Tsai[2]
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Aims: Multisensory stimulation at 40Hz is a promising non-invasive approach for treating Alzheimer's disease (AD). Research from our group and others has demonstrated that 40Hz audiovisual stimulation (GENUS) can reduce amyloid pathology in AD mouse models. Early trials in human AD patients have also shown encouraging results. Recent studies suggest that neural activity plays a critical role in GENUS-mediated amyloid clearance, but the specific neural circuits driving these effects remain unclear. We aimed to identify the circuits activated by GENUS and assess whether their involvement is necessary for GENUS-induced clearance.
Methods: We utilized 6-10 month 5xFAD mice and performed whole brain cFos imaging to map neural activity, and fiber photometry to measure acetylcholine release following GENUS. Next, we used cholinergic antagonists in combination with two-photon imaging to assess the cholinergic system's role in GENUS-mediated increases in vasodilation, vasomotion, and glymphatic influx. Finally, we measured amyloid levels following GENUS in combination with cholinergic antagonists using ELISA and immunohistochemistry.
Results: Whole-brain cFos imaging revealed the basal forebrain as a key region activated by GENUS, with the highest activation observed in its rostral portion, which projects to the prefrontal cortex (PFC). Fiber photometry confirmed that acetylcholine release increased in the PFC during GENUS. GENUS also increased arterial diameter and pulsatility in saline-treated mice, but these effects were attenuated when cholinergic activity was blocked with scopolamine and mecamylamine. Additionally, cholinergic antagonists inhibited GENUS-induced increases in CSF influx. Consistently, cholinergic antagonists inhibited the reduction in amyloid levels typically observed after GENUS, as measured by D54D2 immunohistochemical staining and Aβ1-40 and Aβ1-42 ELISA.
Conclusions: Our findings show that cholinergic signaling is essential for GENUS-induced increases in vasodilation, vasomotion, CSF influx, and amyloid clearance in a mouse model of amyloid pathology.

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SHIFT 01-496

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

ANKS1A REGULATES THE DIFFERENTIAL CLEARANCE OF B-AMYLOID IN THE BRAIN CIRCULATORY SYSTEM.

Jiyeon Lee, Soochul Park, Haeryung Lee
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Aims: The production of β-amyloid peptides in neurons and the formation of senile plaques are hallmarks of Alzheimer's disease (AD). Ineffective clearance of these toxic peptides significantly contributes to AD progression. The brain uses mechanisms like glymphatic drainage, which removes toxins through the lymphatic system, and transcytosis across the blood-brain barrier to clear β-amyloid. We hypothesize that lower molecular weight (LMW) β-amyloid peptides are primarily cleared by the glymphatic system, while higher molecular weight (HMW) peptides, often in multimeric forms, are cleared by vascular pathways. This study investigates the role of ANKS1A in regulating β-amyloid clearance through glymphatic and vascular systems and its implications for neurodegenerative diseases such as AD. Specifically, we aim to determine if the ANKS1A-LRP1 axis in cerebrovascular endothelial cells stabilizes vascular homeostasis and attenuates AD pathology, and if ANKS1A expression in lateral ventricles supports CSF flow and glymphatic clearance of β-amyloid.
Methods: Our research primarily involved in vivo experiments using ANKS1A knockout and 5XFAD Alzheimer's mouse models, where ANKS1A was specifically expressed in brain endothelial cells via an AAV vector system. We also performed glymphatic efflux assays to assess the effect of ANKS1A deletion on CSF-ISF convective flow.
Results: Our results showed a significant increase in the clearance of insoluble β-amyloid plaques in 5XFAD mice where ANKS1A was re-expressed. Additionally, we observed improvements in cerebrovascular stability. The glymphatic efflux ratio significantly decreased in ANKS1A knockout mice, indicating that the absence of ANKS1A disrupted the convective flow between CSF and ISF.
Conclusions: ANKS1A deletion disrupted normal brain clearance mechanisms, leading to toxic waste accumulation and increased risk of neurodegenerative diseases like AD. These findings highlight ANKS1A as a crucial regulator of β-amyloid peptides clearance and a potential therapeutic target for AD.

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SHIFT 01-497

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

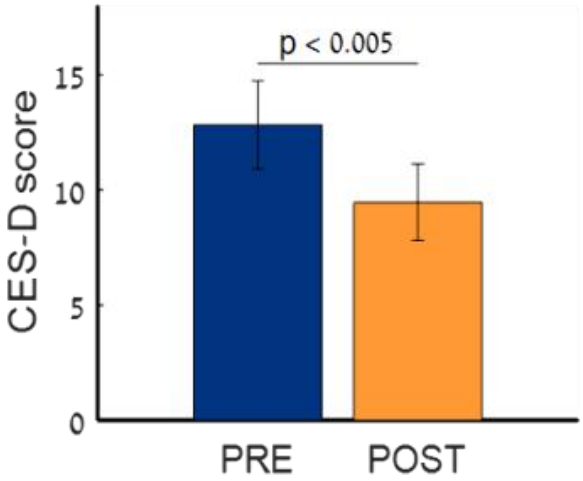
NEUROINFLAMMATION, DEPRESSION AND BRAIN CONNECTIVITY CORRELATES OF A MULTISENSORY DIGITAL INTERVENTION FOR SUBJECTIVE COGNITIVE DECLINE

Shahar Shelly[1], Amir Amedi[2], Merav Catalogna[2], Nira Saporta[3], Bar Nathansohn-Levi[3], Ya'Ira Somerville[2], Orna Zagoory-Sharon[4], Ruth Feldman[4], Liat Edry[2]
[1]Rambam Medical Center, Neurology, Haifa, Israel, [2]Reichman University, The Baruch Ivcher Institute For Brain, Cognition & Technology, Herzliya, Israel, [3]Remepy Health LTD, Ramat Gan, Israel, [4]Reichman University, Center For Developmental Social Neuroscience, Herzliya, Israel

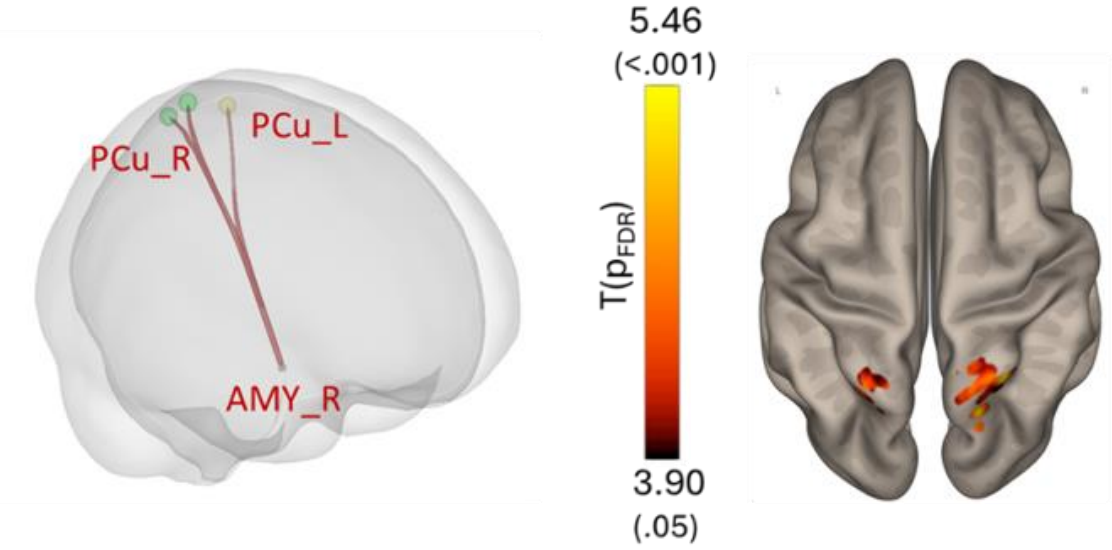
Aims: Depression and age-related neurodegenerative diseases are increasingly linked to neuroinflammation. This study aimed to investigate the impact of a novel, multisensory digital intervention on brain connectivity, psychological well-being, and immune markers in adults experiencing subjective cognitive decline (SCD) and elevated stress levels.
Methods: We conducted a prospective, open-label trial involving healthy adults aged 55-60 with SCD. Participants completed a two-week intervention using a mobile app designed to address stress regulation and multisensory navigation. The app offered (i) stress-regulation techniques grounded in mindfulness, attention-training, and cognitive behavioral therapy (CBT) principles, and (ii) multisensory navigation training, including Hebb-Williams (HW) mazes with a shift from visual to auditory cues and progressive visual masking. Pre- and post-intervention assessments evaluated resting-state functional connectivity (via MRI), inflammation (saliva samples), and psychological status (validated questionnaires).
Results: Seventeen participants, mean age 57.2 years (SD 1.5), completed the study. Key outcomes were as follows: Depressive symptoms, measured by the Center for Epidemiologic Studies Depression Scale (CES-D), decreased by 26.6%, reflecting a large effect size ($d = -0.829$, $p = 0.004$). Reduced connectivity within the default mode network (DMN) was observed. Increased anticorrelation between the DMN and Salience networks (SN) correlated with improved depression scores. A significant 25% reduction in post-intervention salivary IL-18 concentration, with a medium effect size ($p = 0.026$, $d = -0.641$), was documented. This reduction was associated with decreased DMN-amygdala connectivity.

Remepy training mobile application

Self-reported depression CES-D score changes



Regression analysis between post-intervention Amygdala-Precuneus connectivity change and reduction in IL-18 levels



Conclusions: A short-term, daily digital intervention shows promise in reducing depressive symptoms, potentially reducing inflammation, and promoting adaptive changes in brain connectivity within the DMN and SN. These regions are essential for mental well-being and cognitive functioning and are often impacted in the early stages of Alzheimer's disease.

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SHIFT 01-498

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
2-3 April 2025

ASSESSING THE SAFETY AND EFFICACY OF NUZ-001 IN REALBRAIN® 3D HUMAN MICRO-TISSUES

Mark Greenough[1], Krista Dent[1], Christos Papadimitriou[1], Michael Thurn[2], Paul Adlard[1]
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Aims: The advent of 3D human culture models has provided a more physiologically relevant alternative to classical drug testing approaches that rely on in vitro 2D cultures and in vivo rodent models. Tessara Therapeutics have developed the RealBrain® 3D neuronal micro-tissue platform for industry-level high throughput compound screening. The objective of this work is to utilise Tessara's platform to assess the safety and toxicity of compounds from Neurizon Therapeutics, a clinical-stage biotechnology company that is developing NUZ-001 as a novel treatment for indications such as amyotrophic lateral sclerosis and other neurodegenerative diseases.
Methods: Initial assays have focussed on cytotoxicity (LDH) and cell viability (Resazurin) assays following a three-day exposure of RealBrain® micro-tissues to a dose range (0.5μM – 50μM) of NUZ-001 and its major active metabolite.
Results: No loss of cell viability (Resazurin) or elevation of LDH release (a proxy for cytotoxicity) was detected relative to vehicle control. NUZ-001 exhibited a 10-17% elevation in Resazurin signal from 5-50 μM and its major active metabolite exhibited an elevation of 10% in Resazurin signal at 50 μM, relative to vehicle-only control.
Conclusions: The tested compounds were safe and non-toxic in Tessara's 3D human cell-based micro-tissue platform, with data suggestive of a small proliferative/positive effect on cells within the micro-tissue. The therapeutic efficacy of the compounds is now being assessed through other screening modalities, including ADBrain®, Tessara's 3D model of sporadic Alzheimer's disease.

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SHIFT 01-500

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
2-3 April 2025

SIMVASTATIN INDUCED ABOS CLEARANCE BY AUTOPHAGY-DEPENDENT INSULIN-DEGRADING ENZYME SECRETION VIA AMPK/ULK1 PATHWAY

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Aims: Epidemiological evidence indicates that therapeutic approaches to modulate brain metabolism impairment would be a better strategy to treat Alzheimer's disease (AD). The cellular energy sensor AMP-activated protein kinase (AMPK) plays an important role in AD by clearing β-amyloid oligomers (AβOs) and reducing Aβ deposition. This study aimed to investigate the mechanism of SV anti-AD effects by inducing AβOs clearance by AMPK/ULK1 mediating autophagy-dependent insulin degrading enzyme (IDE) secretion.
Methods: We used primary mice cortical neurons with AβOs-induced (50, 100, 1000 nM) pathology and treated with SV for 24 h. The neuroprotective effect of SV and the mechanism of its anti-AD effect was observed on autophagic flux, extracellular IDE and AβOs levels and AMPK/ULK1 pathway related protein expression.
Results: 5 μM SV upregulated p-(Thr172)-AMPK and p-(Ser555)-ULK1 levels. Furthermore, SV reduced intercellular and mitochondrial ROS production and preserved mitochondrial membrane potential (MMP) via AMPK/ULK pathway activation in AβOs treated neurons. Meanwhile, AMPK-mediated autophagy activation is seen after SV exposure. SV significantly increased the IDE expression in mouse primary cortical neurons, and the extracellular IDE levels increased in the neurons exposed to AβOs.
Conclusions: Our results suggest that SV exerts anti-AD effect via IDE up-regulation and secretion induced by AMPK/ULK1 pathway mediating autophagy-dependent secretion.

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SHIFT 01-501

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β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
2-3 April 2025

AMYLOID BETA PEPTIDE MODIFIES PLASMIN ACTIVITY – RELEVANCE TO ALZHEIMER'S DISEASE

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Aims: To assess the impact of Aβ40/42 peptides on plasmin activity and determine the dose-dependent effects in a cell-free in-vitro system
Methods: To examine the interaction between plasmin and soluble Aβ40/42 peptides, plasmin and Aβ40/42 peptides were pre-mixed and plasmin activity was monitored in a plate-reader using a specific fluorogenic substrate of plasmin (D-Ala-Leu-Lys-7-amido-4-methylcoumarin). Dose-dependent and time-dependent effects were studied
Results: A significant dose-dependent stimulation of plasmin activity was observed with both Aβ40/42 peptides (upto 55%). This result suggests that Aβ40/42 peptides have a positive regulatory effect on plasmin activity, enhancing its proteolytic capacity. Although both Aβ40 and Aβ42 peptides significantly increased plasmin activity, no substantial difference was observed between the two in terms of their ability to enhance enzymatic function
Conclusions: Our study highlights a novel role of amyloid peptides (Aβ40/42) in directly modulating plasmin activity in-vitro. Amyloid peptides may interfere with NGF metabolism by modulating plasmin activity, which needs further studies

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SHIFT 01-502

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β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
2-3 April 2025

ELECTROCHEMICAL BIOSENSOR FOR THE DETECTION OF BETA-SECRETASE ACTIVITY

Saim Imran, Meissam Noroozifar, Kagan Kerman
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Aims: β-Secretase (BACE1) plays a pivotal role in initiating the amyloid cascade and is a crucial target for Alzheimer's Disease (AD) treatment. In this proof-of-concept study, we introduce a highly sensitive electrochemical impedance spectroscopy (EIS) method for detecting BACE1 activity.
Methods: The biosensor design, utilizing screen-printed gold electrodes, involved immobilizing a truncated form of amyloid-β peptide containing the BACE1 cleavage sequence with the Swiss mutation via N-hydroxysuccinimide-activated lipoic acid esters. The changes in the surface-immobilized substrate peptide film were monitored using the apparent charge transfer resistance coupled with a redox probe. Optimization of the biosensor involved determining the enzyme incubation time and the immobilized peptide concentration.
Results: The changes in the surface-immobilized peptide substrate film after incubation with BACE1 was monitored using EIS, and the resulting changes in the charge-transfer resistance was proportional to the concentration of BACE1. The biosensor's analytical capabilities were validated with the diluted human serum samples, showcasing its potential for swiftly screening BACE1 proteolytic activity in diverse biological samples.
Conclusions: The reported biosensor did not require the use of labels or fluorophores, which reduced analytical costs and improves the stability of the analytical method. The biosensor also had a small sample size, produced less waste, and provided relatively quick detection. These advantages suggested that the biosensor could eventually allow for more rapid assessment of BACE1 activity, supporting clinical and research assessments of inhibitor discovery targeting BACE1.

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SHIFT 01-504

Poster on Board - Shift 01
COVID-19 / IMPACT ON BRAIN NEURODEGENERATIVE DISEASES / EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES
2-3 April 2025

POST COVID-19 CONDITION IN SARS-COV-2-INFECTED PEOPLE WITH OR WITHOUT DEMENTIA

Minh Tuan Hoang[1], Tamar Abzhandadaze[1], Minjia Mo[2], Maria Eriksdotter[3], Sara Garcia-Ptacek[2]
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Aims: This study aims to compare risks of post COVID-19 condition between SARS-CoV-2-infected people with and without dementia.
Methods: In this observational study, a total of 106,744 people diagnosed with dementia between 01 May 2007 and 30 June 2022 were matched with 320,232 people without dementia by year of birth, sex and living areas. A combination of various Swedish national registries was employed: the Registry of Infectious Diseases, the National Patient Register, the Total Population Register, the Prescribed Drug Register and the Swedish registry for cognitive/dementia disorders – SveDem. Post COVID-19 condition is defined as the development of new symptoms from three months after the initial SARS-CoV-2 infection. People who passed away before or during three months from their initial SARS-CoV-2 infection were excluded. Cox regression was performed to estimate risks of post COVID-19 condition between people with and without dementia.
Results: This study compared the dementia group (n = 10,680 people, median age at SARS-CoV-2 infection = 84 years old) with the non-dementia group (n = 18,032 people, median age at SARS-CoV-2 = 86 years old). Women accounted for 63.6% and 60.1%, respectively in the dementia and non-dementia groups. The dementia group had 203 incident cases of post COVID-19 condition over 4,089,380 persons-days of follow-up, meanwhile the non-dementia group had 641 incident cases of post COVID-19 condition during 7,290,533 persons-days of follow-up. The dementia group had significantly lower risks of post COVID-19 condition, compare to the non-dementia group (adjusted hazard ratio 0.84, 95% confidence interval 0.71–0.99).
Conclusions: Compared to people without dementia, people with dementia had lower risk of post COVID-19 condition after the SARS-CoV-2 infection. Additional studies on the outcomes of people having post COVID-19 condition should be performed in the future.

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SHIFT 01-505

Poster on Board - Shift 01
COVID-19 / IMPACT ON BRAIN NEURODEGENERATIVE DISEASES / NEUROIMAGING OF COVID-19
2-3 April 2025

THE COGNITIVE AND NEUROLOGICAL IMPACT OF COVID-19 IN OLDER ADULTS WITH PRE-EXISTING MILD COGNITIVE IMPAIRMENT

I Yu Chen[1], Yu Ping Liu[2,3], Yang Teng Fan[3], Yen Ling Chiu[1,3]
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Aims: This study aims to examine the interactions between COVID-19 infection, cognitive decline, and brain structural changes in older adults with mild cognitive impairment (MCI).
Methods: We conducted a case-control study involving 72 participants aged 60 to 90 years. The study comprised 30 neurotypical elderly individuals (NT group), 27 individuals with MCI who had not contracted COVID-19 (MCI w/o SARS-CoV-2 group), and 15 individuals with MCI who had previously contracted COVID-19 (MCI w/ SARS-CoV-2 group). All participants underwent neurocognitive assessments and structural brain imaging to measure gray matter volume and white matter fiber integrity at baseline and follow-up. Changes in neurocognitive function and brain structure were analyzed to explore their relationships.
Results: At the behavioral level, the MCI w/ SARS-CoV-2 group exhibited a decline in Stroop Test performance relative to the other groups. At the neural level, reductions in the superior frontal gyrus, hippocampus, and cerebellar lobules VIII and IX were observed in the MCI w/ SARS-CoV-2 group. These reductions were associated with declines in logical memory, executive function, and general cognitive function. Additionally, this group showed significant differences in fractional anisotropy and mean diffusivity of whole-brain white matter and the corpus callosum body.Notably, only mean diffusivity in the corpus callosum body correlated with declines in general cognitive function, semantic working memory, and response inhibition.
Conclusions: Our findings suggest that SARS-CoV-2 infection may negatively impact brain neurons, neural connectivity, and axonal transmission, contributing to cognitive decline in elderly individuals with MCI. These results provide important insights into the neurocognitive effects of COVID-19 in survivors and inform future strategies for prognosis and intervention to mitigate cognitive impairment.

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SHIFT 01-506

Poster on Board - Shift 01
COVID-19 / IMPACT ON BRAIN NEURODEGENERATIVE DISEASES / NEUROLOGICAL MANIFESTATIONS OF COVID-19
2-3 April 2025

PROTEOMIC ANALYSIS OF NEURONAL RESPONSES TO COMMON VIRAL INFECTIONS RELATED TO NEURODEGENERATION

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Aims: Recent studies have shown that infection with common viruses increases the risk of developing neurodegenerative diseases (NDDs) such as multiple sclerosis and Alzheimer's disease. However, the molecular mechanisms of viral infection induced neurodegenerative pathologies in neurons remain unclear. Thus, we aim to understand the underlying mechanisms of neuronal proteome changes induced by common viruses and provide novel insights about neurodegeneration and viral infection.
Methods: We infected induced pluripotent stem cell (IPSC)-derived human neurons with 5 common human viruses: Epstein-Barr virus (EBV), Influenza (H1N1), Coronavirus 229E (HCoV), Herpes Simplex virus 1 (HSV-1), and Varicella Zoster virus (VZV). We infected the neurons with 3 different concentrations of viral loads and collected the cells at 1-, 2-, and 5-days post infection. The neuronal proteins were extracted and digested using a fully automated pipeline. Then data independent acquisition was performed for mass spectrometry based proteomics.
Results: We identified 9956 human proteins and 156 unique viral proteins. Using the WGCNA package for correlation analysis, we identified 17 unique modules of human proteins, 12 of which showed a significant correlation with viral protein intensity. Each viral infection resulted in mostly unique sets of differentially expressed proteins (DEPs). However, both H1N1 and HSV-1 infections downregulated 25 proteins enriched in ubiquitin protein ligase activity. We then analyzed genes from the NULISA neurodegeneration biomarker panel. VZV infection caused 12 out of 19 total NDD-associated DEPs, including the upregulation of NPTX1 and IL6 and the downregulation of PSEN1. Additionally, we discovered upregulation of key proteins in inflammation and apoptosis pathways, such as BCL2 and STAT1, in HCoV, EBV and VZV infection.
Conclusions: These findings suggest that certain shared and virus-specific proteomic changes may play a role in pathways linked to neurodegeneration.

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SHIFT 01-507

Poster on Board - Shift 01
COVID-19 / IMPACT ON BRAIN NEURODEGENERATIVE DISEASES / NEUROPATHOLOGY OF COVID-19
2-3 April 2025

POST-MORTEM SPATIAL TRANSCRIPTOMIC ANALYSIS OF SARS-COV-2-INFECTED ENTERIC NERVOUS SYSTEM

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Aims: The extent of SARS-CoV-2 (SCV2) neurotropism is still debated, with emerging evidence regarding long-term neurological consequences of COVID-19. Our previous histopathological study identified SCV2 in enteric neurons of severe COVID-19 patients who had died during the peak of the 2020 pandemic. Interestingly, Braak's hypothesis of Parkinson's disease (PD) suggests that initial alpha-synuclein pathology in sporadic PD begins in the enteric nervous system (ENS) of susceptible individuals, potentially triggered by a pathogenic insult, before subsequently propagating in a prion-like manner to the brain. Here, we sought to investigate the transcriptional changes associated with ENS invasion of SCV2.
Methods: To specifically explore the transcriptome of these infected ganglia, we used the GeoMx® Digital Spatial Profiler (NanoString Technologies) to profile ~18,000 protein-coding genes in spatially-defined regions of interest (ROIs) containing these SCV2-infected enteric neurons.
Results: Differential expression analysis revealed significant differences in gene expression between COVID-19 (n=3) and control samples (n=3). Upregulated genes related to the antiviral response (e.g. IFI6, HLA-B), translation (e.g. RPL/RPS genes, EIF4G2), unfolded protein response (e.g. CRYAB, HSPA5), mitochondria (e.g. COX6C, NDUFS4), and oxidative stress (e.g. SOD1, PRDX1). Downregulated genes related to neuronal function (e.g. KCNJ9) and signalling (e.g. NPY). Gene set enrichment analysis querying Gene Ontology and KEGG databases highlighted "Coronavirus disease – COVID-19" as a top enriched disease pathway as well as other pathways related to RNA viruses, the viral life cycle and immune response. Intriguingly, the "Parkinson disease" KEGG pathway was also found to be positively enriched in the COVID-19 vs control group.
Conclusions: These findings suggest that SCV2 infection in the ENS may influence pathways relevant to PD pathogenesis. Future in vitro studies will aim to elucidate these shared pathological mechanisms between COVID-19 and PD.

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SHIFT 01-510

Poster on Board - Shift 01
DEMYELINATING DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

DISCOVERY AND OPTIMIZATION OF A SERIES OF VINYL SULFOXIMINE-BASED ANALOGUES AS POTENT NRF2 ACTIVATORS FOR THE TREATMENT OF MULTIPLE SCLEROSIS

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Aims: MS is a neuroinflammatory autoimmune disease characterized by dysregulated adaptive immunity and nerve damage due to the infiltration of autoreactive immune cells into the CNS. Promoting neuroprotection through antioxidative and anti-inflammatory therapeutics, such as Nrf2 activators, offers a promising strategy for treating MS. In an effort to discover and synthesize potent Nrf2 activators, we synthesized a series of vinyl sulfoximine compounds to determine their therapeutic potential as Nrf2 activators in MS.
Methods: We evaluated them for Keap1-Nrf2 pathway-modulating activities, in vitro drug-like properties, and in vivo pharmacokinetic properties to determine a potent lead compound. The selected compound was assessed for its in vitro efficacies as an antioxidative and anti-inflammatory Nrf2 activator. Finally, the lead compound was subjected to an experimental autoimmune encephalitis (EAE) mouse model to evaluate its in vivo therapeutic potential for MS.
Results: Among the synthesized compounds, **10v** exhibited high Nrf2-activating potency, favorable CYP inhibition properties and microsomal stability, along with superior *AUC* and C_{max} values in PK study, and excellent plasma stability. **10v** effectively induced the expression of antioxidant enzymes HO-1 and GCLM in BV-2 microglial cells by activating Nrf2 and facilitating its translocation into the nucleus. **10v** markedly suppressed the production of NO and downregulated pro-inflammatory cytokines IL-1β, TNF-α, and IL-6 in LPS-stimulated BV-2 microglial cells. Oral administration of **10v** significantly attenuated disease severity and reversed disease progression in both prophylactic and therapeutic studies of EAE. Treatment with **10v** effectively reduced demyelination in EAE mice comparable to that of DMF.
Conclusions: These findings suggest that **10v** is a potent Nrf2 activator with promising therapeutic potential for MS.

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SHIFT 01-512

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
2-3 April 2025

THE ROLE OF STRIATAL NURR1 IN THE SOCIAL BEHAVIOR OF PRENATALLY VALPROIC ACID-EXPOSED AUTISM SPECTRUM DISORDERS MODEL MICE

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Aims: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that exhibits neurobehavioral deficits characterized by abnormalities in social interactions, deficits in communication as well as restricted interests, and repetitive behaviors. The basal ganglia is one of the brain regions implicated as dysfunctional in ASD. In particular, the defects in corticostriatal function have been reported to be involved in the pathogenesis of ASD. Surface deformation of the striatum in the brains of patients with ASD and their correlation with behavioral symptoms was reported in magnetic resonance imaging (MRI) studies. In this study, we aimed to elucidate the mechanism of striatal
Methods: RNA seqs, bioinformatic analysis, Golgi staining, quantitative PCR, behavioral assays and multi-electrode arrays were used in this study.
Results: We demonstrated that prenatal valproic acid (VPA) exposure induced synaptic and molecular changes and decreased neuronal activity in the striatum. Using RNA sequencing (RNA-Seq), we analyzed transcriptome alterations in striatal tissues from 10-week-old prenatally VPA-exposed BALB/c male mice. Among the upregulated genes, Nurr1 was significantly upregulated in striatal tissues from prenatally VPA-exposed mice. Viral knockdown of Nurr1 by shRNA significantly rescued the reduction in dendritic spine density and the number of mature dendritic spines in the striatum and markedly improved social deficits in prenatally VPA-exposed mice. In addition, treatment with amodiaquine, which is a known ligand for Nurr1, mimicked the social deficits and synaptic abnormalities in saline-exposed mice as observed in prenatally VPA-exposed mice. Furthermore, PatDp+/- mice, a commonly used ASD genetic mouse model, also showed increased levels of Nurr1 in the striatum.
Conclusions: Taken together, our results suggest that the increase in Nurr1 expression in the striatum is a mechanism related to the changes in synaptic deficits and behavioral phenotypes of the VPA-induced ASD mouse model.

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SHIFT 01-513

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

ROLE OF MYORG MUTATIONS IN PRIMARY FAMILIAL BRAIN CALCIFICATION (PFBC)

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Aims: Homozygous mutations in myogenesis-regulating glycosidase (MYORG) gene lead to primary familial brain calcification (PFBC). MYORG is a putative glycosidase, preferentially expressed in astrocytes and in the endoplasmic reticulum (ER), where it is potentially involved in post-translational modifications.This study aims to address the common pathomechanisms through which different MYORG mutations lead to PFBC, the cell-autonomous and non-cell autonomous function of MYORG in astrocytes, and the morphological, molecular and functional consequences of MYORG mutations.
Methods: MYORG wild-type (WT) and missense mutant transgenes were overexpressed in HEK293T and immortalized astrocytes cells for western blot and immunostaining analysis. Cycloheximide (CHX) chase assay was performed to determine MYORG protein stability and half-life, while MG132 treatment was utilized to investigate the degradation mechanism of these variants. Finally, thapsigargin (TG) and tunicamycin (TM) treatments were employed to elucidate whether different mutant variants differentially modulate the cellular stress response. Additionally, primary astrocyte cultures isolated from MYORG p.Ile658Thr mutant pups were analysed to delineate morphological and molecular changes induced by the mutation.
Results: We found that some *MYORG* mutations result in decreased MYORG expression levels and impaired protein stability. Moreover, *MYORG* mutations may lead to higher basal ER stress and apoptosis, possibly contributing to PFBC. Primary mutant astrocytes exhibit a distinct secretome, suggesting a role for MYORG p.Ile658Thr in causing defects in extracellular matrix (ECM) remodelling, impaired cell adhesion, and tissue response to injury.
Conclusions: Taken together, these results suggest that these mutations destabilize the MYORG protein and share common pathomechanisms leading to PFBC, likely involving a combination of protein misfolding, impaired early stress responses, and heightened apoptotic signalling. These insights provide a foundation for future therapeutic strategies targeting PFBC.

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SHIFT 01-514

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

TRANSPOSABLE ELEMENTS IN HUNTINGTON'S DISEASE: DO THEY HAVE A ROLE IN NEUROINFLAMMATION AND SOMATIC INSTABILITY?

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Aims: Huntington's Disease (HD) is a genetic neurodegenerative disease for which there is currently no disease-modifying treatment. Among several underlying pathogenic mechanisms proposed to be involved in HD pathogenesis is inflammation. Transposable elements (TE), aka 'jumping genes', are being investigated in neurodegenerative diseases as potential drivers of neuroinflammation and disease pathology. TE are thought to drive disease through two main mechanisms; (i) neuroinflammation, as expressed TE gene products trigger an inflammatory response and (ii) through promoting DNA modifications, hastening neuronal cell loss potentially contributing to somatic instability. Previous work by our team has found brain regional specific TE expression correlating with neuroinflammation and local interferon response in Parkinson's disease post mortem tissue. The overarching objective is to ascertain whether the expression of TE's such as LINE-1s and ERVs, occurs in the brain of patients dying with HD and by so doing contributes to CNS neuroinflammation and CAG somatic instability.
Methods: Fresh frozen human brain tissue from three brain regions (prefrontal cortex, striatum and cerebellum) will be investigated across 6 HD and 6 control cases. Single nuclear RNA sequencing (snRNAseq), NanoString neuroinflammation/glial profiling gene panels, and fragment analysis/pacbio long read sequencing will be used to determine TE expression, inflammation and somatic instability respectively.
Results: We found that neuroinflammatory genes are significantly upregulated in Huntington's disease compared to controls, with many linked to astrocyte function. Regionally, the striatum showed the highest number of upregulated genes. These results mirror others' findings and suggest potential astrocyte-driven neuroinflammation in disease pathology.
Conclusions: Currently this pilot study has established an upregulated neuroinflammatory gene profile in HD. Investigations into TE expression and CAG somatic instability correlating with neuroinflammation in HD will be presented at the conference.

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SHIFT 01-515

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS
2-3 April 2025

SUCCESSFUL MANAGEMENT OF CLINICAL TRIALS AMIDST CONFLICT: A CASE STUDY FROM IMMUNOBRAIN

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Aims: To review the strategies employed by Immunobrain in managing a clinical trial where 40% of the sites were located in a conflict area, and to assess the impact on both patient enrollment and data integrity.
Methods: We conducted a comprehensive analysis of enrollment data and site management strategies throughout the clinical trial. This was achieved in close cooperation with the Contract Research Organization (CRO) and involved frequent and personal contact with clinical sites to ensure patient safety and operational continuity. Our focus was on proactive monitoring of the conflict situation and the implementation of risk mitigation measures to ensure both patient safety and data integrity. Importantly, sites were not pressured to conduct any visits during the conflict if there were concerns that patient safety or site personnel safety would be compromised. Regular communication with site personnel and local authorities was maintained to adapt to the rapidly changing environment.
Results: Despite the challenges posed by the conflict, enrollment figures remained robust, with approximately 37% of enrolled patients originating from the conflict-affected area (Israel). Only one patient visit was cancelled due to the situation. Our proactive approach, including real-time monitoring of safety and logistical concerns, facilitated uninterrupted site operations and patient engagement. This strategic management led to successful recruitment targets being met within the stipulated timeframe.
Conclusions: Immunobrain's careful attention to site monitoring and adaptive management strategies enabled the successful continuation of a clinical trial despite significant geopolitical challenges. The experience underscores the importance of dynamic risk assessment and stakeholder communication in maintaining trial integrity and participant safety in conflict zones. Future studies may benefit from implementing similar frameworks in challenging environments.

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SHIFT 01-516

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS
2-3 April 2025

BIOMARKERS FOR NEURODEGENERATIVE DISEASES IN REGULATORY DECISION-MAKING BY THE EUROPEAN MEDICINES AGENCY

Audrey Hermans[1,2], Lysbeth Bakker[2], Marjon Pasmooij[1,3], Peter Mol[1,2,4], Viktoriia Starokozhko[1,4], Angela Bradshaw[5], Lorenzo Guizzaro[4], Loes Den Otter[1,6], André Elferink[1]
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Aims: Biomarkers (BMs) are valuable tools to facilitate early diagnosis of diseases, improve patient selection/stratification, and detect therapeutic effects or safety concerns. This study explores the extent to which BMs are utilised in the development of treatments for neurodegenerative diseases (NDDs), and topics of discussion around BMs in regulatory advice- and decision-making processes and sharing of BM-related data.
Methods: The European Medicines Agency's marketing authorisation application (MAA), qualification- (QA/QO) and scientific advice- (SA) procedures regarding NDDs were screened, and those that mention BMs were analysed. Information was extracted on intended disease, BM-type, and context of use proposed by applicants. BMs were categorised based on nature and function.
Results: In total, 105 procedures involving NDDs that discussed BMs were analysed; 57 SAs (Jan 2020–Dec 2022), 19 QAs/QOs (Jan 2008–Dec 2023), and 29 MAAs (Jan 1995–Dec 2023). The majority of the procedures involved Alzheimer's disease (AD; n=30), Parkinson's disease (PD; n=9), and multiple sclerosis (MS; n=33). Imaging BMs were predominantly used within the studied dossiers. The majority of BMs were used as pharmacodynamic/response BMs. The acceptance and role of BMs differed between diseases. In regulatory procedures for AD, diagnostic BMs guiding patient selection were commonly discussed. In MAAs for MS, BMs (particularly lesions) were accepted as important supportive/secondary endpoints.
Conclusions: Despite the established role of certain imaging BMs, mainly for MS, there remains a major need for more precise and reliable BMs to improve diagnostic accuracy and treatment monitoring for NDDs. To implement novel BMs and facilitate development of new treatments and eventually improve clinical practice, robust evidence bases showcasing biological plausibility or clear clinical benefits are essential. Collaboration and data-sharing among stakeholders is vital in generating this evidence and enhancing the understanding and management of NDDs.

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SHIFT 01-517

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS
2-3 April 2025

EFFECT OF RTMS ON IMPROVEMENT OF BALANCE AND MUSCLE CONTROL IN PATIENTS WITH CEREBELLAR ATAXIA

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Aims: Cerebellar ataxia (CA) involves dysfunction in balance and motor coordination. Previous studies demonstrated that repetitive transcranial magnetic stimulation (rTMS) can enhance motor function. This study investigates whether rTMS treatment would improve balance and muscle control in CA patients.
Methods: 10 CA patients participated successfully completed 5 consecutive days of treatment on cerebellar tonsil with a frequency of 50Hz. We assessed the patients' balance and muscle control using the balance platform (BT4) and surface–electromyography (sEMG). First, the patients were asked to keep balance for 30 seconds in with eye open and closed during BT4 test. we calculated the displacement in the X (ΔX), Y (ΔY) and the Euclidean distance (ΔD) on a two-dimensional plane for every 10ms. Second, we measured the maximum voluntary contraction (MVC) of lateral and medial sides of bilateral gastrocnemius muscles for 3s and calculated the root mean square (RMS). Data were acquired in pre-and post-treatment. A Wilcoxon signed-rank test and Cohen's D were performed to compare the pre- and post-treatment.
Results: In terms of balance, significant differences were found between pre- and post-treatment in mean ΔY($p<0.01$, $d=0.36$), STD ΔY($p<0.005$, $d=0.42$), max ΔD($p<0.01$, $d=0.56$), and STD ΔD($p<0.005$, $d=0.44$) for the eyes-open condition, and max ΔX($p<0.05$, $d = 0.49$), mean ΔX($p<0.05$, $d=0.39$), STD ΔX($p<0.019$, $d=0.46$) and C90 X(x-coordinate position of the center of the 90% confidence ellipse; $p<0.05$, $d=0.93$) for eyes-closed condition. Regarding muscle control, the area under the RMS envelope($p<0.05$, $d=-0.26$) and mean RMS value($p<0.05$, $d=-0.26$) of the left lateral gastrocnemius muscle were significantly different.
Conclusions: This study indicates that rTMS can improve motor function in CA patients. Specifically, rTMS may have a positive effect on muscle activity which may be further helpful to maintain the static balance in CA patients.

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SHIFT 01-518

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
2-3 April 2025

TREM2 P.C60R MUTATION DISRUPTS C51-C60 DISULFIDE BOND IN THE ECTODOMAIN LEADING TO NASU-HAKOLA DISEASE IN A HOMOZYGOUS CARRIER

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Aims: The Triggering Receptor Expressed on Myeloid Cells 2 (TREM2) is an immune receptor expressed by brain's microglia and macrophages. Homozygous carriers of loss-of-function (LOF) TREM2 mutations manifest early-onset dementia, such as Nasu-Hakola disease (NHD) and the behavioral variant of frontotemporal dementia (bvFTD). Heterozygous carriers are at risk for late-onset Alzheimer's disease (AD) and frontotemporal dementia (FTD). Notably, many pathogenic TREM2 mutations reside within the ectodomain responsible for ligand binding. This region features two disulfide bonds, C36-C110 and C51-C60, predicted to be critical for structural integrity. Clinical phenotypes associated with mutations disrupting these bonds are not reported. Herein, we describe the molecular mechanisms of a novel LOF variant, c.178T>C p.C60R, causing NHD in a homozygous carrier.
Methods: Clinical evaluation, MRI and DNA sequencing were performed on a proband. A phenotype of p.C60R was assessed by the full-length TREM2 reporter assay. Mutagenized reporter derivatives were transfected into microglia-like HMC3 cells. Effects at RNA and protein level were visualized by RT-PCR and western blots.
Results: 38-year-old female proband presented with the bvFTD and osseous abnormalities. The patient's MRI supported an NHD diagnosis. Genetic testing identified a novel homozygous TREM2 mutation, c.178T>C p.C60R, as the probable cause. Reporter assays showed significant reduction in TREM2 expression, with less than 15% protein remaining. The defect was partially rescued by MG132 treatment, indicating proteasome-mediated degradation. A comparative analysis with the p.C51Y mutation, enriched in early-onset sporadic AD, demonstrated similar protein loss, confirming the detrimental impact of disrupting the C51-C60 disulfide bond.
Conclusions: The C51-C60 loop is essential for the TREM2 structure and function. Its disruption leads to enhanced protein degradation, significantly reducing TREM2 and contributing to disease pathology.

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SHIFT 01-521

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

NOVEL DIFFERENTIATION OF HIPPOCAMPAL NEURON MORPHOLOGY AMONG THREE GENOTYPES OF DOWN SYNDROME USING MACHINE LEARNING

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Aims: This study applies machine learning to detect subtle morphological changes in hippocampal neurons across three Down syndrome (DS) genotypes, aiming to identify novel biomarkers.
Methods: Hippocampal slices from varied DS mouse models stained for biomarkers of neurogenesis: Doublecortin (DCX), Glial Fibrillary Acidic Protein (GFAP), Neurons (NeuN), and Parvalbumin (PV) were digitized for analysis. DS mouse models of male preadolescent (21 days) and old (18 months) were: T65Dn mice (trisomic for 140 genes corresponding to the distal end of HSA21 and triplication of a fragment of MMU16 between Mrpl39 and Znf295); 2N mice (age-matched control for Ts65Dn group; Ts1Cje mice (triplication of a shorter fragment of MMU16 from Znf295, excluding App; these mice were bred on a C57Bl background, crossed with C3H/HeSnJ mice, and further crossed to B6EiC3Sn F1 to match the genetic background of Ts65Dn mice; and, Ts65Dn mice with only two copies of App. To generate mice with only two copies of APP, female Ts65Dn mice were crossed with male mice hemizygous for APP, resulting in offspring with either 3 (Ts65Dn: APP+/+/+) or 2 copies of APP (Ts65Dn:APP+/+/-)). APython-based machine learning algorithm was used to assess quantity, area, intensity, and distribution patterns among all genotypes and biomarkers for, neurogenesis in developing neurons (DCX); astrocytes (GFAP); neurons (NeuN); and GABAergic neurons (PV). The Nikon Eclipse Ti2-E/B Inverted Light Microscope was used for digitization.
Results: Noteworthy morphological changes between APP presence or absence were captured through this method.
Conclusions: This novel approach provides an unbiased and automated method for detecting subtle morphological differences, particularly in GABAergic neurons, linked to App overexpression in DS.

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SHIFT 01-523

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

THE GLP-1 RECEPTOR AGONIST LIRAGLUTIDE AMELIORATES L-DOPA THERAPY COMPLICATIONS IN A RAT MODEL OF PARKINSON´S DISEASE

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Aims: L-DOPA is still the most effective therapy to improve motor symptoms in Parkinson´s disease (PD). However, with disease progression, this therapy causes motor fluctuations and involuntary movements termed L-DOPA-induced dyskinesia (LID). Antidiabetic drugs mimicking or enhancing the biological effects of glucagon-like peptide-1 (GLP-1) are being considered for repurposing as a disease-modifying treatment in PD. It is not yet clear whether this class of compounds can improve the efficacy and/or prevent the complications of L-DOPA pharmacotherapy. Here, we investigate whether add-on treatment with the GLP-1 receptor agonist Liraglutide can prevent the development of L-DOPA therapy complications in a well-characterised rat model of PD-LID.
Methods: The study is conducted in parkinsonian rats with unilateral 6-OHDA lesions of nigrostriatal dopamine (DA) neurons. Animals are treated daily with saline or dyskinesiogenic doses of L-DOPA (6, 12, and 24 mg/kg) alone or combined with liraglutide (0.1 mg/kg) for 3 weeks. Abnormal involuntary movements (AIMs) and motor fluctuations are assessed. Thereafter the rat brains are analysed through biochemical and histomolecular assays to investigate the treatment´s mechanisms of action.
Results: The data showed significant reduction of AIMs and better "off-time" motor performance in animals cotreated with the highest L-DOPA dose combined with Liraglutide compared to L-DOPA alone. Liraglutide also significantly reversed L-DOPA related pathological vascular changes by counteracting angiogenesis and blood brain barrier leakage for large plasma proteins in the basal ganglia. Furthermore, Liraglutide cotreatment reduces microglia activation and its vascular interaction in the same brain areas.
Conclusions: Liraglutide cotreatment with L-DOPA prevents LID, and prolongs L-DOPA treatment effect. It also reduces the maladaptive microvascular and glial changes induced by dyskinesiogenic L-DOPA treatment in the parkinsonian rat model.

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SHIFT 01-524

Poster on Board - Shift 01
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

METABOLIC ANALYSIS OF SARCOPENIC MUSCLE IDENTIFIES POSITIVE MODULATORS OF LONGEVITY AND HEALTH SPAN IN C. ELEGANS

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Aims: Sarcopenia is the age-related degeneration of skeletal muscle, resulting in loss of skeletal muscle tone, mass, and quality. Skeletal muscle is a source of systemic metabolites and macromolecules important for neuronal health, function and healthy neuronal aging. Age-related loss of skeletal muscle might result in decreased metabolite and macromolecule availability, resulting in reduced neuronal function or increased susceptibility to unhealthy aging and neurodegenerative diseases. We aimed to identify muscle metabolite candidates that regulate healthy aging.
Methods: C57BL/6J mice were aged to young adult (4 months) and old age (25 months) and skeletal muscle was collected. Using a low molecular weight enriched metabolomics protocol, we assessed the metabolic profile of skeletal muscle from young adult and old mice. These candidate metabolites were tested in *C. elegans* assays of lifespan, health span, muscle-, and mitochondrial morphology under normal and stressed conditions.
Results: Age related muscle loss was confirmed by reduced muscle mass, muscle fiber degeneration, reduced myosin intensity, in addition to a metabolic shift and increased DNA damage in skeletal muscle. We assessed the metabolic profile of skeletal muscle from young adult and old mice and identified 20 metabolites that were significantly changed in aged muscle. We identified four candidate metabolites (beta-alanine, 4-guanidinobutanoic acid, 4-hydroxyproline, pantothenic acid) that when supplemented in *C. elegans* provided robust gero- and mitochondrial protection. These candidates also affected life-, and health span in *C. elegans* models of amyotrophic lateral sclerosis and Duchenne muscular dystrophy.
Conclusions: Our findings support that aging muscle can be used to identify novel metabolite modulators of lifespan and health and may show promise for future treatments of neurodegenerative and neuromuscular disorders.

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SHIFT 01-525

Poster on Board - Shift 01
LYSOSOMAL STORAGE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

THE ROLE OF AMPK/MTOR SIGNALLING IN PTZ-INDUCED KINDLING IN MICE: EFFECTS OF TICAGRELOR AND DAPAGLIFLOZIN

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Aims: The study aimed to investigate the neuroprotective effects of ticagrelor and dapagliflozin in a chemically induced kindling model in animals.
Methods: Chemical kindling was induced in Swiss albino mice through 14 intraperitoneal injections of pentylenetetrazol (PTZ, 35 mg/kg) administered every other day from day 1 to day 27. Seizure activity was recorded using the Racine scale for 30 minutes following each PTZ infusion. Treatments included oral administration of dapagliflozin (2.5 and 5 mg/kg) and ticagrelor (50 and 100 mg/kg) alone or in combination (dapagliflozin 2.5 mg/kg and ticagrelor 50 mg/kg) alongside PTZ over 33 days. On day 33, a PTZ challenge test was performed, and seizure progression was recorded on video. Following the challenge test, animals were euthanized, and brain tissue was harvested to assess biochemical, neurochemical, molecular and histopathological changes induced by kindling. Biochemical parameters were measured using standard protocols, including malondialdehyde (MDA), nitrite, superoxide dismutase, and acetylcholinesterase activity. High-performance liquid chromatography (HPLC) was used to estimate adenosine and inosine levels in brain tissue, while hematoxylin and eosin (H&E) staining was employed to observe neuronal morphology. Protein levels of AMPK/mTOR were quantified using western blotting.
Results: Intraperitoneal administration of PTZ (35 mg/kg) effectively induced kindling in animals, characterized by repeated generalized tonic-clonic seizures, were attributed to increased oxidative stress, acetylcholinesterase activity, and degenerative changes in the mice's brains. An imbalance in adenosine and its metabolite inosine levels was also observed in PTZ-kindled animals. However, combination therapy with dapagliflozin and ticagrelor significantly reversed these degenerative changes, preserved neuronal integrity, and provided neuroprotection against PTZ-induced kindling.
Conclusions: The findings suggest that maintaining the brain's bioenergetic balance by targeting AMPK/mTOR could be a promising therapeutic strategy for managing epilepsy.

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SHIFT 01-526

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
2-3 April 2025

COGNITIVE TEST PERFORMANCE IN OLDER ADULTS WITH AND WITHOUT MOTORIC COGNITIVE RISK

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Aims: Objective: Subjective Cognitive Concern (SCC) and slowed gait have been related to increased risk for dementia. Motoric cognitive risk (MCR) combines (SCC) with slowed gait speed. This study explores how slow gait speed and SCC independently and together affect cognitive performance of cognitively unimpaired older adults in a diverse population.
Methods: Methods: Data from 2302 cognitively unimpaired participants from an epidemiological study of aging was utilized. Four groups were created based on the presence/absence of slow gait on a four-meter gait speed walk test and SCC (no deficits N= 1120, SCC only N=893, slow gait only N= 119, MCR N= 170). ANCOVAS co-varying age, education and depression examined group differences on measures of memory, attention, executive functions and language.
Results: Results: The participants had a mean age of 64.73 (8.42) and a mean education of 13.60 (4.29). ANCOVAs demonstrated significant differences between the groups on all cognitive tests. Post hoc tests showed that slowed gait and MCR groups performed significantly worse than the other groups on attention, memory and language with no differences between the slow gait and MCR groups. MCR group performed significantly worse than the other groups on measures of executive functions.
Conclusions: Conclusion: The findings indicate that slowed gait is significantly related to cognitive performance and the addition of SCC has an even greater impact on executive functions in cognitively unimpaired older adults. These relationships suggest the potential clinical value of these two easily obtainable measures as predictors of cognitive decline.

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SHIFT 01-527

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
2-3 April 2025

THE COMPARISONS OF ABNORMAL BEHAVIOR AND CAREGIVER BURDENS BETWEEN EARLY ONSET DEMENTIA (EOD) AND LATE ONSET DEMENTIA (LOD) : KOREAN MULTICENTER STUDY

Jay Kwon[1], Kyungsoo Lee[2]
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Aims: To investigate the differences of etiology, behavioral features and burdens of their caregivers between EOD and LOD in Korea.
Methods: We enrolled 1341 clinically demented patients who satisfied working inclusion criteria from 31 dementia centers nationwide in Korea. 200 EOD (age; 58.3 + 5.8, 76 male, education; 10.3 + 3.4 years, MMSE; 20.9 + 4.9) and 1133 LOD (age; 76.5 + 5.7, 394 male, education; 5.4 + 3.8, MMSE; 18.7 + 5.3) patients were evaluated using an electronic case report form which include information about demographic findings, probable etiologic disease, general cognitive status, neuropsychiatric inventory(NPI) and caregiver burden. Their cognitive tests, NPI and the assessment of caregiver burden were followed after 3 months and 6 months.
Results: The most frequent etiologic disease in both group was Alzheimer's disease (63.5% in EOD and 63.3% in LOD). Multi-infarct dementia was more popular in LOD, but Frontotemporal dementia in EOD. Among the items of NPI, delusion, hallucination and abberant motor behavior were more frequent in LOD ($p<0.01$). Despite of rarer prevalence, caregiver of EOD patients had greater stress for delusion, abberant motor behavior and abnormal sleep behavior than LOD. The MMSE score was negatively correlated with the frequency and severity of NPI and caregiver burden ($p<0.001$).
Conclusions: We suggest that future study including EOD has to be differently approached to LOD in aspect of patients and caregiver. It should be warranted to establish the recommendation for caregiver of EOD patients who have been overlooked.

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SHIFT 01-530

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / QUALITY OF LIFE
2-3 April 2025

PREDICTIVE FACTORS FOR FALLS IN PATIENTS WITH DEMENTIA AND MILD COGNITIVE IMPAIRMENT

Inyoung Choi
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Aims: There is a tendency to regard falls as inevitable events, especially in dementia patients with behavioral and psychological symptoms. Nevertheless, efforts are needed to find aspects that can minimalize these fatal events. As a basic step, I compared related factors between patients who had experienced falls and those who had not among dementia or mild cognitive impairment patients. Additionally, I aimed to present a predictive model for factors influencing the occurrence of falls.
Methods: Among patients with dementia or mild cognitive impairment who visited the neurology outpatient clinic from January 1 to June 30, 2023, those who had experienced falls within the past 6 months were selected. They were compared with patients who had not experienced falls.

Table 1. Demographics and characteristics of control group and fall-down patients

	control (n=30)	fall-down patients (n=29)	*p*-value
age (yr)	82.23 ± 7.74	82.97 ± 6.73	0.903
sex (female, n (%))	17 (56.67)	25 (86.21)	0.020
education (yr)	7.43 ± 4.95	4.10 ± 4.84	0.007
MMSE	16.23 ± 7.30	16.76 ± 6.89	0.849
GDS	4.90 ± 0.92	4.59 ± 1.09	0.207
anti-dementia med (n)	1.40 ± 0.50	1.24 ± 0.44	0.196
med for BPSD control (n)	0.83 ± 1.09	1.10 ± 1.01	0.195
oCVA (n (%))	5 (16.67)	8 (27.59)	0.360
hypertension (n (%))	17 (56.67)	22 (75.86)	0.170
diabetes mellitus (n (%))	10 (33.33)	6 (20.69)	0.382
dyslipidemia (n (%))	18 (60.00)	13 (44.83)	0.301
living alone (n (%))	3 (10.00)	5 (17.24)	0.472
gait pattern (n (%))			
independent gait	19 (63.33)	16 (55.17)	0.601
cane gait	8 (26.67)	8 (27.59)	1.000
walker gait	2 (6.67)	2 (6.90)	1.000
wheelchair gait	1 (3.33)	3 (10.34)	0.353

MMSE: mini-mental state examination, GDS: global deterioration scale,

BPSD: behavioral and psychological symptoms of dementia

oCVA: old cerebrovascular accident

Results:

Table 2. Univariate simple logistic regression

	partial regression coefficient	OR (95% CI)	*p*-value
age	0.014	1.015 (0.944-1.090)	0.694
sex	1.564	4.779 (1.330-17.170)	0.017
education yr.	-0.14	0.869 (0.776-0.974)	0.016
MMSE	0.011	1.011 (0.939-1.088)	0.773
GDS	-0.319	0.727 (0.430-1.228)	0.233
anti-dementia med	-0.74	0.477 (0.156-1.464)	0.196
med for BPSD control	0.253	1.288 (0.779-2.129)	0.323

MMSE: mini-mental state examination, GDS: global deterioration scale,

BPSD: behavioral and psychological symptoms of dementia

Table 3. Univariate multiple logistic regression

	partial regression coefficient	OR (95% CI)	*p*-value
sex	1.470	4.351 (0.986-19.205)	0.052
education yr.	-0.140	0.870 (0.752-1.005)	0.059
GDS	-0.748	0.473 (0.241-0.931)	0.030

GDS: global deterioration scale

Table 4. Multiple logistic regression with interaction

	partial regression coefficient	OR (95% CI)	*p*-value
GDS	-1.057	0.347 (0.154-0.785)	0.011
education yr.	-0.142	0.867 (0.750-1.003)	0.055
GDS*sex	0.349	1.417 (1.000-2.009)	0.05

GDS: global deterioration scale

The fall group showed a higher proportion of females (56.67% vs. 86.21%, p=0.020) and lower education years (7.43 ± 4.95 vs. 4.10 ± 4.84, p=0.007). There were no differences between the two groups in age, MMSE scores, GDS scores, number of anti-dementia medications, or number of medications for controlling BPSD. There were also no differences in underlying conditions such as history of previous cerebral infarction, hypertension, diabetes, and dyslipidemia between the groups. The proportion of patients living alone did not differ between the groups, nor did the proportions of patients with each gait pattern. In the univariate logistic regression analysis, sex and education years were identified as significant variables with odds ratios of 4.779 and 0.869 (p=0.017, 0.016, respectively). In the logistic regression analysis using multiple variables, the odds ratio for GDS was 0.473 (p=0.030).

Conclusions: The fall group had a higher proportion of females and lower education years. To prevent falls, more careful observation may be needed in early-to-moderate dementia and MCI patients.

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SHIFT 01-532

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / SUPPORT DEVICES & MONITORING
2-3 April 2025

ENHANCING SAFETY AND INDEPENDENCE FOR PEOPLE WITH DEMENTIA USING OPEN-INTERFACE SENSORS AND AI VOICE REMINDERS FOR FALL PREVENTION, KITCHEN MONITORING, AND OUTDOOR ACTIVITY TRACKING.

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Aims: Our research focuses on the implementation of open interface sensor networks through open interface home assistant software for bathrooms to prevent falls, smart monitoring systems to track kitchen safety, outdoor activities tracking with the purpose of mitigating these risks.
Methods: We will investigate, in particular, how real-time AI voice reminders through Google Assistant may nurture safe behaviors and reduce accident likelihood while supporting greater independence in daily activities. Preliminary results from such a combined approach, using technology and home automation with sensor systems, indicate an enhanced level of physical safety and contribute to a better quality of life by enabling a supportive environment that extends the possibility of independent living
Results: Data from the sensor network humidity levels, temperature readings, GPS coordinates were logged automatically into a secure database. The frequency of fall-related incidents, accidents, and other hazardous situations were tracked. Additionally, usage statistics for AI reminders (e.g., how often they were triggered and acknowledged by the participant) were recorded.
Conclusions: This study has also demonstrated the feasibility of integrating open-interface sensors, AI voice reminders, and home automation systems to enhance safety and independence for individuals living with dementia. Real-time AI reminders, sensor networks for fall prevention, kitchen safety, and outdoor activity tracking have shown encouraging results in mitigating risks and facilitating daily living.In the following weeks, this is to be tested in participants' houses in order to get the feedback from care givers and participants families. This technology promotes a supportive home environment in which persons with dementia can remain independent longer. The results show that assistive technologies for support play an essential role in the care of dementia and provide valuable lessons for further development and practical use in the future.

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SHIFT 01-533

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / SUPPORT DEVICES & MONITORING
2-3 April 2025

APPLICATION OF A CALL-BASED SYSTEM USING LONG-TERM MEMORY INTERGRATED LARGE LANGUAGE MODEL(LLM) FOR MONITORING INDIVIDUALS AT HIGH RISK FOR DEMENTIA

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Aims: This study investigates the application of a call-based AI system that integrates long-term memory (LTM) into large language models (LLMs) to monitor the health of individuals at high risk for dementia. The system aims to enhance the detection and management of early dementia symptoms, providing continuous health monitoring and intervention.
Methods: A total of 100 subjects at high risk for dementia were enrolled from the Seongdong-gu Center for Dementia. Following a dropout of 20 participants, 80 subjects were included in the final analysis. Participants received twice-weekly calls from NAVER's AI-based CLOVA CareCall system, resulting in a total of 63 interactions per participant. Each call was structured to assess and monitor key health indicators, including sleep patterns, dietary habits, physical activity, and social engagement, and to provide emotional support. Comprehensive evaluations, including demographic analyses, cognitive function assessments, depression scale evaluations, and participant satisfaction surveys, were conducted at baseline and post-intervention.
Results: A paired t-test was conducted to evaluate the effectiveness of the intervention on cognitive and emotional outcomes. Results indicated a significant reduction in depressive symptoms from baseline to post-intervention ($p < 0.001$) and a decline in memory recall ($p = 0.024$). No significant changes were found in orientation ($p = 0.358$), language function ($p = 0.545$), or total cognitive score ($p = 0.125$). These findings indicate a potential impact of the intervention on reducing depressive symptoms.
Conclusions: This study suggests that a call-based AI system may serve as a valuable tool for ongoing health monitoring in individuals at elevated risk for dementia.

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SHIFT 01-534

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT
2-3 April 2025

SUPPORTING SUPPORTERS: APPLYING LANGERIAN MINDFULNESS IN CAREGIVER SUPPORT FOR DEMENTIA, A PROSPECTIVE STUDY

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Aims: Mindfulness is a continuously adapting and evolving discipline, dating back 25 centuries to the teachings of the Buddha. Mindfulness-based interventions (MBI) have demonstrated promising findings in increasing cognition and well-being. However, the applications of MBIs, specifically Langerian Mindfulness in Dementia caregivers have not yet been robustly explored. Hence, this prospective study aims to apply Langerian Mindfulness in reducing caregiver burden and stress to enhance the positive support that they can provide. This study will be the first of its kind to apply Langerian Mindfulness in enhancing caregiver support.
Methods: This study will be a between-subject randomized controlled trial. Prior to part-taking in an 8-week Langerian Mindfulness training program, caregivers of patients with Dementia will be interviewed to express and survey their well-being, resilience, health, hope, and connectedness to their person with Dementia. This interview will be done again after the intervention.
Results: Based on prior Mindfulness research findings, we expect to find a positive increase in reports of well-being, resilience, and health in caregivers. Additionally, we expect to find an increase in feelings of connectedness between caregiver and patient. We are agnostic to how feelings of hope will be impacted by this intervention.
Conclusions: Following expected findings of improvements in well-being, resilience, health and connectedness of caregivers, it will be safe to say that Langerian Mindfulness can be a helpful aid in Caregiver support. Langerian Mindfulness provides specific and dynamic benefits, such as not being limited to solely meditation-based training. Hence, this provides a new avenue for exploring caregiver support for people with Dementia and Cognitive dysfunction with more limited resources and less interest in meditation. This can in turn further enhance the quality of caregiver support.

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SHIFT 01-535

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT
2-3 April 2025

RETROSPECTIVE CONNECTIONS CAN GIVE IDENTITY TO RELATIONSHIPS WITH DEMENTA PATIENTS: A SELF-REPORT

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Aims: When family members of people with Dementia and Cognitive Dysfunction become caregivers, they must navigate a great emotional loss by coming to terms with losing a meaningful and intimate connection overtime. With this emotionally difficult and time-consuming situation, caregivers may become socially isolated and feel alienated when their loved one can no longer converse with them or communicate. Hence, this study aims to report how connection and relationship with a person with Dementia and Cognitive Dysfunction can be enlivened and enhanced through reframing thought patterns.
Methods: This study provides a self-report of a person with lived experience who reports being a caregiver to a Dementia patient with Cognitive Dysfunction. A reframed thought pattern was applied by the caregiver, associating the patient with their past hobbies and personality while also creating art work to acknowledge the accomplishments of the person with Dementia. Through interviews and rigorous discussion, this study assesses reports from the caregiver's experience and perspective shift towards the patient following retrospective personality association.
Results: Findings of the reports demonstrated accounts of increased connectedness between the patient and caregiver. Reports of positive associations to the person with Cognitive Dysfunction were mentioned. The caregiver reported a more meaningful and socially fulfilling connection with the patient. Keywords such as "love," "commitment," "person" were mentioned during this interview.
Conclusions: Following findings in this study, it is evident that reframing thought can impact the well-being of caregivers and also their perspective towards the person with Dementia and Cognitive Dysfunction. Furthermore, this can help revive a social aspect while making the connection more meaningful with Dementia patients. In turn, this can also provide more respect for people with Dementia and reduce stigma towards them.

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SHIFT 01-536

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT
2-3 April 2025

INFORMAL CAREGIVERS' PERCEIVED COMPETENCE IN MILD COGNITIVE IMPAIRMENT CARE

Pascual Sanchez-Juan[1], Elena Garcia-Arcelay[2], Mariló Almagro[1,3], Mircea Balasa[4], Gerard Piñol[5], Mercè Boada[6], Lamberto Landete[7], Eloisa Navarro[8], Inmaculada Abellán[9], Angel Berbel[10], Beatriz Espejo[11], Miquel Baquero[12], Juan Marin[13], Emilio Franco[14], Alberto Villarejo-Galende[15], Felix Viñuela[16], Inmaculada Feria Vilar[17], Carmen Perez-Vieitez[18], Norberto Rodriguez-Espinosa[19], Albert Puig-Pijoan[20], Guillermo Amer[21], Eloy Rodriguez-Rodriguez[22], Jesús Rodrigo[3], Javier Ballesteros[23], Jorge Mauriño[2], Sagrario Manzano[8]
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Aims: The caregiver's self-perceived efficacy in the caregiving role or sense of competence is still underexplored in the context of mild cognitive impairment (MCI). The aim of this study was to assess the sense of competence in informal caregivers of patients with MCI.
Methods: A non-interventional, cross-sectional study was conducted at 19 memory clinics in collaboration with the Spanish Confederation of Alzheimer's Disease (CEAFA). Individuals providing informal care for patients diagnosed of MCI (National Institute on Aging and the Alzheimer's Association clinical criteria) and a Global Deterioration Scale score of 3 were included. The feeling of being able to care for the patient was assessed using the 7-item Sense of Competence Questionnaire (SCQ). Associations between the SCQ and outcome measures were analyzed using Spearman's rank correlations.
Results: A total of 196 caregivers were studied. Mean (SD) age was 63.5 (13.1) years and 63% were female. A

68.4% were spouses of patients with a mean age of 72.9 (7.0) years, a median disease duration of 2.0 years (IQR 1.0-4.0), and a median Mini-Mental State Examination score (IQR) of 26.0 (23.0-27.0).
Mean (SD) SCQ score was 26.1 (6.1). Sense of competence was positively correlated with caregiver-patient relationship (rho=0.725, p=<0.001), resilience (rho=0.343, p=<0.001), quality of life (rho=0.378, p=<0.001), and negatively with caregiver burden (rho=-0.630, p<0.001), perception of stigma (rho=-0.396, p<0.001), anxiety (rho=-0.315, p<0.001), and depression (rho=-0.314, p<0.001).
Conclusions: The sense of competence was found to be moderate to high among a sample of individuals informally caring for patients with MCI. Targeted interventions to enhance resilience and improve the quality of the patient-caregiver relationship could provide valuable support to those dealing with MCI care.

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SHIFT 01-537

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT
2-3 April 2025

HOPELESSNESS IN INFORMAL CAREGIVERS OF PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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Aims: Understanding informal caregivers´ feelings about future events and their negative expectations in the context of caring for patients with mild cognitive impairment (MCI) is still limited.
This study aimed to assess the hopelessness experienced by caregivers of patients with MCI.
Methods: A non-interventional, cross-sectional study was conducted at 19 memory clinics in collaboration with the Spanish Confederation of Alzheimer´s Disease (CEAFA). Individuals providing informal care for patients diagnosed of MCI (National Institute on Aging and the Alzheimer´s Association clinical criteria) and a Global Deterioration Scale score of 3 were included.
Hopelessness was measured by using the Beck Hopelessness Scale (BHS). Associations between the hopelessness and outcome measures were analyzed using a logistic regression.
Results: A total of 196 caregivers were studied. Mean (SD) age was 63.5 (13.1) years and 63% were female. A

68.4% were spouses of patients with a mean age of 72.9 (7.0) years, a median disease duration of 2.0 years (IQR 1.0-4.0), and a median Mini-Mental State Examination score (IQR) of 26.0 (23.0-27.0). A 19.9% (n=39) of participants reported moderate-to-severe hopelessness. Mean BHS score was 5.5 (3.6). These individuals were older, had fewer years of education, an stronger perception of stigma, used more avoidant coping strategies, and perceived their social support as inadequate. Higher scores of hopelessness were positively correlated with anxiety (OR=1.18 [95%CI 1.03, 1.35] p=0.012) and depression (OR=1.36 [95%CI 1.14-1.63]mp=0.0001), and negatively correlated with resilience (OR=0.94 [95%CI 0.93, 0.96] p=0.0001), and an active working status (OR=0.17 [95%CI 0.05, 0.58] p=0.005)

Conclusions: Almost 20% of informal caregivers of patients with MCI experienced moderate-to-severe hopelessness.

Interventions aimed at reducing depressive symptoms, anxiety, and enhancing resilience may be crucial to mitigating hopelessness in this population.

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SHIFT 01-538

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
2-3 April 2025

VIRTUAL COGNITIVE CARE PROGRAM FOR MILD COGNITIVE IMPAIRMENT AND EARLY DEMENTIA IMPROVES COGNITIVE SELF-EFFICACY

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Aims: The primary objective is to evaluate the improvement in cognitive self-efficacy in patients with mild cognitive impairment (MCI) or early dementia who have undergone digital multi-domain cognitive interventions virtually.
Methods: A total of 65 participants diagnosed with mild cognitive impairment (MCI) or early dementia were enrolled over an 18-month period in the Neuroglee Connect program, which includes digital multi-domain interventions like cognitive training, brain health education on healthy lifestyle habits, memory support tools, mind & body wellness exercises delivered remotely on their mobile/tablet devices. Participants first completed a 10-week "Train" phase, engaging in these weekly assigned tasks. Following the initial 10-week period, participants transitioned to the "Sustain" phase, which lasted up to 6 months. Participants' performance was evaluated throughout the 10-week "Train" phase. The program also included virtual visits with a personalized care team including MD, NP, LCSW. The visits were scheduled based on the needs of the patients & their caregivers. Furthermore, participants were assessed immediately following the 10-week train phase for perceived improvement in performing activities in light of known memory changes using a screening tool (Cognitive Self Efficacy) administered by Neuroglee.
Results: Among the participants who completed the Neuroglee Connect™ program, 52% of them reported a perceived improvement in performing activities in light of known memory changes as measured by assessment tool (Cognitive Self Efficacy ePROs) administered by Neuroglee. Additionally, 92% of patients completed their virtual care visits as scheduled.
Conclusions: Using a digital platform that focuses on multi-domain cognitive interventions and provides educational information on healthy lifestyle habits may improve perceived cognitive performance in patients with mild cognitive impairment (MCI) and early dementia.

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SHIFT 01-539

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
2-3 April 2025

NEUROPHYSIOLOGICAL EVIDENCE FOR TRANSFER EFFECTS AFTER COMBINED MNEMONIC STRATEGY TRAINING AND HIGH-DEFINITION TRANSCRANIAL DIRECT CURRENT STIMULATION

Benjamin Hampstead[1], Patrick Pruitt[1], Quentin Devignes[1], Scott Peltier[1], Annalise Rahman-Filipiak[1], Bruno Giordani[1], Anthony Stringer[2], K. Sathian[3], Alexandru Iordan[1]
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Aims: While cognitive training interventions are increasingly recognized for their potential benefits across the "normal" to dementia continuum, evidence of transfer to untrained tasks remains limited. We evaluated the effects of mnemonic strategy training (MST) and high-definition transcranial direct current stimulation (HD-tDCS) for memory deficits in those with amnestic mild cognitive impairment (MCI). Here, we report neurophysiological outcomes for an untrained N-back working memory task (i.e., transfer effects), at the primary endpoint after 5 consecutive daily sessions.
Methods: A total of 107 participants with amnestic MCI were randomized in a 2x2 design to either MST or an autobiographical recall (ABR) control condition delivered concurrently with either active or sham HD-tDCS. HD-tDCS was delivered at 2mA for ~20 minutes per session and targeted the left inferior frontal gyrus (IFG), a brain region engaged by both MST and working memory. A total of 78 participants completed an fMRI-based N-back task both pre- and 3-4 days post-intervention, with three conditions: 0-back, 2-back, and semantic. We evaluated changes from baseline within and between groups using brain-wide univariate analyses.
Results: Within-group post- vs. pre-intervention univariate analyses (2-back>0-back) showed greater activation in the left IFG for the active MST group, and no changes for the sham MST, active ABR, or sham ABR groups. Group by session interaction analyses further confirmed greater left IFG activation for the active MST group relative to the other groups. There were no changes for the semantic>0-back contrast.
Conclusions: The combination of MST with HD-tDCS appears to facilitate transfer of left IFG enhanced activation post- relative to pre-training to an untrained working memory task that involves similar neural mechanisms. Future work will evaluate persistence of effects.

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SHIFT 01-540

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
2-3 April 2025

EVALUATION OF A GAMIFIED COGNITIVE TRAINING APP AND ITS IMPACT ON MILD COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor symptoms, including cognitive impairment which impacts quality of life. With limited medical treatments available, non-pharmacological options like cognitive training are crucial, though evidence of effectiveness is mixed. This single-blinded randomized-control-trial assessed the effectiveness of a home-based user adaptive and gamification-based cognitive training app on cognitive functioning in PD patients with mild cognitive impairment (PD-MCI) over a 12-week period.
Methods: Thirty-nine participants (age ≥ 40, 18 female) with PD-MCI (MoCA 19-26 or relevant CERAD sub score) were recruited and randomly assigned to the intervention or waitlist control group. Participants were instructed to train three times a week for 30 minutes using the cognitive training app. The primary endpoint was overall cognitive performance, assessed by the Screening Module of the Neuropsychological Assessment Battery (S-NAB) after 12 weeks. Secondary endpoints included psychological well-being (Health49), anxiety, depression (HADS-D), and cognitive self-assessment (FLei). Multiple regressions were conducted with pre-test scores and group indicators, controlling for potential randomization issues from the small sample size.
Results: Participants in the intervention group (n = 18) had significant improvements in S-NAB scores with a mean increase of +7.11, compared to a decrease of -2.9 in the control group (n = 21, $p < .05$). No significant effects were observed for secondary outcomes, including psychological well-being, anxiety, depression, or cognitive self-assessment.
Conclusions: Initial findings indicate the app's positive effect on cognitive abilities, suggesting it may serve as an effective cognitive training tool for PD-MCI patients. Further research is needed to explore the app's broader impact and long-term benefits. Additionally, customized content may be necessary to improve patient-related outcomes such as psychological well-being and quality of life.

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SHIFT 01-541

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
2-3 April 2025

COMBINING HD-TDCS WITH MNEMONIC STRATEGY TRAINING ENHANCES FUNCTIONAL NETWORK CONNECTIVITY IN THOSE WITH MILD COGNITIVE IMPAIRMENT

Alexandru Iordan[1], Patrick Pruitt[1], Quentin Devignes[1], Scott Peltier[1], Annalise Rahman-Filipiak[1], Bruno Giordani[1], Anthony Stringer[2], K. Sathian[3], Benjamin Hampstead[1]
[1]University of Michigan, Ann Arbor, United States of America, [2]Emory University, Atlanta, United States of America, [3]Pennsylvania State University, Hershey, United States of America

Aims: We evaluated the effects of mnemonic strategy training (MST) and high-definition transcranial direct current stimulation (HD-tDCS) for memory deficits in those with amnestic mild cognitive impairment (MCI) in a 2x2 double-blind randomized controlled trial. Here, we report functional network connectivity results at the primary endpoint after 5 consecutive daily sessions.
Methods: A total of 78 participants with amnestic MCI completed functional magnetic resonance imaging (fMRI) before and 3-4 days after the 5-day intervention. During each MRI session, participants completed four functional runs, two during the encoding of object-location associations and the other two during face-name association encoding. Novel stimuli were used during each fMRI session. During the intervention sessions, participants completed either MST or an autobiographical recall (ABR) control condition and received active or sham HD-tDCS (2mA for 20 minutes/session) that targeted the left inferior frontal gyrus. Changes in brain connectivity, relative to baseline, were evaluated using network contingency analysis focusing on the brain's "high-level" association networks.
Results: For the active MST group, post- vs. pre-intervention analyses showed greater connectivity of the cingulo-opercular control network with the frontoparietal, default-mode, and ventral-attention networks, and between the default-mode and dorsal-attention networks, during performance of the face-name task. In addition, results showed greater connectivity of the default-mode network with the frontoparietal and ventral-attention networks during performance of the object-location task. Group by session interaction analyses further confirmed greater connectivity between the cingulo-opercular and frontoparietal control networks for the active MST group relative to the active ABR group, during face-name but not during object-location encoding.
Conclusions: Combining HD-tDCS and MST elicits enhancement of communication between task-relevant association networks in those with amnestic MCI. Future work will evaluate the persistence of effects at the brain level.

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SHIFT 01-542

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
2-3 April 2025

DIGITAL MULTIDOMAIN LIFESTYLE INTERVENTION FOR MILD COGNITIVE IMPAIRMENT: PROTOCOL FOR A PROSPECTIVE, MULTICENTER, RANDOMIZED, DOUBLE-BLINDED, AND CONTROLLED TRIAL

Myung Jin Ko[1], Hyun Jung Han[1], Yeonjoo Nam[2,3], Tae Hui Kim[2,3]
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Aims: This prospective, multicenter, double-blind, randomized controlled trial aims to evaluate the efficacy of *Silvia-Rx*, a digital multidomain intervention platform delivered via a tablet-based application, in enhancing cognitive function and reducing dementia risk among older adults with mild cognitive impairment (MCI).
Methods: A total of 180 participants aged 60 years or older, diagnosed with MCI, will be recruited across five sites. All participants will be randomly assigned in a 1:1 ratio to either the intervention or control group. The intervention group will receive a 12-week, 60-session multidomain intervention program, which includes adaptively leveled cognitive training, episodic memory exercises, physical activity programs, mindfulness practices, tailored education on dementia risk factors, daily mood and sleep check-ins, and a daily diary to support healthy lifestyle management and dementia risk reduction. The control group will receive only general health education contents and daily mood and sleep check-ins, delivered on a tablet device identical in appearance to that of the intervention group, over the same study period.
Results: The primary outcome will focus on the between-group comparison of changes in Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) total scores from baseline to study completion. Secondary outcomes will include assessments of depression, anxiety, stress, sleep quality, quality of life, and instrumental activities of daily living. Adherence to each intervention program will be used to assess feasibility. Outcomes will be measured both at baseline and post-intervention.
Conclusions: This trial will add new insights into the potential effectiveness and validity of a digital multidomain intervention in enhancing cognitive health and reducing dementia risk in older adults with MCI.

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SHIFT 01-543

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS
2-3 April 2025

DESIGNING AND TESTING A MULTI-DOMAIN SMARTPHONE INTERVENTION FOR PATIENTS WITH MILD COGNITIVE IMPAIRMENT

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Aims: Multi-domain interventions combining physical activity and cognitive trainings, have shown promise in slowing cognitive decline in individuals with mild cognitive impairment (MCI). With advances in smartphones and digital services, it is now possible to offer these interventions remotely while collecting data on user engagement. We developed a smartphone-based multi-domain intervention tailored for individuals with MCI and report on its application in a sample of MCI patients.
Methods: The program was developed for MCI patients aged 60–79, featuring a physical activity component adapted to each participant's fitness level, with exercises focused on walking and stretching. The cognitive training component included verbal and nonverbal activities designed to target multiple cognitive areas and was adapted to individual ability levels to encourage progress. Cognitive training consisted of verbal and nonverbal exercises along with a memory diary. Participants were divided into two groups: one accessed only the physical activity program, while the other engaged in both the physical and cognitive components.
Results: Eighteen participants used the app, with 11 in the physical training-only group and 7 in the combined program group. Engagement was generally higher in the physical activity component than in cognitive training. Participants who used the physical activity program alone showed a more pronounced improvement in cognitive function compared to those who used both interventions.
Conclusions: A smartphone-based, multi-domain intervention for patients with MCI was successfully developed, aimed at maintaining cognitive function. Further clinical trials are planned to confirm its efficacy.

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SHIFT 01-544

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

FEASIBILITY OF IDENTIFYING ACUTE INTRACEREBRAL HEMORRHAGE EVENTS USING DIAGNOSTIC CODING AMONG VETERANS WITH MILD COGNITIVE IMPAIRMENT OR ALZHEIMER'S DEMENTIA

Dan Berlowitz[1], Ying Wang[2], Joel Reisman[1], Peter Morin[3], Vanesa Carlota Arasa[4], Brant Mittler[5], Raymond Zhang[6], Amir Tahami Monfared[6], Michael Irizarry[6], Quanwu Zhang[6], Weiming Xia[3]
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Aims: This study evaluated the feasibility of using existing data collection systems with ICD-10 coding to accurately capture acute ICH events in patients with mild cognitive impairment (MCI)/ Alzheimer's dementia (AD).
Methods: We identified 200 patients with inpatient ICH ICD-10 code(s) in the first or second position of discharge diagnosis records from the administrative database of the Veterans Affairs Health System (VAHS; 2024). Corresponding discharge summary notes were manually reviewed to confirm presence, location, and etiology of ICH events.
Results: An acute ICH event was documented within discharge summary notes in 161/200 of patients corresponding to ICD-10 coding for ICH in the administrative database, which amounts to a positive predictive value (PPV) of 80.5% for confirming the presence of ICD-10 coded ICH event. The remaining 39/200 patients identified by ICD coding mostly had other documentation of relevant events in the discharge notes including e.g., stroke, either lacunar or basal ganglion but with no evidence of hemorrhage. Bleed location(s) was described in the discharge summaries in 151/161 confirmed ICH events. Among ICD-10 codes for ICH that specified a location, 79/110 had a location description consistent with the ICD-10 coding (PPV=71.8%). ICH etiology was noted for 56 of 161 patients and 12 of 56 (PPV=21.4%) cases had a description of etiology consistent with the ICD codes.
Conclusions: The use of ICD-10 codes for reporting presence of acute ICH events except for etiology in patients with MCI/AD carried a high PPV, validated through manual review of clinical notes in routine healthcare practice of the VAHS. The unconfirmed cases based-on the review of discharge summaries could be a result of miscoding; alternatively, the related ICH events might have been documented in other specialist notes.

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Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

IMPLEMENTING A CONSENSUS-DRIVEN ALZHEIMER'S DISEASE CARE PATHWAY AND EDUCATIONAL PILOT WITHIN PRIMARY CARE SETTINGS

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Aims: Organizations such as the Alzheimer's Association advocate for earlier detection of dementia and Alzheimer's disease (AD) to enable timely support. Earlier AD detection requires establishing pathways to appropriately screen, diagnose, and refer patients. This pilot seeks to educate and encourage primary care practitioners (PCPs) to adopt AD care pathways, understand implementation barriers, and identify optimization opportunities.
Methods: In May 2023, a group of multidisciplinary dementia experts convened to develop an AD consensus care pathway. The care pathway was implemented among three sites: University of North Carolina (UNC) and Midwestern University (MWU) clinics in Illinois and Arizona. The site leads completed educational sessions with PCPs while administering baseline, 1-month, and 3-month follow-up assessments.
Results: Twenty PCPs across all sites completed the baseline assessment, and 4 UNC PCPs completed both follow-up assessments to date. Although 90% (n=18) of participants believed adopting a care pathway could improve early diagnosis of AD at baseline, only 10% were familiar with any recommended AD protocol. UNC baseline results indicated that 0-25% of participants agreed with statements regarding an understanding of when to refer, what differences exist between different AD stages or the appropriate use of available biomarker testing. 100% of participants agreed with such statements following training. Participants reported multiple barriers to implementing pathway guidelines, including time limitations for conducting assessments and inability to order tests within the electronic health record (EHR).
Conclusions: The initial results from the pilot highlighted gaps in PCP awareness and training which improved after the educational intervention, with initial data indicating increased confidence and understanding of AD risk stratification, diagnosis, and referral practices. Future opportunities to enhance care pathway adoption include embedding it directly into the EHR to streamline processes.

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SHIFT 01-546

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

PATIENT ADVISORY BOARD FOR DEMENTIA RESEARCH (PART-BEIRAT): A QUALITATIVE EXAMINATION OF STAKEHOLDER PERSPECTIVES REGARDING PARTICIPATORY RESEARCH

Marcel Daum[1], Eva Drewelow[2], Kai Gerullis[2], Ingo Kilimann[3], Birgit Völlm[2], Stefan Teipel[4], Olga Biernetzky[3]
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Aims: As part of our ongoing PART project, we aim to establish a sustainable structure to include underrepresented patient groups with neurodegenerative diseases in participatory research. One of our milestones involved gathering multi-perspective experiences, opinions, ideas and concerns regarding participatory research.
Methods: Guided interviews were conducted with professional researchers and clinicians as well as with patients with neurodegenerative diseases and relatives. They were asked to imagine the structure, roles and objectives of participatory research in general, as well as those of a participatory advisory board specifically. Additionally, they shared their perspectives on the opportunities and challenges associated with this participatory research as well as framework conditions and support needs for successful implementation. The interviews were audio-recorded and transcribed. Data was analysed with MAXQDA using thematic analysis.
Results: In total, 10 interviews with stakeholders and 10 interviews with patients and relatives were conducted. Data indicate great interest in participatory research, although the term was mostly unknown and experience was very limited. The respondents identified opportunities for participatory research, but also challenges that need to be overcome for implementation. Both groups emphasised the importance of participatory research and a participatory advisory board, especially in the field of neurodegenerative diseases.
Conclusions: The results will be incorporated into the structure of the advisory board, so that participatory research in the field of neurodegenerative diseases can be tailored to the needs and expectations of both researchers and patients and relatives.

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Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

PRE-DIAGNOSTIC FEATURES OF DEMENTIA IN A PRIMARY CARE DATASET

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Aims: Dementia is the leading cause of death in the UK (Office of National Statistics). General practice dementia data is regularly recorded from London General practices (GP) (NHS England), where London is simplistically grouped into 4 regions. The risk of dying from dementia is increased in deprived areas such as East London. Greater understanding of risk factors and patient characteristics is needed to inform and implement preventative medicine approaches. This includes the in-depth study of dementia apatient cohorts to further understanding of clinical attributes and comorbidities that correlate with progression into dementia.
Methods: A cohort study of 'dementia' and 'coded patients from an East London GP practice (>10,000 patients). Analysis and characterisation of dementia cohort demographics, medical history and drug chart is being undertaken with a focus on different dementia types, including vascular dementia incidence and current dementia severity. Early prodromal dementia symptoms are being recorded. These data will be analysed in comparison to an age-matched control cohort from the GP practice to ascertain any early symptoms that correlate with dementia type or severity.
Results: *Data is currently under analysis*
Conclusions: *Data is currently under analysis*

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SHIFT 01-548

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

HEARING LOSS AND THE RISK OF DEMENTIA: A LONGITUDINAL ANALYSIS OF THE KOREAN NATIONAL HEALTH INSURANCE SERVICE SENIOR COHORT

Jae Won Jang
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Aims: Hearing loss is implicated as a potentially modifiable risk factor for dementia. Recent research suggests a correlation between age-induced hearing loss and dementia. The aim of this study is to investigate the association between hearing loss and dementia.
Methods: This study analyzed data from 440,017 subjects from The Korean National Health Insurance Service-Senior Cohort (2002-2008), excluding those diagnosed with dementia before hearing loss and those diagnosed with hearing loss after 2008. Statistical analysis included Pearson's chi-squared test and Cox proportional hazards model. Subjects with hearing loss were matched with a control group, considering factors such as age and gender. Subgroup analysis was conducted for Alzheimer's disease (AD) and vascular dementia (VaD).
Results: Subjects with hearing loss showed a 1.183 times higher risk of all-cause dementia than those without (adjusted hazard ratio for 3-year timespan, 95% CI=1.138–1.230). The adjusted hazard ratios for AD across 3, 5, 7, and 10-year timespans were 1.190 (95% CI=1.141–1.241), 1.195 (95% CI=1.143–1.248), 1.199 (95% CI=1.143–1.257), and 1.173 (95% CI 1.104–1.245), respectively. No significant association was found between hearing loss and VaD.
Conclusions: Hearing loss consistently increased the risk of all-cause dementia and AD over various timespans, suggesting a complex interplay between hearing loss and neurodegenerative diseases. These findings emphasize the importance of early intervention and ongoing cognitive monitoring in individuals with hearing loss.

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SHIFT 01-549

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

EXPLORING THE RELATION BETWEEN PHYSICAL ACTIVITY, ALZHEIMER'S DISEASE PLASMA BIOMARKERS, AND COGNITION

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Aims: Physical activity (PA) is a non-pharmacological intervention for dementia prevention. The relationship between PA and Alzheimer's disease (AD) plasma biomarkers remains underexplored. Our objective is to investigate the association between PA, plasma biomarkers (Aβ42/40, pTau217, GFAP, NfL), and cognition, and whether plasma biomarkers mediate the effect of PA on cognitive function.
Methods: This is a cross-sectional multi-center cohort recruited between January 2018 and December 2020. Participants included 1,144 individuals with unimpaired cognition, mild cognitive impairment, or dementia. PA was assessed via the International Physical Activity Questionnaire and categorized into quartiles. Plasma levels of Aβ42/40, pTau217, GFAP, and NfL were measured. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) and Clinical Dementia Rating-Sum of Boxes (CDR-SB).
Results: Among the 1,144 participants (mean age 70.9 years, 65.0% female), higher PA levels were significantly associated with lower pTau217 (Estimate (Standard Error) -0.141 (0.055), p = .01) and NfL (-0.124 (0.049), p = .01) compared to the lowest quartile. GFAP showed no significant association, but a trend was noted (fully adjusted model: -0.097 (0.051), p = .06). Higher PA quartiles (Q) had better cognitive outcomes, with higher MMSE scores (adjusted for age, sex, education years, Aβ uptakes Q2-Q4: 0.929 (0.313)–0.939 (0.321), p = .007) and lower CDR-SB scores (Q2-4: -0.333 (0.160) to -0.551 (0.164), p = .001). Mediation analysis showed that pTau217 and NfL partially mediated the effect of PA on cognition, with PA also having a direct association, particularly with CDR-SB scores.
Conclusions: Higher PA levels are associated with lower pTau217 and NfL, and better cognition, suggesting that PA may delay cognitive decline by modulating neurodegeneration and AD-specific tau pathologies. These findings support PA as a potential intervention for managing cognitive impairment.

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SHIFT 01-550

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

DIFFERENTIAL DIAGNOSIS OF NORMAL COGNITION, MILD COGNITIVE IMPAIRMENT AND DEMENTIA IN ILLITERATE SUBJECTS: CIST (COGNITIVE IMPAIRMENT SCREENING TEST) AND K-MMSE

Byeong C. Kim[1], Seong-Min Choi[2], Soo Hyun Cho[1], Min-Kyung Song[1,3], Sujeong Jang[4], Han-Seong Jeong[4]
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Aims: The Cognitive Impairment Screening Test (CIST) was developed by the Korean Ministry of Health and Welfare and has been used at dementia centers of South Korea since January 2021. The CIST consists of orientation, memory, attention, visuospatial function, language, and executive function (a total score of 30). The CIST's results are determined as normal cognition if they are above the cutoff score depending age and education level. This study aimed to evaluate the usefulness of CIST among normal cognition (NC), mild cognitive impairment (MCI), and dementia in illiterate subjects.
Methods: We retrospectively included the illiterate subjects who visited the dementia relief centers of Gwangju City and the dementia clinic of Chonnam National University Hospital. The evaluation tools used for the differential diagnosis of normal cognition, MCI and dementia were either Seoul Neuropsychological Screening Battery (SNSB) or Korean version of the Consortium to Establish a Registry for Alzheimer's disease (CERAD-K). All subjects were tested CIST and K-MMSE for screening.
Results: This study included 110 subjects in total: 27 with NC, 37 MCI, and 36 dementia for analysis. Demographic data show in age (mean±SD years: 78.11±3.18, 80.68±5.38, and 84.33±5.63) and female gender proportion (92.6, 83.8, and 91.7%) among three groups (NC, MCI, and dementia). These three groups demonstrated CIST scores (mean±SD: 15.89±4.88, 11.32±3.12, and 7.51±3.71) and K-MMSE scores (mean±SD: 20.96±3.80, 17.72±4.24, 10.43±5.29). The correlation between total CIST and K-MMSE scores was a statistically significant in all three groups.
Conclusions: We founded that there was a well correlation between CIST and K-MMSE among NC, MCI, and dementia with illiteracy.

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SHIFT 01-551

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

DEMENTIA TREATMENT PATTERNS ASSOCIATED WITH NATIONAL POLICY IN KOREA AMONG PATIENTS WITH NEWLY DIAGNOSED ALZHEIMER'S DISEASE

Jun Hong Lee
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Aims: South Korea has actively addressed combating dementia since 2008, expanding mandatory long-term care insurance (LTCI) for dementia patients in 2014. This study aimed to investigate changes in treatment patterns for Alzheimer's disease (AD).
Methods: This multicenter, retrospective, observational study of patients with newly diagnosed AD analyzed electronic medical records from 17 general hospitals. Based on their time of AD diagnosis, categorized into Cohort 1 (1 July 2011 to 30 June 2014) and 2 (1 July 2014 to 30 June 2017).
Results: Subjects (N=3,997) divided into Cohorts 1 (n=1,998) and 2 (n=1,999), were mostly female (66.4%) with a mean age of 84.4 years. Cohort 1 subjects were significantly older (P<0.0001) and had a lower number of comorbidities (P=0.002) compared with Cohort 2. Mean Mini-Mental State Examination (MMSE) scores in Cohorts 1 and 2 at the time of AD diagnosis or start of initial treatment were 16.87 and 17.09, respectively (P=0.2790). At 1 year, mean MMSE scores in Cohorts 1 and 2 increased to 17.89 and 17.43, respectively (P=0.1524). Donepezil was the most frequently administered medication overall (75.01%), with comparable rates between cohorts. Discontinuation and switch treatment rates were significantly lower (49.72% *vs*. 58.01%; P<0.0001), and mean duration of initial treatment significantly longer, in Cohort 2 *vs*. 1 (349.28 *vs*. 300.21 days; P<0.0001).
Conclusions: Comparison of cohorts before and after revision of the national LTCI system for dementia patients found no significant difference in mean MMSE scores (time of AD diagnosis or start of initial treatment). The reduction in the proportion of patients who discontinued or changed their initial treatment, and the significant increase in mean duration of treatment, are attributed to revision of the LTCI policy which enabled increased patient access to long-term care.

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SHIFT 01-552

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
2-3 April 2025

STRUCTURAL BRAIN CHANGES AS MEDIATORS OF THE IMPACT OF BODY COMPOSITION ON GAIT VELOCITY IN MILD COGNITIVE IMPAIRMENT

Yeo Jin Kim[1], Dongwon Lee[1], Ingyu Park[2], Sang-Kyu Lee[3], Hui-Chul Choi[3], Moo-Eob Ahn[3], Ohk-Hyun Ryu[3], Unjoo Lee[2]
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Aims: The gait disturbances, such as changes in walking speed, rhythm, and stability, is known to associated with cognitive decline and are more easily observed than subtle cognitive changes. However, the underlying mechanisms contributing to gait dysfunction in individuals with MCI remain poorly understood. This study investigated whether body composition mediates structural brain alterations, thereby influencing gait speed in MCI patients.
Methods: Eighty patients diagnosed with MCI were recruited from three dementia centers in Gangwon-do, Korea. MCI was defined as a Clinical Dementia Rating (CDR) global score of ≥ 0.5, with a memory domain score of ≥ 0.5. Gait velocity was quantitatively assessed using GAITRite, a device designed for gait analysis and body composition was assessed using dual-energy X-ray absorptiometry. 3D Slicer and FreeSurfer softwares were used to measure the gray matter. BIANCA software in FSL was used for the white matter hyperintensities in MRI images. The MRI images, including T1 weighted and FLAIR MRI images in DICOM format. Causal mediation analyses were conducted to examine whether the association between the body composition and gait velocity was mediated by gray matter and white matter measurements.
Results: The total bone mineral density (BMD), total area, total body fat, BMD, bone mineral content (BMC), fat mass of both legs, lean BMC of the left leg, BMD, BMC, fat mass of both arms, and the total and lean mass of the left arm were associated with gait velocity. The gray matter volume, the curvature index and the volumes of white matter hyperintensity significantly mediated the associations between body composition parameters and gait velocity.
Conclusions: Body composition is associated with gait velocity and is mediated by structural changes in gray matter and white matter.

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SHIFT 01-553

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
2-3 April 2025

INTERPLAY OF NON-MOTOR SYMPTOMS IN NOVO PARKINSON'S DISEASE: ASSOCIATION AMONG COGNITION, FATIGUE, DEPRESSION, ANXIETY, AND DYSAUTONOMIA

Kyum-Yil Kwon
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Aims: This study investigates the interrelationship between non-motor symptoms such as cognition, fatigue, depression, anxiety, and dysautonomia in patients with de novo Parkinson's disease (PD). The aim is to determine the correlation between these symptoms and their impact on the clinical profile of these patients.
Methods: A total of 82 patients with de novo PD were assessed. Non-motor symptoms were evaluated using standardized scales: Montreal Cognitive Assessment (MoCA) for cognition, Parkinson's disease Fatigue Scale (PFS) for fatigue, Beck Depression Inventory (BDI) for depression, Beck Anxiety Inventory (BAI) for anxiety, and Scales for Outcomes in Parkinson's disease – Autonomic (SCOPA-AUT) for dysautonomia. Partial correlation analysis was performed, adjusting for demographic and disease-related variables.
Results: Fatigue, as measured by PFS, showed significant positive correlations with depression (BDI; $r = 0.5183$, $p < 0.0001$), anxiety (BAI; $r = 0.4062$, $p = 0.0003$), and dysautonomia (SCOPA-AUT; $r = 0.5549$, $p < 0.0001$). Depression (BDI) was also positively correlated with anxiety (BAI; $r = 0.6252$, $p < 0.0001$) and dysautonomia (SCOPA-AUT; $r = 0.4702$, $p < 0.0001$). Anxiety (BAI) demonstrated a significant positive correlation with dysautonomia (SCOPA-AUT; $r = 0.3716$, $p = 0.001$). However, cognition, as assessed by MoCA, did not show a significant correlation with the other non-motor symptoms.
Conclusions: Non-motor symptoms in patients with de novo PD are interrelated, particularly fatigue, depression, anxiety, and dysautonomia, which are closely connected. These findings suggest the need for a comprehensive approach in managing these symptoms to improve the overall quality of life in these patients.

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SHIFT 01-554

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / CAREGIVER SUPPORT
2-3 April 2025

NAVIGATING COMPLEX NEURODEGENERATIVE CARE: A SUPPORTIVE CARE CLINIC INITIATIVE

Natalie Hellmers[1], Melissa Lopez[1], Abigail Weiss[1], Andrea Yoo[2], Hwai Yin Ooi[2], Harini Sarva[2]
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Aims: To evaluate early findings from our center's newly established Lifestyle, Improvement, Fitness and Togetherness (LIFT) Supportive Care and Wellness Program offered to advance Parkinson's Disease and Alzheimer's Disease patients.
Methods: Patients were referred by doctors from our practice and scheduled for an hour-long visit with the supportive care nurse practitioner and social worker. Pre-appointment surveys were provided and at the end of their visit each left with an individualized care-plan selected using the wellness framework.
Results: Currently 80 patients are enrolled and had a primary visit. Patient ages ranged from 59 to 91 (Mean 76, SD+/- 9.4) . Over 60% arrived with caregivers (spouse, son, daughter, friend). Life satisfaction scores of patients were below the general health population (Mean 35.07, SD+/- 12.62, range 13-56). Fall prevention, future life planning, and access to physical therapy were frequently requested topics. Zarit Burden Interview scores of caregivers indicated a moderate to severe range (Mean 33.25, SD +/- 12.3, range 20 to 54). Patients and caregivers expressed satisfaction from their preliminary visit.
Conclusions: The LIFT program attempts to offer problem-focused visits with allocation of resources towards needs that are important to patient and caregiver. Early findings indicate that there is a sense of caregiver burden and decreased quality of life in this population that needs more support. This program will be updated and adapted over time to align with the shifting needs of our patients.

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SHIFT 01-555

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / MOTOR COORDINATION & EXERCISE
2-3 April 2025

ASSOCIATION BETWEEN GAIT MONITORING USING WEARABLE SENSORS AND SACOPEINA ASSESSING MUSCLE MASSS, STRENTHS AND PHYSICAL PERFORMANCE IN ELDERY PEOPLE

Seol-Heui Han[1], Jinyoung Shin[2], Hyun Jung Han[3]
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Aims: Gait parameters are indicators that correlate with the onset of sarcopenia and decline in physical performance. However, studies exploring the correlation between real-time gait monitoring using wearable sensors and sarcopenia are limited. This study aimed to investigate the association between gait parameters measured using wearable sensors and sarcopenia based on measurements of muscle mass, strength, and physical performance in community-dwelling older adults.
Methods: In a cross-sectional study of 91 participants aged ≥ 65 years, gait parameters including step count, step length, cadence, single and double support times, vertical oscillation, and instantaneous vertical loading rate (IVLR) were analyzed in relation to sarcopenia. This study was performed at an outpatient clinic of a university hospital in Seoul, Korea, between July 10, 2023, and November 1, 2023. Sarcopenia was defined by various measurements: calf circumference, SARC-F questionnaire responses, handgrip strength, appendicular skeletal muscle mass index (SMI) using bioelectrical impedance analysis, 5-time chair stand test, and short physical performance battery (SPPB).
Results: Among the 91 participants (45 men and 46 women; mean age: 74.1 for men and 73.6 for women), gait speed, vertical oscillation, and IVLR were negatively associated with the 5-time chair stand test and SARC-F, and positively associated with SPPB. Vertical oscillations are also associated with grip strength. Gait speed and single support time were associated with SMI. However, the statistical significance of the association disappeared after adjusting for age, sex, waist circumference, body mass index, and comorbidities. The relationship between these gait parameters and sarcopenia was independently consistent (Bonferroni correction, $p < 0.05$) in the multiple regression analysis.
Conclusions: Gait monitoring with wearable sensors correlated with sarcopenia in older adults, confirming its utility in assessing muscle mass, strength, and physical performance.

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SHIFT 01-556

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / MOTOR COORDINATION & EXERCISE
2-3 April 2025

PARKINSON'S DISEASE AND ROUTINE TRAFFIC STOPS: AN EXPLORATION OF PATIENT EXPERIENCES AND PERCEPTIONS

Rebecca Irvine[1], Alexis Kruger[2], Alfred Quaicoe[3], Roshni Kotwani[4], Anna Hohler[5], Oceanis Vaou[6]
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Aims: Parkinson's disease (PD) is a chronic, debilitating neurological disorder which can impair motor function, behavior, and even cognition as the disease progresses. Due to their medical status, PD patients have a reduced ability to complete complex motor tasks, such as driving. There is currently a lack of research into the effectiveness of police officers accurately discerning PD symptoms from similar symptoms exhibited as a result of alcohol intoxication. This study aimed to investigate PD patients' perceptions of police interactions during routine traffic stops.
Methods: A survey was conducted amongst 58 patients with Parkinson's Disease, and 52 age-matched controls. The primary study objective was the self-reported response to questions about the frequency of police stops and incidents of mishandling by these interactions.
Results: Our study found a statistically significant difference in the perception of mistreatment and misclassification of intoxication in the PD cohort, compared to age-matched controls.
Conclusions: We propose the need for a more extensive training program surrounding PD and other neurological conditions for law enforcement officers to ensure that patients are being evaluated appropriately and fairly.

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SHIFT 01-557

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / MOTOR COORDINATION & EXERCISE
2-3 April 2025

EDUCATIONAL ATTAINMENT AND MOTOR RESERVE AS A MODIFIER OF LONG-TERM MOTOR FUNCTION IN PARKINSON'S DISEASE

Mia Kim[1], Thomas Tropea[2]
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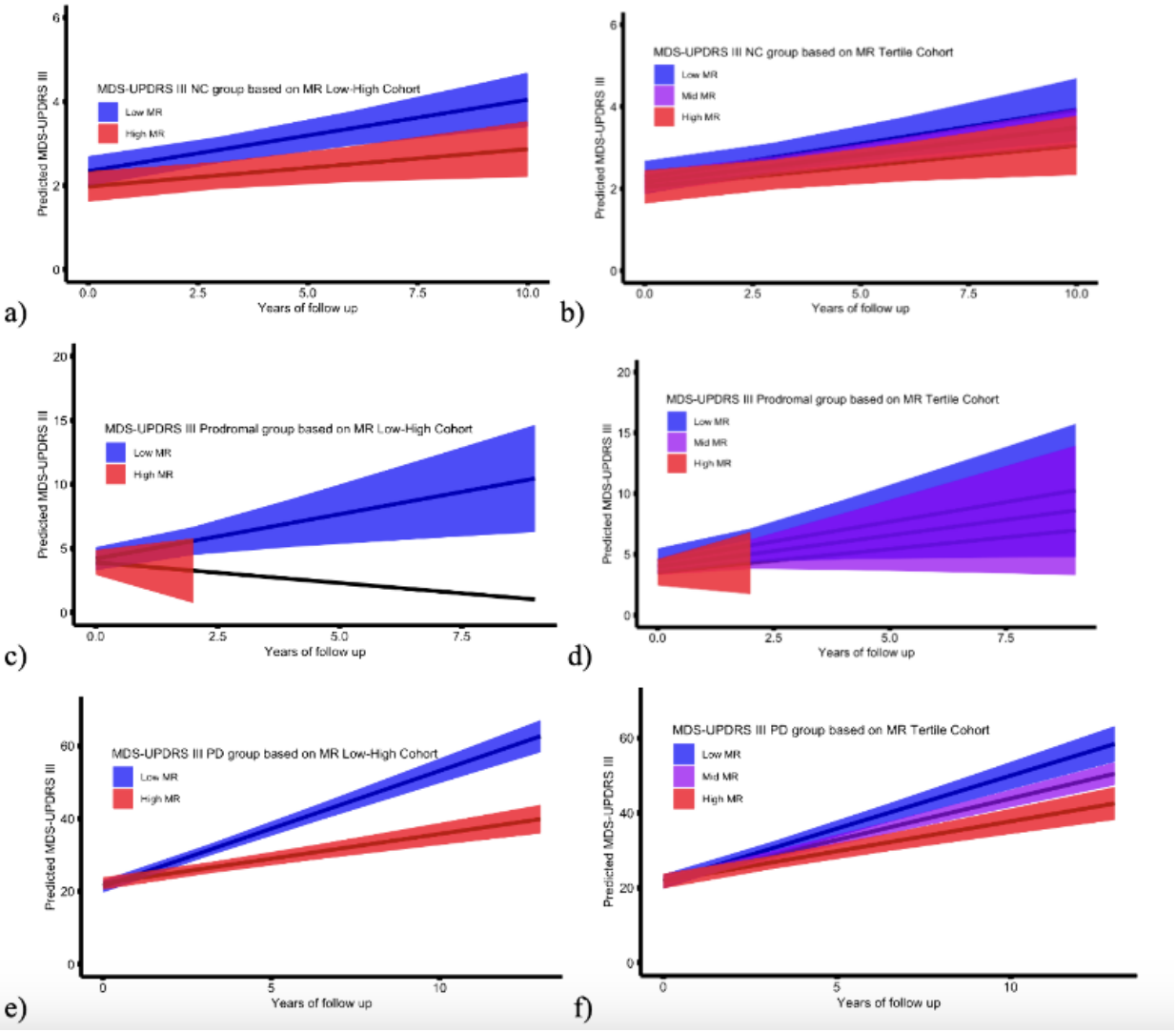
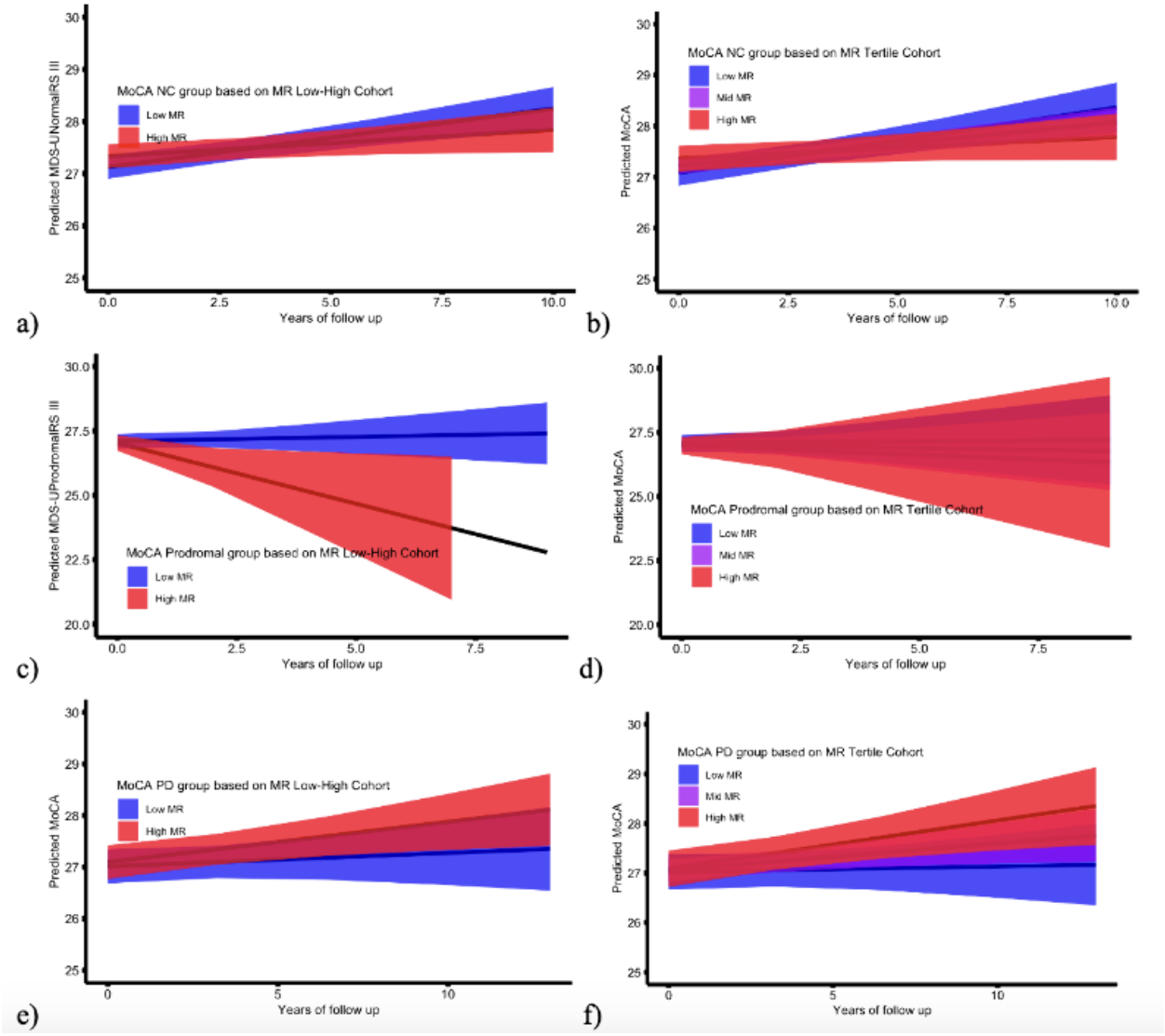
Aims: The goal of this research was to elucidate the impacts of the phenomena of motor reserve (MR) on longitudinal motor function in Parkinson's Disease (PD).
Methods: A de novo proxy for MR was constructed as a linear scaling factor from a baseline of the average years of education from 2022 U.S. census data, and the recommended amount of weekly exercise from the Department of Health and Human Services.
One-way Analysis of Variance (ANOVA) was used to compare the low and high MR groups at baseline, of which no significant differences were found.
Linear mixed-effects models (LMEs) with baseline age, baseline Unified Parkinson's Disease Rating Scale Part III (UPDRS-III)/Montreal Cognitive Assessment (MoCa), and sex covariates were used to compare participants' cognitive and motor function over time.

Figure 1. Predicted MDS-UPDRS III for NC (a,b), Prodromal (c,d), and PD (e,f) Participants Based on Low-High Dichotomization (a,c,e) and Tertiles (b,d,f)



Results:

Figure 2. Predicted MoCa for NC (a,b), Prodromal (c,d), and PD (e,f) Participants Based on Low-High Dichotomization (a,c,e) and Tertiles (b,d,f)



In terms of motor function, for the PD groups, both in low-high dichotomization and tertiles of MR there was a significant difference in the interaction term of UPDRS III as predicted over years of follow-up by MR ($p = 0.0000$ for both, Figure 1.e. & 1.f).

Comparatively, no significant differences were found for the prodromal group ($p = 0.16$ for dichotomized groups, $p = 0.76$ for tertiles, Figure 1.c. & 1.d) or NC groups ($p = 0.13$ for dichotomized groups, $p = 0.34$ for tertiles, Figure 1.a. & 1.b).

Conclusions: These findings suggest that PD participants with high MR may experience lesser detriments to motor function over time than those with low MR (as well as for high, medium, and low tertiles). The fact that no such differences were found for the MoCa LME's (Figure 2) indicates MR may predominantly be influencing symptoms related to motor function, rather than cognitive function—a potential distinction from cognitive reserve.

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SHIFT 01-560

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
2-3 April 2025

THE HEATLHCARE PATHWAYS OF PEOPLE WITH A MIGRATION BACKGROUND AND PARKINSON'S DISEASE OR ATYPICAL PARKINSONISM: NEEDS, BARRIERS, AND EXPERIENCES

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Aims: This study aims to explore the healthcare experiences and treatment needs of people with a migration background and Parkinson's disease (PD) or atypical parkinsonism (AP) living in the Netherlands. The symptoms and patterns of disease progression vary significantly across individuals which leads to wide differences in patient needs and preferences. These needs may be further influenced by factors such as language barriers, cultural background, and disease knowledge. Additionally, the advanced care pathway, which involves frequent check-ups, and ongoing adjustments to treatment, poses unique challenges for these individuals. This study seeks to identify factors impacting their experiences, access to and unmet needs.
Methods: We use qualitative research methods. To date, six in-depth interviews have been conducted with people living with PD or AP, with additional interviews planned for a total of approximately twenty participants. Participants that are included have diverse backgrounds (i.e. Moroccan, Turkish, Dominican, Cape Verdean). Data is collected on participant's healthcare pathway, including their experiences with diagnosis, treatment, and ongoing care. The interviews are transcribed verbatim and analyzed using Atlas.ti.
Results: The data is currently being analyzed. Preliminary findings reveal that many participants reported delays in receiving a diagnosis. This is demonstrated by one participant who stated, "Two years I was day and night with my complaints. Day and night and she [general practitioner] said you don't have anything, take a paracetamol". To date, other reported challenges include language barriers and lack of PD knowledge.
Conclusions: It is of importance to ensure that care is sufficiently tailored to the diverse populations and that their needs are met. Results of this study will identify key areas for improving the healthcare pathway for people with a migration background and PD or AP.

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SHIFT 01-561

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
2-3 April 2025

APATHY IS ASSOCIATED WITH POOR SLEEP QUALITY IN PATIENTS WITH EARLY PARKINSON'S DISEASE

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Aims: Apathy and sleep disturbance are common non-motor symptoms (NMSs) in early Parkinson's disease (PD), but the relationship between the two has not been well investigated. This study aimed to determine the extent to which apathy and sleep disturbances are present in people with early PD and whether apathy affects sleep quality.
Methods: We enrolled early PD patients with modified Hoehn-Yahr (mHY) stages 1 to 3 and disease duration ≤ 5 years. Demographic characteristics were collected, and motor and non-motor symptoms including apathy and sleep disturbance were investigated with relevant scales. Spearman correlation and Partial correlation analyses were used to determine the relationship between variables.
Results: Of 302 PD patients, apathy was found in 97 (32.1%) patients. Apathetic PD patients had significantly longer formal education, higher mHY stage, and higher parts II score of Unified Parkinson's Disease Rating Scale (UPDRS-II score). In terms of non-motor variables, patients with apathetic PD had significantly higher Non-Motor Symptom Scale (NMSS) total; Beck Depression Inventory (BDI); Apathy evaluation Scale (AES-S); and Pittsburgh Sleep Quality Index (PSQI) global scores than patients with non-apathetic PD. Spearman correlation analysis showed that sex, formal education, UPDRS-II; NMSS total; MMSE; BDI; and AES-S scores were significantly correlated with the PSQI global score. For each component of the PSQI, only sleep latency differed between apathetic and non-apathetic PD patients. Partial correlation analyses to determine the association between apathy and sleep disturbance revealed a significant positive correlation.
Conclusions: Apathy is not uncommon and is associated with poor sleep quality in early PD. Identifying and treating apathy may help improve sleep quality in early PD patients with sleep disturbances.

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SHIFT 01-562

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / QUALITY OF LIFE
2-3 April 2025

FATIGUE AND QUALITY OF LIFE IN PATIENTS WITH EARLY PARKINSON'S DISEASE

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Aims: Fatigue is a common and disabling non-motor symptom of Parkinson's disease (PD) and can significantly affect the health-related quality of life (HRQoL) of PD patients. This study aimed to investigate the clinical determinants of fatigue and its impact on HRQoL in patients with early PD.
Methods: The study included 199 early PD patients with modified Hoehn-Yahr (mHY) stage 1-3 and a disease duration of ≤ 5 years. Demographic information was collected, and motor and non-motor symptoms were evaluated using relevant scales.
Results: Fatigue was present in 44 of the 199 PD patients (22.1%). PD patients with fatigue were older and had a higher age of symptom onset compared to those without fatigue. Analysis of covariance (ANCOVA), controlling for age and symptom onset age, revealed that PD patients with fatigue had higher scores in mHY stage, the Unified PD Rating Scale-II (UPDRS-II), the Fatigue Severity Scale (FSS), and the Parkinson's Disease Questionnaire-8 (PDQ-8) compared to patients without fatigue. Clinical variable independently associated with the FSS score was the UPDRS-II score. Univariate regression analysis revealed that PDQ-8 scores were significantly associated with age, sex, symptom onset age, formal education duration, mHY stage, UPDRS-III, UPDRS-II, MMSE, and FSS scores. In multivariate regression analysis, the independent predictors of PDQ-8 scores were UPDRS-II and FSS scores.
Conclusions: This study suggests that fatigue is an independent predictor of HRQoL in early PD. Therefore, identifying and managing fatigue could help improve HRQoL in patients with early PD.

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SHIFT 01-563

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / QUALITY OF LIFE
2-3 April 2025

EXPLORING THE IMPACT OF DIAGNOSIS FOR PEOPLE WITH PARKINSON'S DISEASE AND THEIR CAREGIVERS IN TANZANIA

Miriam Giblin[1], Natasha Fothergill-Misbah[2], Matthew Breckons[2], Catherine Dotchin[3], Harry Wilson[1], Marieke Dekker[4], Jane Rogathe[4], Sarah Urasa[4], Declare Mushi[4], Richard Walker[3]
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Aims: This research aims to understand the impact that a diagnosis has on PwP and their caregivers in Tanzania, to inform future policy and practice to better support people impacted by PD in Tanzania.
Methods: Qualitative data were collected using semi-structured interviews with PwP and caregivers in the Kilimanjaro region of northern Tanzania. Purposeful maximal variation sampling was used to recruit participants. Audio recordings were translated and transcribed and reflexive thematic analysis was applied.
Results: Twelve PwP and eight caregivers were interviewed. Data from interviews identified that a diagnosis shifted uncertainty from being driven by the unknown cause of symptoms and complex diagnostic journeys to the challenge of navigating a diagnosis of PD with limited information. Most participants reported acceptance and relief upon receiving a diagnosis. A diagnosis had varied impacts on hope for PwP and their caregivers, however consistent hope manifested through spirituality.
Conclusions: Receiving a diagnosis of PD is important to PwP and caregivers in Tanzania. It provides a sense of legitimacy and is a gateway to accessing medicines. Increasing awareness of PD and removing the financial barriers to healthcare would increase diagnoses. This should be accompanied by better availability of specialist neurological and informal services for PwP.

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SHIFT 01-564

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / SUPPORT DEVICES & MONITORING
2-3 April 2025

EFFECTS OF ROTIGOTINE ON SLEEP IN PARKINSON'S DISEASE PATIENTS: A PARKINSON'S KINETIGRAPG STUDY

Carin Janz[1], Sotirios Grigoriou[1], Malcolm Horne[2], Filip Bergquist[3], Nil Dizdar[4], Per Odin[1]
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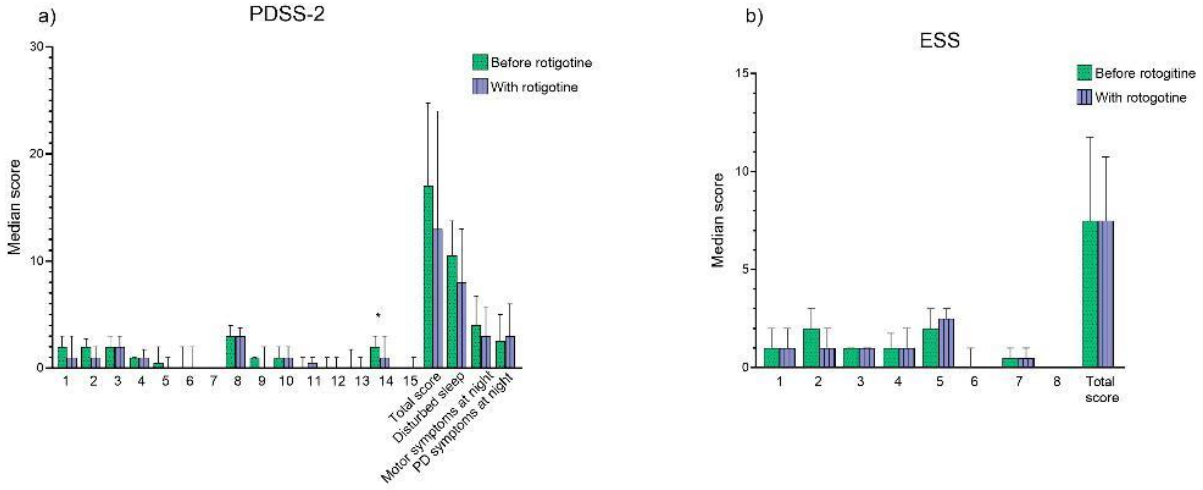
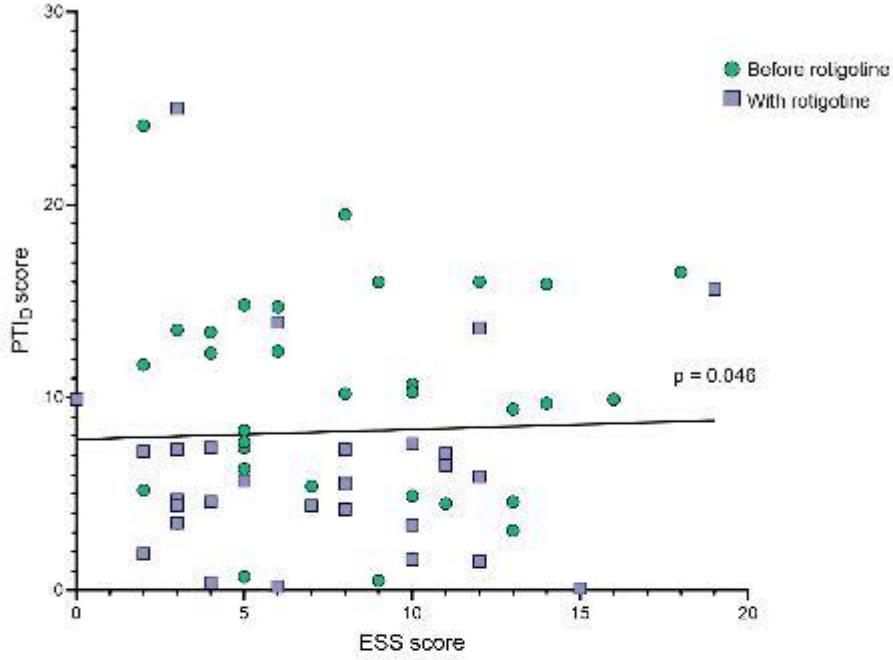
Aims: The aim was to investigate the effect of rotigotine on sleep in Parkinson's disease (PD) patients using the Parkinson's Kinetigraph (PKG) and questionnaires. Secondarily, the effects of rotigotine on daytime sleepiness, motor symptoms, quality of life and correlations between PKG variables and rating scales were investigated.
Methods: 32 PD patients with sleep disturbances were included in this observational study. Before start of treatment and during stable dose with rotigotine patients were assessed with Parkinson's disease sleep scale 2 (PDSS-2), Epworth Sleepiness Scale (ESS), Parkinson's disease quality of life questionnaire (PDQ-8), European Quality of life five dimensions (EQ-5D-5L) questionnaires and PKG recordings (24h/day for 6 days). Clinicians evaluated sleep using global impression scale and PD severity using Clinical Impression of Severity Index for Parkinson's Disease (CISI-PD).
Results: Rotigotine did not significantly improve total PDSS-2 or PKG nighttime scores. Treatment improved percent time tremor (PTT; $p<0.001$), percent time immobile during daytime (PTID; $p<0.001$), CISI-PD ($p<0.001$), PDQ-8 ($p=0.014$), and EQ-5D-5L ($p=0.002$). No significant correlations were found between PTI_D and ESS-total ($\rho=-0.046$, $p = 0.718$) or between combined sleep score (CSS) and PDSS-2 total ($\rho=-0.065$, $p = 0.612$). Subtotals for "Disturbed sleep", and "PD symptoms at night" improved on PDSS-2 ($p=0.013$ and $p=0.041$) for patients with PDSS-2 ≥18 at baseline and total PDSS-2 improved in dopamine agonist (DA) naïve patients

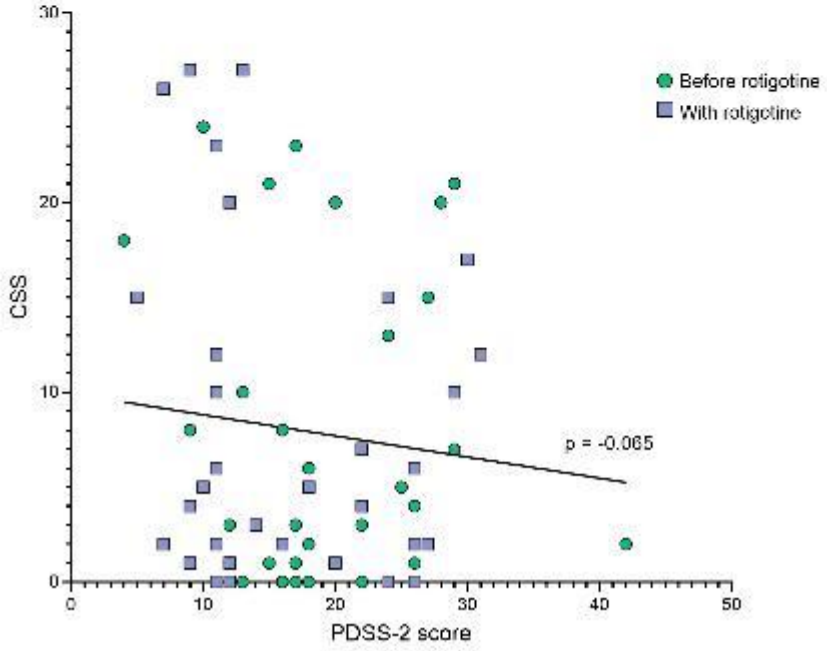

a)
PDSS-2
Median score
Before rotigotine
With rotigotine
Total score
Disturbed sleep
Motor symptoms at night
PD symptoms at night
b)
ESS
Median score
Before rotogitine
With rotogotine
Total score

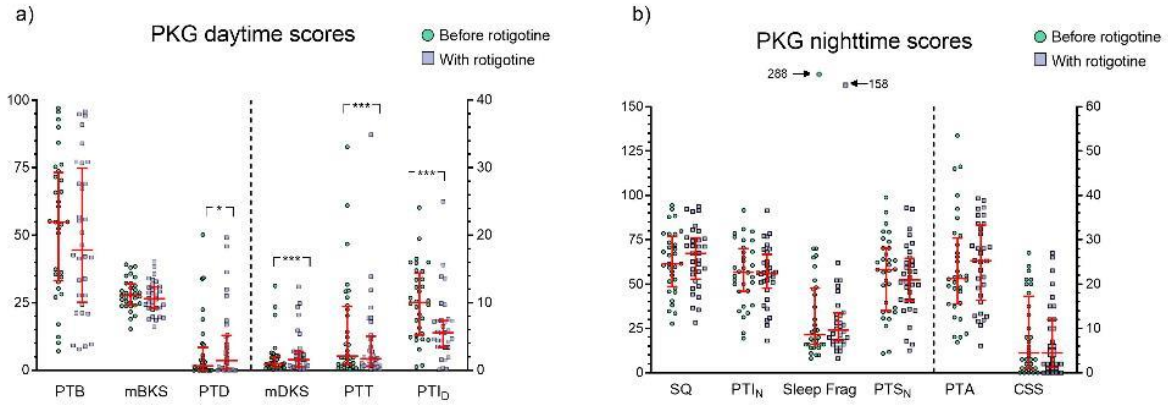
(p=0.013).

a) Correlation between ESS and PTI_D



b) Correlation between PDSS-2 and CSS





Conclusions: Rotigotine treatment was associated with improvement in motor function and quality of life. Also, sleep improved in DA-naive patients and those with more severe baseline symptoms. Daytime sleepiness was not exacerbated. Whether the improved PTI_D reflects a positive impact on daytime sleepiness or just improved mobility and to what extent PKG nighttime scores accurately represent sleep variables remains to be investigated in further studies.

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SHIFT 01-565

Poster on Board - Shift 01
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / SUPPORT DEVICES & MONITORING
2-3 April 2025

PATIENTS PERSPECTIVE ON THE FINANCIAL BURDEN OF ALS IN THE REPUBLIC OF KAZAKHSTAN AND A CALL FOR CHANGE

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Aims: Aim: Given the unmet needs of ALS patients in the Republic of Kazakhstan (RK) and the importance of financial and economic data for dialogue with state healthcare authorities, a survey on indirect medical costs was conducted among patients and/or their caregivers.
Methods: Methods: The survey included 33 patients or their caregivers in 2024.
Results: Results: The primary predictors of high disease costs were progressive loss of individual autonomy. ALS patients require vital, costly equipment necessary for maintaining respiratory, mobility, and communication functions. The cost of non-invasive ventilation devices, power wheelchairs, electric patient lifts, electric hospital beds, Tobii eye-tracking devices (for computer control), and laptops with specific parameters ranged within 3 875 000 tenge (8 218 USD). Medical expenses are diverse and include medications for symptomatic treatment, massage therapy, supplies for maintaining NIV, specialized nutrition for gastrostomy patients, canes, walkers, neck and foot orthoses, and back braces. Excluding specific treatments like riluzole/edaravone, the cost of the aforementioned expenses is 431 322 tenge (914 USD). Government social security assistance is currently limited to providing two mechanical wheelchairs annually, diapers, sanitary pads, and sanitary products worth tenge (USD). The average annual total treatment cost for one patient was tenge (euro) per patient, which exceeds the average per capita cost in the RK (per capita income is 261,186 tenge as of 2023).
Conclusions: The disease is one of the most expensive in terms of direct medical and non-medical costs, far exceeding the average per capita income in the RK. Societal assistance should be improved

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SHIFT 01-566

Poster on Board - Shift 01
PRION DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

EVALUATION OF ELECTROENCEPHALOGRAPHIC RECORDINGS IN PATIENTS WITH NEUROPATHOLOGICALLY CONFIRMED CREUTZFELDT-JAKOB DISEASE

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Aims: We aimed to re-evaluate the EEG recordings in patients with neuropathologically confirmed Creutzfeldt-Jakob disease applying the recently adapted American Clinical Neurophysiology Society (ACNS) criteria, 2021. A total of 51 EEG recordings in 16 sporadic CJD were analyzed.
Methods: We retrospectively reviewed the EEG data of patients with postmortem confirmed CJD who were admitted at the Medical University of Vienna between 2001 and 2021. Only patients with available EEG recordings at our center were included for this analysis.
Results: Generalized periodic discharges (GPD) and rhythmic delta activity (RDA) occurred frequently resembling generalized brain dysfunction. Nevertheless, the differentiation from ictal activity was challenging, as 25% fulfilled the criteria of the recently proposed ictal-interictal continuum (IIC). In contrast, we could not detect any status epilepticus applying the new criteria in our study cohort. Furthermore, the EEG alterations varied among the different CJD molecular subgroups.
Conclusions: Repetitive EEGs over time showed, as expected, significant changes which may provide hints for early diagnosis. Therefore, assessing the EEG recordings according to the ACNS criteria 2021 could prevent unnecessary escalation of antiseizure medication and subsequent treatment in intensive care units in a subgroup of CJD patients.

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SHIFT 01-568

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / ANIMAL MODELS
2-3 April 2025

UNDERSTANDING THE ROLE OF THE RETROSPLENIAL CORTEX IN PARKINSON'S DISEASE

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Aims: Recent research has identified metabolic differences in the retrosplenial cortex (RSC) that differentiate cognitively normal people with Parkinson's disease (PD) from those with cognitive impairment. Since there remains relatively little investigation of this pathway in PD, this project sought to investigate the anatomical and functional characteristics of catecholaminergic denervation of the RSC.
Methods: To achieve this, we (1) characterised the loss of tyrosine hydroxylase (TH+) innervation into the RSC in 6-OHDA and alpha-synuclein viral vector models of PD, (2) anatomically traced TH+ innervation to the RSC to identify the source of the afferent projection, and (3) investigated the functional consequences of TH denervation of the RSC.
Results: (1) PD model animals exhibited a significant reduction in TH+ projections to the RSC compared to controls. (2) The RSC was found to receive TH+ projections predominantly from the locus coeruleus, with no appreciable contribution from the ventral tegmental area (VTA) or substantia nigra. (3) Loss of TH+ innervation into RSC impaired short-term memory in the object recognition test and induced long-term spatial memory impairments in a spatial discrimination task. (4) Further immunohistochemical analyses are underway on post-mortem tissue to validate whether denervation of the RSC is evident in the human PD brain.
Conclusions: LC projection to RSC may play an important role in PD and may contribute to cognitive features of the disease such as short-term memory deficits and spatial memory dysfunction.

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SHIFT 01-569

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
2-3 April 2025

THE POTENTIAL RELEVANCE OF AHNAK PATHWAYS IN THE BLOOD-BRAIN BARRIER TO PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES

Yong Kim[1], Yu Young Jeong[1], Chi Chang Sung[2], Gaetan Barbet[2]
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Aims: Anxiety and depression are the most prevalent neuropsychiatric symptoms affecting 30 to 50% of Alzheimer's (AD) or Parkinson's disease (PD) patients. Ahnak protein is a major binding partner of S100a10, alterations of which have been implicated in the etiology of major depressive disorder and antidepressant actions. Our recent studies using mice showed a pivotal role of Ahnak in the regulation of depression-like behavior. Of note, several reports from other groups indicate increased Ahnak levels in AD brains. In the brain, Ahnak protein is highly expressed in vascular endothelial cells (ECs), the lining of which and their tight junctions constitute the blood-brain barrier. However, Ahnak function in ECs remains to be uncovered. We aim to investigate the Ahnak function in ECs using EC-specific Ahnak KO mice and explore its relevance to depression, anxiety, and neurodegenerative diseases.
Methods: We generated EC-specific Ahnak KO mice. We performed various behavioral assays to measure depression-like, anxiety, and chronic stress-induced changes in social interaction. We also used EC-specific translating ribosome affinity purification (TRAP) in conjunction with RNA sequencing to identify genes and pathways altered by Ahnak deletion in ECs. We used flow cytometry and immunohistochemistry methods to characterize EC-specific Ahnak KO mice.
Results: EC-specific Ahnak KO mice display baseline antidepressant-like and anxiolytic behavior and a stress-resilience phenotype. EC-specific TRAP/RNA-seq data indicate that Ahnak deletion in ECs increases a variety of immune modulation molecules. In addition, EC-specific Ahnak KO decreases the number of monocytes and neutrophils in blood and inhibits lipopolysaccharides-induced microglia activation in the brain.
Conclusions: Our results suggest that Ahnak deletion in ECs induces antidepressant-like and anxiolytic behavioral phenotypes, possibly via immune modulation mechanisms. The increased Ahnak levels in AD might be related to psychiatric symptoms of the disease.

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SHIFT 01-571

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

ELUCIDATING THE ROLE AND MECHANISM OF TUFM IN LGR5 ACTIVATION WITHIN WNT SIGNALING IN NEUROGENIC TUMOR CELLS AND ENHANCING OF NEURAL STEM CELLS USING TUFM

Seon Ju Lee[1], Hyunhee Park[1], Eun Ji Lee[2], Jeong-Min Baek[2], Yejin Ryu[1], Min-Ju Kim[2], Hyuk Sung Kwon[1], Seong-Ho Koh[1,2], Hyun-Jung Yu[3]
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Aims: Neurodegenerative diseases and tumors share interconnected pathways, and there is a need for comprehensive studies to understand these shared or conflicting mechanisms. Wnt signaling pathway plays pivotal roles in the cellular survival and death across neural stem cells and neurogenic tumor cells. In our prior investigations, we observed consistent regulation of elongation factor Tu (TUFM) expression in both cell types, mediated by the modulation of Lgr5 and R-spondin within the Wnt signaling cascade. We hypothesize that TUFM possesses the capacity to simultaneously regulate both cell types, along with the aim to elucidate its role and mechanism in enhancing the functionality of neural stem cells and proposing a novel therapeutic approach for neurodegenerative diseases.
Methods: We conducted transcriptome analysis and proteomics to identify the transcription factors and proteins affected by TUFM regulation in both human neural stem cells (hNSCs) and neurogenic tumor cells (SH-SY5Ys). The cells were induced to overexpress TUFM via cDNA transfection and to inhibit TUFM using a TUFM inhibitor. Samples with regulated TUFM expression were performed total-RNA sequencing for mRNA analysis and 2-dimensional polyacrylamide gel electrophoresis (2D-PAGE), followed by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF/MS) for protein identification. Through bioinformatics analysis, mechanistic studies were conducted to investigate the association of TUFM with other genes and proteins, alongside Lgr5 in the Wnt signaling pathway.
Results: Samples with regulated TUFM expression were cultured: hNSC (S1); hNSC + TUFM overexpression (S2); hNSC + TUFM inhibition (S3); SH-SY5Y (S4); SH-SY5Y + Lgr5 inhibition (S5); SH-SY5Y + TUFM overexpression (S6); SH-SY5Y + TUFM inhibition (S7). Total-RNA sequencing analysis identified 68 genes, including RNA, 45S pre-ribosomal N3 (RNA45SN3), RNA, 45S pre-ribosomal N2 (RNA45SN2), U1 spliceosomal RNA (LOC124904613), RNA, U1 small nuclear 2 (RNU1-2), and ectodermal-neural cortex 1 (ENC1), which exhibited consistent alterations in both cell types under TUFM regulation. Through proteomics analysis, common changes in protoporphyrinogen oxidase (PPO), suppressor APC domain-containing protein 2 (SAPCD2), katanin p60 ATPase-containing subunit A-like 2 (KATNAL2), Rab GTPase-binding effector protein 2 (RABEP2), ribitol-5-phosphate xylosyltransferase 1 (RXYLT1), and organic solute carrier partner 1 (OSCP1) were observed in the two cell types under TUFM regulation. Bioinformatics

analysis confirmed the association between the mentioned genes and proteins and the TUFM, Lgr5, and Wnt signaling pathway.

Conclusions: The cellular activities of genes and proteins associated with the TUFM, Lgr5, and Wnt signaling pathway were validated in SH-SY5Y cells and hNSCs. Based on our previous research findings, we have confirmed that substantial involvement of splicing and mRNA transcription among various mechanisms. Modulating splicing factors triggers the activation of TUFM and Lgr5 within the Wnt signaling pathway, consequently enhancing the functionality of hNSCs. These mechanisms suggest the potential effectiveness of this approach in treating neurodegenerative diseases.

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SHIFT 01-572

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS
2-3 April 2025

EFFECTIVENESS OF COMBINATION THERAPY OF DONEPEZIL AND CHOLINE ALPHOSCERATE ON BEHAVIORAL PSYCHOLOGICAL SYMPTOMS IN ALZHEIMER'S DISEASE

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Inje Univ. IlsanPaik Hospital, Psychiatry, Goyang, Korea, Republic of

Aims: In this study, the effects of the donepezil monotherapy and the donepezil and choline alphoscerate combination therapy on behavioral psychological symptoms of Alzheimer's disease were compared.
Methods: This study was conducted as a prospective, randomized, open-label study for 12weeks. Among those who visited the Dementia Clinic at Inje University Ilsan Paik Hospital, 128people aged 60years or older who met the diagnostic criteria for 'Neurocognitive disorder due to Alzheimer's disease' defined in the DSM-5. According to randomization, 64patients were administered donepezil and 64patients were administered donepezil and choline alphoscerate for 12weeks. The Korean neuropsychiatric inventory(K-NPI), Geriatric depression scale was evaluated at baseline, week4 and week12, and the MMSE, Global Deterioration Scale(GDS), and Alzheimer's Disease Assessment Scale-Cognitive Subscale(ADAS-Cog) were evaluated at baseline and week12. This study was approved by the IRB committee and conducted.
Results: This analysis included 41donepezil administered patients and 42donepezil and choline alphoscerate combined administered patients and there was no statistically significant difference in age and education level in the two groups. There were no statistically significant differences between the two groups in the changes of MMSE, GDS, geriatric depression scale, the global NPI severity, frequency and caregiver distress, and NPI sub-items between baseline and week12. In the cognitive domain, there were also no statistically significant differences between the two groups in the changes of ADAS-Cog sub-items between baseline and week12. Monotherapy group and combination therapy group showed no significant improvement in the global NPI severity and frequency and the caregiver distress, NPI sub-items, geriatric depression scale, MMSE, GDS, ADAS-Cog scores after 12weeks of treatment.
Conclusions: There was no significant difference in the improvement of behavioral psychological symptoms and cognitive functions between donepezil and choline alphoscerate combination therapy and donepezil monotherapy.

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SHIFT 01-576

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
2-3 April 2025

POST-TRAUMATIC STRESS DISORDER AND REM-SLEEP BEHAVIOR DISORDER: EXPLORING GENETIC ASSOCIATIONS AND CAUSAL LINKS

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Aims: Isolated rapid-eye movement (REM) sleep behavior disorder (RBD), characterized by dream enactment during REM sleep, is considered a crucial early stage of synuclein-related neurodegenerative diseases such as Parkinson's disease and Lewy body dementia. Clinical reports suggest that RBD is more common in individuals with Post-Traumatic Stress Disorder (PTSD) compared to those without PTSD. In this study, we explore potential genetic and causal relationships between PTSD and neurodegeneration-related RBD to identify shared mechanisms and potential pathways for targeted interventions.
Methods: In the current analysis, we performed polygenic risk score (PRS) analysis, genetic correlation, and Mendelian randomization using the latest Genome-Wide Association Studies (GWAS) summary statistics for PTSD and isolated-RBD from European populations. PRS for PTSD was calculated with PRS-ContinuesShrinkage for each RBD case and control, followed by a logistic regression model to examine the associations. Genetic correlation was assessed using linkage-disequilibrium (LD) score regression, and Mendelian randomization was conducted with Two-SampleMR.
Results: PRS analysis showed a significant association between PTSD and isolated- RBD, with a 31.8% increase in RBD odds per unit increase in PTSD PRS (OR=1.318, 95% CI=1.117–1.558), indicating a higher genetic risk for PTSD is linked to a greater likelihood of RBD. However, the genetic correlation was small, and MR analysis did not show a causal relationship between the traits.
Conclusions: The PRS analysis reveals a strong association between PTSD and isolated- RBD, consistent with clinical reports. PRS analysis is more accurate for polygenic traits like PTSD as it aggregates the effects of numerous genetic variants, each contributing a small but cumulative effect. In contrast, MR and genetic correlation can be biased due to the reliance on a limited set of significant variants and the influence of potential pleiotropy.

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SHIFT 01-577

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
2-3 April 2025

DEPRESSION TREATMENTS AND RISK OF DEMENTIA: A 23-YEAR COHORT STUDY USING AKRIVIA HEALTH SECONDARY MENTAL HEALTHCARE DATA

Panagiota Kontari[1], Maxime Taquet[2], Ana Todorovic[1], Sophie Gibbons[1], Judith Harrison[3], Will Pettersson-Yeo[2], Benjamin Fell[1]
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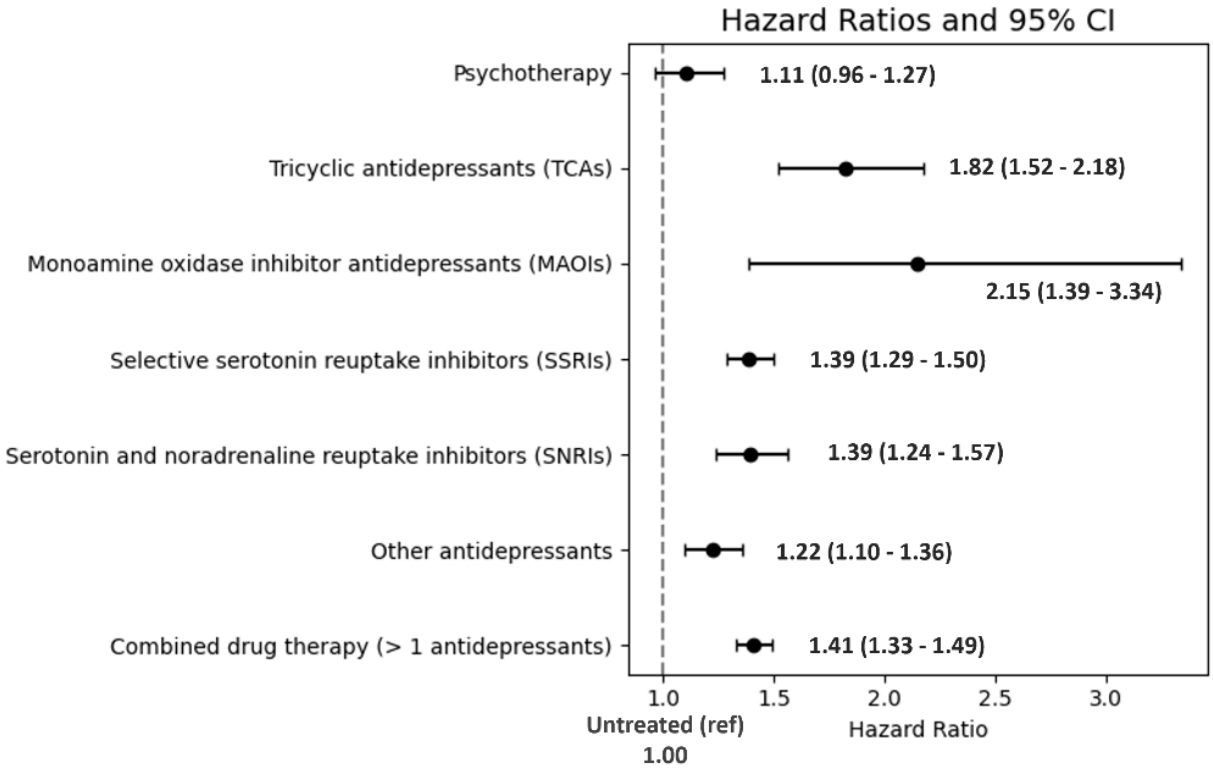
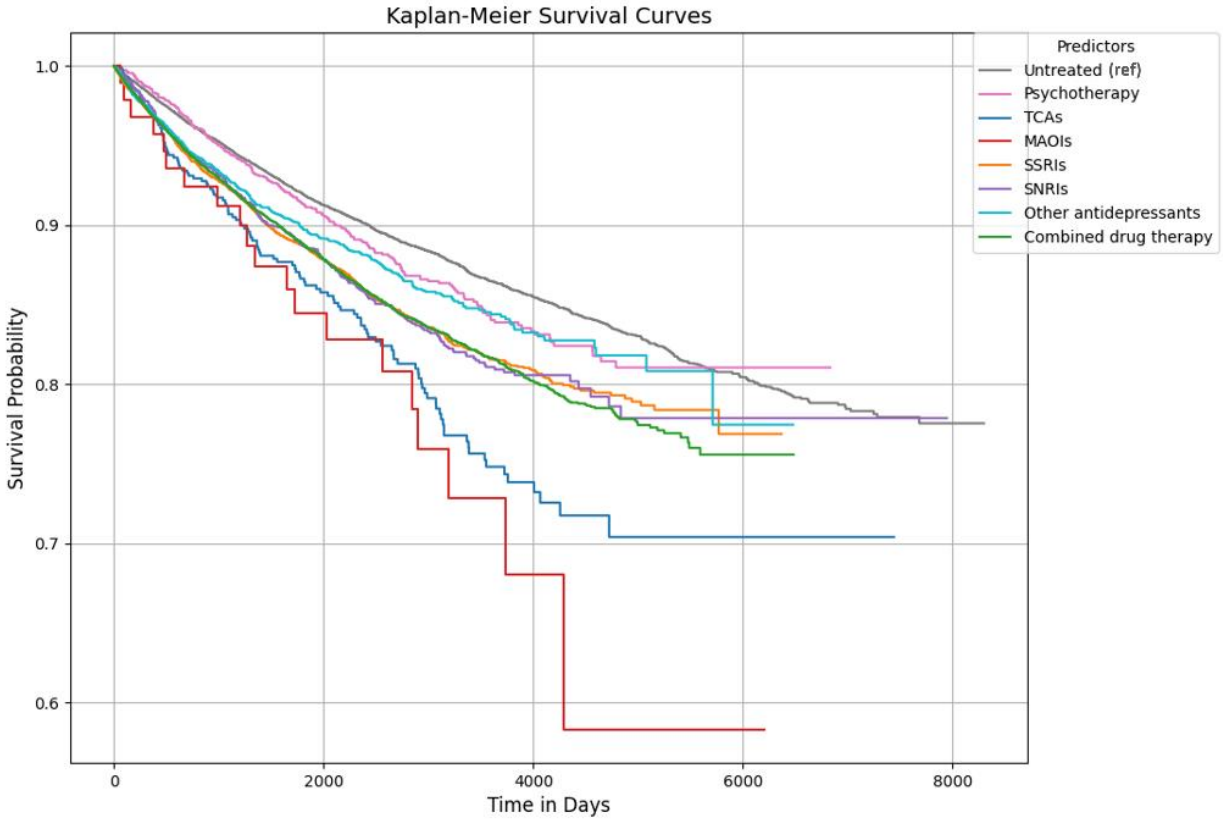
Aims: Depression has been suggested as a modifiable risk factor for dementia. However, the impact of depression treatments on dementia risk remains unclear. This study assesses the association between exposure to different antidepressants and psychotherapy, and the risk of dementia.
Methods: Using Akrivia Health's mental healthcare database (anonymised electronic health records for 5.1 million patients in the UK), we identified all patients with major depressive disorder diagnosed between January 2000 and September 2022, aged 40 or older at diagnosis, without comorbid bipolar disorder and/or schizophrenia, and dementia-free two years post-depression diagnosis. Patients were categorised into eight groups based on treatment type: psychotherapy only, tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), other antidepressants, and combined pharmacotherapy (≥ 2 antidepressants), with untreated patients as reference. Cox proportional hazards regression models estimated hazard ratios (HR) for dementia, adjusted for age, gender, and ethnicity.
Results: A total of 56,423 individuals were identified (6,904 developed dementia during follow-up, 59% female, mean [SD] age: 67.6 [10.7]). Compared to untreated patients, all patients treated with antidepressants, but not those treated with psychotherapy only, showed a significantly greater risk of dementia, especially MAOIs (HR=2.15, 95% confidence interval [CI] 1.39–3.34) and TCAs (HR=1.82, 95% CI 1.52–2.18). TCAs conferred a significantly greater risk than SSRIs (HR=1.39, 95% CI



1.29–1.50).



Conclusions: This study showed that antidepressants, especially MAOIs and TCAs, are linked to an increased risk of dementia. The increased risk may be due to anticholinergic effects of antidepressants as well as residual confounding due to depression severity. Further research is needed to understand the

underlying mechanisms and help clinicians balance the benefits of depression treatment with the risk of dementia.

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SHIFT 01-580

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

THE NEURAL CORRELATES OF METAMEMORY DURING ASSOCIATIVE RECALL IN OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT

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[1]Western University, Neuroscience, London, Canada, [2]Western University, School Of Kinesiology, London, Canada

Aims: To examine the associations between memory beliefs and functional activation during associative memory recall in older adults with mild cognitive impairment (MCI).
Methods: Twenty-eight participants aged 60 to 80 years (mean age = 72.61 years; SD = 4.64; 53.57% female) with MCI were recruited based on validated screening tests. Memory beliefs were examined using the Multifactorial Memory Questionnaire, which evaluates metamemory in older adults across three scales: (1) satisfaction with memory functioning, (2) self-appraisal of memory ability, and (3) self-reported use of memory strategies. Structural and functional MRI scans were performed on a 3T Siemens scanner. Structural scanning included a T1 MPRAGE sequence, and functional imaging was conducted during an associative memory task involving recalling face-place pairs. Functional activation maps were generated using cluster-corrected whole-brain analysis ($z > 2.3$, $p < 0.05$) to determine regions of interest (ROIs). Pearson correlation analyses were performed between metamemory scale scores and mean activation within these ROIs.
Results: Significant activations during associative recall were identified in the occipital fusiform cortex and lateral occipital cortex, superior division. The self-appraisal of memory ability scale positively correlated with activation in the lateral occipital cortex ($r=0.4881$, $p=0.0155$). No significant correlations were observed with the other metamemory scales or with activation in the occipital fusiform cortex.
Conclusions: The positive correlation between self-appraisal of memory ability and activation in the lateral occipital cortex suggests that individuals with higher confidence in their memory abilities engage visual processing regions more during associative recall. These results suggest that greater memory beliefs could enhance the recruitment of visual processing regions and may function as a compensatory mechanism in MCI. This relationship provides insight into the neural mechanisms underlying cognitive self-perceptions and memory function.

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SHIFT 01-582

Poster on Board - Shift 01
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

VIRTUAL COGNITIVE CARE PROGRAM FOR MILD COGNITIVE IMPAIRMENT AND EARLY DEMENTIA REDUCES ANXIETY AND DEPRESSION SYMPTOMS

Hayley Arrowood[1], Aniket Rajput[2], Bikram Gangwar[2], Paul Wright[1]
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Aims: To assess the symptoms of anxiety and depression in patients with mild cognitive impairment (MCI) or early dementia who have received digital multi-domain interventions remotely.
Methods: We enrolled 65 participants diagnosed with mild cognitive impairment (MCI) or early dementia over an 18-month period into the Neuroglee Connect™ program, which digital multi-domain interventions like cognitive training, brain health education, memory support tools, mind & body wellness exercises delivered remotely on their mobile/tablet devices. Participants first completed a 10-week "Train" phase, engaging in these weekly assigned tasks. Following the initial 10-week period, participants transitioned to the "Sustain" phase, which lasted up to 6 months. Additionally, they were provided with educational resources on healthy lifestyle habits. Initial screening for symptoms of depression was conducted using self-reported tools, such as the PROMIS-Depression and the Center for Epidemiologic Studies Depression Scale (CES-D10). Participants were also screened for symptoms of anxiety using the PROMIS-Anxiety and the Generalized Anxiety Disorder 7-item (GAD-7) screening tools. Assessments were repeated after completion of the train phase.
Results: Among the participants who completed the Neuroglee Connect™ program, 58% of them reported a reduction in anxiety symptoms as measured by the PROMIS-Anxiety and GAD-7 screening tools. Additionally, 58% of participants reported a decrease in depression symptoms based on the PROMIS-Depression and CES-D10 screening tools.
Conclusions: Using a digital platform that focuses on multi-domain cognitive interventions and provides educational resources on healthy lifestyle habits reduces symptoms of anxiety and depression in patients with mild cognitive impairment (MCI) and early dementia.

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SHIFT 01-583

Poster on Board - Shift 01
TAUPATHIES / ANIMAL MODELS / PRIMATES, NATURALLY OCCURING MODELS AND BRAIN ORGANOIDS
2-3 April 2025

DEEP PHENOTYPING OF ALZHEIMER'S-LIKE TAUOPATHY, BBB DYSFUNCTION, AND DYSMETABOLISM IN NATURALLY AGING RHESUS MACAQUES

Li Gong, Zunyuan Yang, Zunwei Yao, Licai Zeng, Mingling Wu, Fabao Gao, Wen Zeng
Sichuan Primed Shines Biotech Co., Ltd., Chengdu, China

Aims: It remains controversial whether the phenotypes of naturally aging rhesus macaques are consistent with those of Alzheimer's disease (AD) patients, due to the limited availability of very old cohorts. We characterized a cohort of aged rhesus macaques with AD-like phenotypes.
Methods: Sixty rhesus macaques, including 20 middle-aged monkeys (14-19 years), 20 old monkeys (20-23 years), and 20 oldest old monkeys (27-30 years), were subjected to clinically relevant circulating and imaging biomarker measurements. Specifically, we measured the levels of p-tau 181 and 231, total tau, and amyloid-beta in cerebrospinal fluid (CSF). Blood-brain barrier (BBB) permeability was assessed using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). Blood biochemistry parameters were used to evaluate metabolic status, while urine samples were collected for renal function assessment. Brain tissues from deceased monkeys underwent histopathological examination.
Results: The mean levels of p-tau 181 and 231, and total tau in the oldest old monkeys were significantly higher than those in the middle-aged (p=0.0000, 0.0000, 0.0000, respectively) and old monkeys (p=0.0006, 0.0056, 0.0003, respectively). The mean amyloid-beta level showed a decreased trend with age. BBB permeability was positively correlated with CSF tau levels, age, and blood glucose in these monkeys. Monkeys with higher BBB permeability exhibited decreased estimated glomerular filtration rate. Cortical amyloid-beta plaques and $AT8^{+}$ hyperphosphorylated tau were detected in the aged monkeys. A reduction (32±11%) in the number of Nissl-stained neurons in the prefrontal region, and a reduction (23±6%) in cholinergic axon density in the superficial cortex were observed in the oldest old compared to the middle-aged monkeys.
Conclusions: A cohort of naturally aging rhesus macaques exhibits phenotypes and high-risk factors of AD. This resource provides an unprecedented opportunity to understand disease progression and to evaluate novel therapeutic strategies.

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SHIFT 01-588

Poster on Board - Shift 01
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
2-3 April 2025

SLEEP FRAGMENTATION AND SEX AFFECT NEUROINFLAMMATION IN THE ALZHEIMER'S DISEASE MOUSE MODEL, APPSAA KNOCK-IN MICE

Marilyn Duncan, Haleigh Whitlock, Michael Murphy, Sridhar Sunderam, Bruce O'Hara, Theresa Macheda, Margaret Andres, Adam Bachstetter
University Of Kentucky Medical School, Dept. Of Neuroscience, Lexington, United States of America

Aims: Aims: To determine how the AD risk factors, sleep fragmentation and sex, affect neuropathology in an AD model, APP^{SAA} knock-in mice
Methods: Methods: APP^{SAA} mice of both sexes (8 months old) were studied using a piezoelectric sleep recording system coupled with an automated sweeping bar for sleep disruption. Mice experienced either undisturbed sleep (US) or chronic sleep fragmentation (SF) for four 1-hour intervals distributed during the light phase for five days/week. After five weeks, all mice were euthanized and brains were dissected and frozen. A panel of ten neuroinflammatory markers (e.g., IL1β, IL-33, CCL2, CXCL2, & CXCL10), were measured by qRt-PCR and Aβ levels were measured by ELISA.
Results: Results: Females showed less total sleep than males due to reduced dark phase sleep. SF decreased total sleep, mainly in the light phase during SF. Among all mice, percent sleep during the final week of the study was inversely correlated with quantity of neuroinflammation. Among the US mice, females had higher expression of neuroinflammatory markers than males in the neocortex and equivalent expression in the hippocampus. Among the SF mice, only males showed an increase in neocortical neuroinflammatory markers with expression levels similar to those in US females. SF did not affect hippocampal neuroinflammation or hippocampal or neocortical Aβ levels.
Conclusions: Conclusions: In the APP^{SAA} model of AD, female sex deleteriously affects sleep and neuroinflammation, two processes known to affect AD neuropathology. SF selectively increases neuroinflammation in the male neocortex, suggesting that this AD risk factor can potentiate AD progression. Also, the results suggest that sex differentially affects the response to an AD risk factor (SF), and that brain regions and pathological processes (neuroinflammation versus Aβ accumulation) may be differentially sensitive to SF.

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SHIFT 01-589

Poster on Board - Shift 01
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
2-3 April 2025

BEHAVIORAL, ELECTROPHYSIOLOGICAL, AND BIOMARKER LEVEL CHANGES IN THE RTG4510 MOUSE MODEL OF ALZHEIMER'S DISEASE

Taleen Hanania, Herman Fernandes, Mei Kwan, Jose Beltran, John Shea, Afshin Ghavami
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Aims: rTg4510 mice conditionally express mutant human Tau in various forebrain regions using Tet-off expression system. This model recapitulates tau pathology observed in AD with age-dependent neuronal loss resulting in cognitive impairment. The objective of the study was to assess age associated behavioral, electrophysiological, and biomarker changes.
Methods: Female tTA and rTg450 mice were purchased from JAX labs. Locomotor activity was assessed in the open field chambers. Cognitive performance was assessed using the Y maze and Morris water maze tests. Basal synaptic transmission and LTP were assessed by extracellular field potential recording at the Schaffer collateral-CA1 pyramidal. Nf-L levels were measured by Quanterix and inflammatory and Tau by MSD technologies.
Results: rTg4510 mice showed hyperactivity starting at 4 months of age. Cognitive deficits were seen in the Morris water maze during acquisition and probe tests. Although spontaneous alterations were decreased in rTg4510 mice, number of entries were increased indicating hyperactivity. rTg4510 mice showed elevated tau levels in plasma and CSF at 3 and 6 months of age, with an 11 fold increase in CSF but only two fold increases in plasma at 6 months. Plasma and CSF Nf-L levels were increased in rTg4510 mice at 6, but not at 3 months. Among the inflammatory markers assessed, only IL-1b was increased in CSF at three months of age. Basal synaptic transmission and LTP were impaired at 6 months of age. Behavioral and electrophysiological effects and levels of all biomarkers were restored by Doxycycline (Dox) treatment.
Conclusions: Neuropathological changes in rTg4510 mice appear as early as 3 months of age and become widespread by 6 months. Behavioral and biomarker changes can be reversed by Dox treatment, making this model ideal for evaluating Alzheimer's disease therapies.

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SHIFT 01-591

Poster on Board - Shift 01
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
2-3 April 2025

V337M-TAU MUTATION LINKED TO FAMILIAL FTD DYSREGULATES PROTEOME IN IPS-NEURONS AND THEIR EXTRACELLULAR VESICLES

Megan Hong[1], Vijaya Pandey[2], Aria Mehrpour[3], James Wohlschlegel[2], Joseph Loo[3], Gal Bitan[4]
[1]University of California - Los Angeles, Neurology/chemistry And Biochemistry, Los Angeles, United States of America, [2]David Geffen School of Medicine, Biological Chemistry, Los Angeles, United States of America, [3]University of California - Los Angeles, Chemistry And Biochemistry, Los Angeles, United States of America, [4]David Geffen School of Medicine, Neurology, Los Angeles, United States of America

Aims: Aim 1: Characterize patient-derived iPSC-derived neurons (iPS-N) and their small extracellular vesicles (sEV) by proteomics to assess systems changes between healthy and disease states during neuronal differentiation and aging. Aim 2: Study proteomic differences in disease-relevant iPS-N sEVs from different dementias and movement disorders. Aim 3: Test and validate newly discovered biomarkers in patient blood samples.
Methods: iPS-Ns, sEV isolation, immunocytochemistry (ICC), fluorescence microscopy, electron microscopy (EM), nanoparticle tracking analysis (NTA), liquid chromatography-tandem mass spectrometry (LC-MS-MS), data-independent acquisition mass spectrometry (DIA-MS), proteomic analysis, statistical modeling
Results: V337M-tau mutant iPS-Ns from a familial FTD patient and a CRISPR corrected control are received as neural progenitor cells and cultured to mature neurons until cell death. Cells are fixed and collected at representative time points to track differentiation by ICC and fluorescence microscopy. sEVs are collected from the same cells over the time course to track changes in sEV release over neuronal maturation. Proteomics is performed on sEVs from mature neurons and the neurons themselves over cell maturation. sEV morphology and distribution is analyzed by EM and NTA. Tau mutant neurons seem to express more proteins and release less through EVs.
Conclusions: Tau mutation demonstrates dysregulation of the proteome in both sEVs and cells over iPS-N maturation. Tau mutation may cause neurons to retain proteolytic stress by impairing sEV release.

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SHIFT 01-592

Poster on Board - Shift 01
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS
2-3 April 2025

UNVEILING TAU INTERACTIONS WITH RIBOSOMES AND RNA IN NEURODEGENERATIVE DISEASES

Tristyn Garza[1,2], Christian Lessard[2], John Koren Iii[2], Stefan Prokop[3], Jose Abisambra[2]
[1]University of Florida Genetics Institute, Gainesville, United States of America, [2]University of Florida, Department Of Neuroscience, Center For Translational Research In Neurodegenerative Diseases, Mcknight Brain Institute, Brain Injury, Rehabilitation, And Neuroresilience (brain) Center, Gainesville, United States of America, [3]University of Florida, Department Of Pathology, Center For Translational Research In Neurodegenerative Disease, Mcknight Brain Institute, Fixel Institute For Neurological Diseases, Gainesville, United States of America

Aims: Neurons require *de novo* protein synthesis for optimal performance, and this feature is impaired in early stages of Alzheimer's Disease (AD). We determined that pathological tau interacts robustly with rRNA and ribosomal proteins in human AD brains. However, the mechanisms that drive these interactions and their downstream effects remain elusive. Our overall objective is to identify the pathogenicity of tau-ribosome/RNA interactions. Given the disease-associated interaction between tau, rRNA, and rpS6, a major regulator of ribosome synthesis, we hypothesized that tau impairs ribosome synthesis.
Methods: Using enhanced crosslinking immunoprecipitation (eCLIP) in human AD and control brains we identified the types of RNA that associated with pathogenic and non-pathogenic tau. Then, performing polysome profiles on *in vitro* models of tau overexpression, we measured changes in ribosome association. Finally, using RiboSeq on human AD and control brains, we identified aberrant translational regulation on specific transcripts.
Results: eCLIP data show association of pathological tau with coding and non-coding RNAs that are unique in AD. Polysome profiling showed that tau more closely associates with free RNA shifting formation of ribosomal subunits. Finally, ribosome footprinting and RNA-sequencing revealed that translation is selectively regulated.
Conclusions: We identified unique RNAs and ribosomal proteins that complex with tau, leading to altered ribosome assembly. These changes are associated with translation dysregulation unique to AD, suggesting that translational dysregulation is a consequence of tau-mediated impaired ribosome stability.

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SHIFT 01-593

Poster on Board - Shift 01
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / NETWORK BIOLOGY, CONNECTOME, PROTEIN-PROTEIN INTERATIONS
2-3 April 2025

THE ALZHEIMER'S DISEASE GENETIC RISK FACTORS BIN1 AND PTK2B INTERACT IN DROSOPHILA AND RODENT NEURONS

Valentin Leclerc, Xavier Hermant, Tommy Malfoi, Jean-Charles Lambert, Pierre Dourlen
Univ. Lille, Inserm, CHU Lille, Institut Pasteur de Lille, U1167-RID-AGE Facteurs de risque et déterminants moléculaires des maladies liées au vieillissement, Lille, France

Aims: The most common forms of Alzheimer's disease (AD) are multifactorial, with a significant genetic component. *BIN1* and *PTK2B* are two genetic risk factors that modulate tau toxicity in Drosophila. We aimed at testing an interaction between BIN1 and PTK2B *in vivo* especially at the synaptic level.
Methods: Using Drosophila larval neuromuscular junctions (NMJs) as a model, we assessed the synaptic phenotypes of double knockout (KO) Drosophila for BIN1 and PTK2B and compared them to those of single KO. We further tested colocalization in primary rat neurons using proximity ligation assay (PLA).
Results: PTK2B KO Drosophila are known to have enlarged NMJs with more ramifications, while BIN1 KO Drosophila exhibit smaller or normal NMJs. Our results confirmed an increased number of synaptic boutons in PTK2B KO and no alteration in BIN1 KO. In the PTK2B-BIN1 double KO, loss of BIN1 prevented the NMJ enlargement associated with PTK2B loss, indicating an epistatic effect of the loss of BIN1 on PTK2B loss. Regarding the ramifications, we observed an increase in BIN1 KO. The double KO exhibited an even higher number of ramifications, demonstrating a synergistic effect of the loss of the two genes for this readout. Furthermore, we observed a close colocalization between BIN1 and PTK2B in primary rat neurons using PLA, suggesting conservation of this interaction in mammals.
Conclusions: This work provides the first evidence of a functional interaction between BIN1 and PTK2B *in vivo*, suggesting that these two AD genetic risk factors could participate in a common signaling pathway relevant to AD.

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SHIFT 01-594

Poster on Board - Shift 01
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / TAU, TAU ISOFORMS
2-3 April 2025

MAPT EXON 10 SPLICING REGULATION IN HUMANISED TAU MOUSE MODELS

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Aims: Humanised tau mouse models carry a human MAPT gene instead of the endogenous mouse gene. These mice better model human tauopathy due to their expression of the human tau sequence and their human-like regulation of expression and splicing. While these models support more human-relevant tauopathy research, they also allow improved investigation of human tau splicing regulation *in vivo*. This is of fundamental interest but is also relevant for splice-modifying therapeutics and for understanding disease-causing tau mutations. Furthermore, these mice allow us to study the dynamic developmental splicing of human MAPT in a mammalian environment, which has previously been essentially impossible. Here, we aimed to investigate human MAPT splicing regulation in both development and adulthood. This work also aimed to inform the future use of such models by providing data on tau splicing in non-overexpressing humanised lines from both RIKEN and the MODEL-AD consortium.
Methods: To achieve this, we used RT-PCR to measure exon 10 (E10) inclusion/exclusion in mRNA from mouse brain homogenates. Samples were collected at timepoints spanning the developmental shift from E10 exclusion to inclusion, and in adulthood.
Results: Humanised tau models exhibit nearly 50% E10 inclusion in adulthood (approximately the human adult ratio), compared to 100% inclusion for mouse MAPT. Human MAPT also switches towards E10 inclusion more slowly during the 2-3 weeks after birth, and various disease-causing mutations increased E10 inclusion both before and after this period.
Conclusions: Overall, there are inherent differences between human and mouse MAPT in terms of sensitivity to developmental splicing factors. The effects of various mutations are well-predicted by the E10 stem-loop model of MAPT pre-mRNA splicing, and the results have important implications for interpreting data from humanised MAPT mouse models harbouring splice-shifting mutations.

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SHIFT 01-595

Poster on Board - Shift 01
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / TAU, TAU ISOFORMS
2-3 April 2025

EVALUATION OF THE MOLECULAR CHARACTERIZATION OF HUMAN 4-REPEAT (4R) TAU EXTRACTS FROM TAUOPATHIES

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Aims: 4-repeat (4R) tauopathies including progressive supranuclear palsy (PSP), are characterized by 4R-tau accumulation. Current animal models often fail to replicate the complexity of human tauopathies, limiting treatment development. The objectives of this study were to isolate and characterize 4R tau from postmortem brains of patients with tauopathies and compare its properties to synthetic tau.
Methods: 4R tau was extracted from insoluble and soluble fractions of autopsy-confirmed taupathy-brain tissue using sarkosyl extraction. Isolated tau was compared to synthetic tau using immunocytochemistry (ICC), western blotting (WB), transmission electron microscopy (TEM), and quantitative real-time PCR (qRT-PCR) analyses. Additionally, iPSC-derived cells from tauopathy donors were treated with both isolated and synthetic tau.
Results: WB using a 4R-specific antibody confirmed effective oligomer formation by isolated tau. TEM revealed more extensive and thicker fibrillary structures in isolated tau compared to synthetic tau. Treatment of iPSC-derived cells with isolated tau induced significantly higher pro-inflammatory cytokine secretion and cellular reactivity than synthetic tau.
Conclusions: Tau isolated from the postmortem brains of tauopathy patients formed distinct oligomers and fibrils compared to synthetic tau, resulting in stronger inflammatory and reactive cellular responses in iPSC-derived neural cells. This study highlights the importance of using patient-derived tau for more accurate modeling of tauopathies and the development of targeted therapeutics.

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SHIFT 01-600

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, APOPTOSIS, CELL DEATH
2-3 April 2025

RESCUING DEFICIENT CHROMATIC REMODELING CHAPERONE RETINOBLASTOMA BINDING PROTEIN 7 (RBBP7) ATTENUATES AUTOPHAGY, NEUROINFLAMMATION, AND TAU PATHOGENESIS IN TAUOPATHIES.

Jessica Judd[1], Wendy Winslow[2], Matthew Huentelman[3], Ignazio Piras[3], Nathaniel Hansen[3], Ritiin Sharma[3], Patrick Pirrotte[3], Nikhil Dave[4], Ramon Velazquez[2,5]
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Aims: Epigenetic dysfunction contributes to pathogenesis observed in Alzheimer's Disease (AD) and primary tauopathies, including frontotemporal dementia. The lysine (K) acetyltransferase p300 is aberrantly activated in tauopathies. p300 acetylates tau at K residues, including K280, promoting tau aggregation and inhibiting autophagic clearance. Autophagy – the breakdown of old and damaged cellular components – is deficient in tauopathies. Acetylation by p300 inhibits autophagy machinery (Atg) proteins 5 and 7. AD brains with high tau burden exhibit deficient autophagy; autophagic flux markers p62 and LC3-II are disrupted. Retinoblastoma Binding Protein 7 (Rbbp7) chaperones chromatin-remodeling proteins, including p300. We recently found neuronal-specific downregulation of Rbbp7 mRNA in AD brains, which negatively correlates with neuronal p300 levels. Rbbp7 is downregulated in the PS19 mouse model of tauopathy, and genetically rescuing neuronal Rbbp7 in hippocampal CA1 reduces tau acetylation and phosphorylation, and p300 levels. We examine whether rescuing deficient neuronal Rbbp7 rescues autophagy, reduces neuroinflammation, and attenuates tau pathogenesis by altering p300.
Methods: To rescue neuronal Rbbp7, we retro-orbitally injected mice with AAV/PHP.eB-CamkII-Rbbp7 (AAV-Rbbp7) in PS19 and NonTg mice at 3.5 months, prior to tau pathogenesis. Tissue was collected at 8.5 months.
Results: AAV-Rbbp7 significantly increased hippocampal Rbbp7 protein while reducing p300. Atg5, Atg7 p62, and LC3-II were dysregulated in PS19 compared to NonTg, and AAV-Rbbp7 in PS19 restored autophagy marker to NonTg levels. Phosphorylated tau at Threonine 181 and Serine 396 was decreased by AAV-Rbbp7. Cytokine multi-plex panel showed that AAV-Rbbp7 reduced 15 cytokines in PS19 to NonTg levels, demonstrating a reduction of neuroinflammation.
Conclusions: This work illustrates that rescuing deficient neuronal Rbbp7 restores autophagy and reduces pathological tau burden and neuroinflammation, providing growing evidence that Rbbp7 has significant therapeutic effects for multiple aspects of tauopathies such as AD.

SHIFT 01-601

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / BLOOD-BRAIN BARRIER
2-3 April 2025

PLASMA MEDIATED PROTEOLYTIC CLEAVAGE OF TAU IN CSF ASSOCIATED WITH BLOOD BRAIN BARRIER DYSFUNCTION

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Aims: Alzheimer's disease (AD) is a major neurodegenerative disorder characterized by the accumulation of amyloid plaques and neurofibrillary tangles. Recent findings have shown that African Americans (AAs) with AD exhibit lower levels of total tau and phosphorylated tau in the cerebrospinal fluid (CSF) despite no racial differences in tau protein abundance in brain. The molecular mechanisms underlying lower CSF tau in cognitively impaired individuals, including AAs, remain unclear. This study aims to investigate the role of blood-brain barrier (BBB) dysfunction and plasma proteolytic enzymes (PPEs) in reducing CSF tau levels, related to CSF subtypes.
Methods: We performed network analysis and molecular subtyping on 483 CSF samples using quantitative proteomics. Enzymatic activity of thrombin and plasminogen was measured in pooled samples from the six identified CSF subtypes. Based on the elevated enzymatic activity observed in Subtype-3, we investigated *in-vitro* tau cleavage by PPEs, including thrombin and plasminogen. Subsequently, we conducted *ex-vivo* tau cleavage studies using plasma and CSF pools from each subtype. Lastly, tau immunoassays and proteomics were performed by incubating AD CSF with plasma to identify reductions in CSF tau.
Results: Proteomics studies revealed that one of six major CSF subtypes (Subtype-3) had higher levels of BBB related proteins, including albumin, thrombin, and plasminogen. *In-vitro* studies confirmed that recombinant tau is cleaved by PPEs, such as thrombin and plasminogen. The specificity of cleavage was confirmed using chemical inhibitors. Additionally, *ex-vivo* studies demonstrated recombinant tau cleavage by plasma and Subtype-3 CSF pools. Immunoassays and proteomics further confirmed the reduction in AD CSF tau following dilution with increasing concentration of plasma.
Conclusions: Our findings suggest that tau is cleaved *in-vivo* by PPEs, likely due to plasma infiltration into CSF secondary to BBB dysfunction.

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SHIFT 01-602

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

EFFECT OF AGING AND AMYLOIDOSIS ON THE SPREADING OF TAUOPATHY IN A RODENT MODEL OBTAINED BY FOCAL OVEREXPRESSION OF TAU

Cécile Adamski, Pauline Léal, Charlotte Duwat, Gwenaëlle Aurégan, Sueva Bernier, Marjorie Benfissa, Déborah Fourmy, Caroline Jan, Fanny Petit, Karine Cambon, Alexis-Pierre Bemelmans
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Aims: In Alzheimer's disease (AD), tauopathy progresses according to a well-established spatiotemporal pattern, strongly correlated with the evolution of symptoms. Countering this phenomenon appearing as a therapeutic avenue of choice, we therefore developed a model to study its mechanisms and the influence of two aggravating factors of AD, ageing and amyloidosis.
Methods: Tauopathy was modeled by unilateral injection of an AAV inducing overexpression of the 1N4R isoform of human Tau (AAV-Tau) into the dentate gyrus (DG) of adult mice. Spreading was then assessed one to three months after AAV-Tau injection by quantification of neurons secondarily affected by tauopathy in the contralateral DG. This model was then applied to aged mice and APP/PS1dE9 mice to study the effects of ageing and amyloidosis on tauopathy spread, respectively.
Results: As early as 1 month post-injection, we detected the presence of neurons secondarily affected by AAV-Tau-induced tauopathy in different parts of the contralateral hippocampus such as the polymorphic layer of the DG and the CA1 layer, thus validating the relevance of this model to study the spreading of tauopathy. We then compared the level of spreading between 2 cohorts of C57Bl/6J mice aged 4 and 15 months respectively at the time of AAV-Tau injection. One month later, we did not observe any difference in spreading between the two cohorts. We also applied our model to APP/PS1dE9 mice and observed in this context a notable increase in the number of secondarily affected neurons, with a significant rise of approximately fourfold in the contralateral hippocampus.
Conclusions: We have developed a relevant mouse model to study the spreading of toxic forms of the Tau protein and shown that the presence of amyloid plaques aggravates this phenomenon.

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SHIFT 01-603

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

IN VITRO INTRA- AND INTER-CELLULAR TAU SEEDING AND PROPAGATION IN HUMAN NEURONS

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Aims: Tauopathies are characterised by intracellular accumulation of tau neurofibrillary tangles. CNS spatial progression of tangles reflects neuronal connectivity, leading to the proposal that tau neuronal release and uptake contributes to the propagation of pathology. We sought to develop a novel model of tau seeding using human excitatory neurons to enable understanding of the mechanisms underlying seeding and propagation.
Methods: Initiation of tau seeding in different iPSC-derived cortical neuron genotypes was tested with recombinant human monomeric and fibrillar tau species to identify conditions and genotypes which facilitated seeding, followed by propagation to other neurons. Seeding and propagation of tau aggregation was live monitored using Amytracker520 dye in an OPERA-Phenix high content imaging system.
Results: Tau aggregation was infrequently induced in non-demented control neurons over 10 days by extracellular fibrillar MTBR tau (K18) in combination with monomeric K18. No seeding was observed in cell-free environments or HEK cells when exposed to the same combination. MAPT IVS10+16 neurons demonstrated robust seeding of tau aggregation when treated with K18 fibrils plus monomer, considerably more than non-demented neurons. Live imaging of intraneuronal tau aggregation found that initial seeding in individual neurons was followed by the appearance of tau aggregation in surrounding neurons over 7 days, suggestive of extracellular propagation between neurons.
Conclusions: Robust seeding of tau aggregation within human neurons requires extracellular tau MTBR fibrils and is greatly enhanced in neurons expressing the MAPT IVS 10+16 mutation. Following initial seeding of aggregation, spatial progression to surrounding neurons was observed. We are currently investigating cellular mechanisms underlying this progression, including whether it is by receptor-mediated uptake of tau from initially seeded neurons.

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SHIFT 01-604

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TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

VLDLR INTERACTS WITH TAU AND MEDIATES ITS CELLULAR UPTAKE

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Aims: Tau endocytosis and trafficking is modulated by two members of the LDL receptor family: the low-density lipoprotein receptor-related protein (LRP1) and sortilin-related receptor (SORL1) which both facilitate tau uptake and promote seeding of endogenous tau aggregation (Cooper et al 2021, Cooper et al 2024). Here we test the hypothesis that the very low-density lipoprotein (VLDLr), an apoE receptor associated with lipid metabolism and reelin signaling, might serve a similar function. Furthermore, we examine the effect of apoE and reelin on tau-VLDLr interactions.
Methods: Surface plasmon resonance (SPR) was used to investigate binding interactions between tau, VLDLr, reelin, and apoE. To determine if VLDLr mediates tau uptake, we assessed the uptake of recombinant ^{125}I-labeled 2N4R tau labeled in LRP1-deficient CHO cells (CHO 13-5-1) stably expressing VLDLr and compared the uptake to non-expressing control cells.
Results: SPR data showed that tau binds soluble forms of the VLDLr with high affinity (K_D = 22 ± 3 nM). The binding was inhibited by receptor associated protein (RAP), which inhibits binding of ligands to LDL receptor family members, as well as by all apoE variants and reelin. Cells expressing VLDLr internalized significantly more ^{125}I-labeled tau than control cells in a process that was blocked by RAP.
Conclusions: These experiments identify VLDLr as the third receptor capable of binding tau and mediating its internalization. This activity raises the possibility that the VLDLr may contribute to the spreading of pathogenic forms of tau in the AD brain, and future studies are exploring the physiological significance of tau-VLDLr interactions and the apoE effects on these interactions.

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SHIFT 01-605

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

KNOCKOUT OF INNATE IMMUNITY PROTEIN IFITM3 DECREASES TAU SECRETION IN VITRO

Abigail Cross, Lauren Jonas, Yue-Ming Li
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Aims: *IFITM3* is an interferon stimulated gene that produces a transmembrane protein with a canonical role in antiviral restriction. IFITM3 is also implicated in Alzheimer's Disease (AD) as a gamma secretase modulatory protein, altering levels of Amyloid Precursor Protein cleavage to increase the production of Amyloids. In the 5XFAD amyloid mouse model, knockout of IFITM3 attenuates amyloid pathology. We have found that knockout of IFITM3 also reduces tau pathology in PS19 mice, as well as reducing seeding and spread of exogenous tau pre-formed fibrils in pre-pathology PS19 mice. The current studies aim to elucidate the role of IFITM3 specifically in the seeding and spread of tau pathology.
Methods: We used *in vitro* models to quantify tau secretion, including a glioblastoma cell line and human induced pluripotent stem cell (hiPSC) derived neurons. In glioblastoma cells, full length tau with the HiBiT tag was overexpressed and quantified via luciferase assay. In hiPSC-derived neurons, endogenous levels of secreted tau were measured via Meso Scale Discovery (MSD) assay.
Results: We have found that IFITM3 knockout decreases tau secretion *in vitro*. In cell lines overexpressing tau, this decrease is consistent across WT, P301S, and P301L/S320F tau, as well as between vesicular and free tau. In hiPSC-derived neurons, IFITM3 knockout decreases endogenous tau secretion.
Conclusions: IFITM3 contributes to tau spread by facilitating tau secretion from neurons. Additional studies are needed to determine the role of IFITM3 in neuronal uptake of tau and seeding of pathology.

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SHIFT 01-606

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
2-3 April 2025

DISSECTING THE ROLE OF EARLY PRE-TANGLE TAU AGGREGATES AND REACTIVE ASTROCYTES IN ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) is marked by significant structural changes in the brain, yet the earliest molecular alterations remain elusive. Emerging evidence suggests that tau multimerization into small aggregates is among the initial events leading to the accumulation of hyperphosphorylated tau in neurofibrillary tangles (NFTs), promoting tau seeding. While tau pathology is associated with neurons, astrocytes also play a crucial role in the disease and potentially contribute to tau seeding. However, differences in astrocytic tau inclusions between different tauopathies, such as Progressive Supranuclear Palsy (PSP) and AD, are not well understood and warrant further investigation.
Methods: This study visualises early tau multimers *in situ* using the tau proximity ligation assay (tau-PLA) across various brain regions from post-mortem human samples representing Braak stages 0–VI. Tau seeding activity is assessed through seeding amplification assays, including real-time quaking-induced conversion (RT-QuIC) and fluorescence resonance energy transfer (FRET). Additionally, *in vitro* experiments with primary human astrocytes treated with tau extracted from AD and PSP brain homogenates will assess differences in tau uptake, degradation, seeding, and toxicity.
Results: Our findings reveal that tau multimerization occurs extensively in early pre-symptomatic Braak stages, well before tau pathology is detectable by immunohistochemistry (IHC). Notably, high seeding activity of tau is detected in cases with tau multimers but without NFTs. Additionally, morphological changes in reactive astrocytes, as indicated by GFAP-IHC staining, are observed in these early AD pathology cases compared to healthy controls.
Conclusions: These results suggest that tau multimerization may initiate AD pathology before tau hyperphosphorylation and NFT formation, emphasising the role of astrocytes in the early stages of AD. This research provides crucial insights into the molecular events driving early AD progression.

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SHIFT 01-607

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
2-3 April 2025

FUNCTIONAL EFFECTS OF PDE11A ALZHEIMER'S DISEASE-ASSOCIATED VARIANTS

Elvis Amurrio, Marie Danaher, Porschderek Kargbo, Sonia Lin, Michy Kelly
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Aims: PDE11A, an enzyme degrading cAMP/cGMP, is enriched in the memory-related hippocampal formation. The PDE11A variants R202H and L756Q are associated with early-onset AD. Although expression of the variants increased phosphorylation of tau *in vitro*, direct effects on PDE11A function were not reported. This gap in knowledge needs filling because PDE11A expression increases with age, and this age-related increase is exacerbated in elderly TBI patients that develop AD vs. those that do not. Interestingly, age-related increases in PDE11A ectopically cluster in hippocampal "ghost axons". Present aims: 1) understand if age-related clustering of PDE11A is a protective mechanism intended to sequester excess PDE11A, 2) determine if PDE11A-R202H and PDE11A-L756Q interfere with this age-related clustering and/or catalytic activity of the enzyme.
Methods: PDE11A-WT, PDE11A-R202H, or PDE11A-L756Q were expressed in 1) HT22 mouse hippocampal cells or 2) the mouse hippocampal formation. A radiotracer assay measured phosphodiesterase activity. Biochemical fractionation and immunofluorescence assessed PDE11A subcellular compartmentalization. Age-related clustering of PDE11A was disrupted using tadalafil, with cognitive effects tested using social odor recognition memory (SOR).
Results: PDE11A age-related clustering reflects liquid-liquid phase separation (LLPS; a.k.a. biomolecular condensation): PDE11A forms spherical clusters that progressively fuse over time in a concentration-dependent and reversible manner. Disrupting PDE11A LLPS in the aging mouse brain with tadalafil impaired SOR. Interestingly, both PDE11A4^{R202H} and PDE11A4^{L756Q} reduced PDE11A LLPS, while PDE11A4^{R202H} increased and PDE11A4^{L756Q} decreased catalytic activity.
Conclusions: Age-related clustering of PDE11A by LLPS serves to sequester excess PDE11A in the aging brain, and the AD-linked variants disrupt this protective mechanism in addition to altering catalysis. This suggests PDE11A^{R202H} and PDE11A^{L756Q} cause PDE11A to be physiochemically/biochemically altered in a fundamentally different way than healthy aging to drive more widespread deficits than healthy aging alone.

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SHIFT 01-610

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

RELATIONSHIP BETWEEN SOLUBLE TREM2 AND OTHER BIOMARKERS OF SPORADIC ALZHEIMER'S DISEASE

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Aims: The activation of microglia plays a central role in the pathophysiology of Alzheimer's disease. A soluble fragments of trigger receptor expressed on myeloid 2 (sTREM2) can serve as a marker for microglia and has been demonstrated to be overexpressed in AD. However, the relationship between sTREM2 and other biomarkers in AD has not yet been proven.
Methods: Plasma and cerebrospinal fluid (CSF) were taken from participants enrolled from 2018 to 2020 at Asan Medical Center to confirm the relationship between sTREM2 and AD biomarker. Samples were stratified according to amyloid positivity and clinical status.
Results: Our results showed that CSF sTREM2 levels were closely correlated with CSF T-tau and P-tau, but not with Aβ42, and also with CSF neurofilament light chain (NfL). Furthermore, inverse correlation was observed between CSF and plasma sTREM2 levels. Previous studies have shown that elevated sTREM2 levels in the early AD stage are associated with tau pathology and not with Aβ42.
Conclusions: sTREM2 is involved in microglia activation and neuroinflammation due to tau-associated neurodegeneration. Furthermore, the correlation between plasma sTREM2 and CSF NfL argues that both situations were affected by microglia activation and neuroinflammation. However, the relationship between CSF and plasma sTREM2 in AD requires further study. Therefore, we suggest that there may be a correlation between neuroinflammation and tau-induced neurodegeneration.

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SHIFT 01-611

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
2-3 April 2025

ADIPONECTIN DEFICIENCY EXACERBATES TAUOPATHY AND NEUROINFLAMMATION IN THE HUMAN TAU P301S MUTATION TRANSGENIC MICE

Zifei Zhang[1], Leung-Wah Yick[1], Wenying Zou[1], Huiwen Xue[1], Jason Shing-Cheong Kwan[1], Roy Chun-Laam Ng[2], Koon-Ho Chan[1]
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Aims: Tauopathy is one of the pathological hallmarks of several neurodegenerative diseases including Alzheimer's disease. It is characterized by intraneuronal accumulation of hyperphosphorylated tau proteins. Adiponectin (APN) is an adipokine released from adipocytes. It regulates glucose metabolism by enhancing insulin sensitivity and exerts anti-inflammatory effects. APN in low molecular weight forms has been shown to cross the blood-brain barrier. However, whether APN contributes to tau-mediated neurodegeneration remains unclear. We hypothesize that APN deficiency exacerbates tauopathy with enhanced microgliosis and aggravated neuronal loss.
Methods: To study whether APN deficiency promotes tauopathy development, APN knockout (*APN*$^{-/-}$) mice were crossbred with human tau P301S mutation transgenic (Tau^{P301S}) mice to generate APN-deficient tauopathy (Tau^{P301S}; *APN*$^{-/-}$) mice. The anxiety-like behavior, cognitive function, and memory and learning function of 9-month-old wildtype, *APN*$^{-/-}$, Tau^{P301S}, and Tau^{P301S}; *APN*$^{-/-}$ mice were assessed by open field test, novel object recognition test, and Morris water maze test respectively. Hyperphosphorylated tau accumulation, microgliosis, and neuronal loss in the brain were examined by immunofluorescent staining. The plasma level of the proinflammatory cytokine interleukin-6 (IL-6) was quantified by ELISA.
Results: Despite there were no significant differences in the behavioral test findings across the groups, the immunoreactivity of hyperphosphorylated tau (AT8) in the hippocampus and cortex of Tau^{P301S}; *APN*$^{-/-}$ mice were significantly higher than that in wildtype, *APN*$^{-/-}$, and Tau^{P301S} mice. The immunoreactivity of microglia marker ionized calcium-binding adaptor molecule 1 (Iba1) was significantly higher in Tau^{P301S}; *APN*$^{-/-}$ mice than that in the other groups. Tau^{P301S}; *APN*$^{-/-}$ mice showed significantly less neuronal nuclei (NeuN) positive neurons than in Tau^{P301S} mice. The plasma level of IL-6 in Tau^{P301S}; *APN*$^{-/-}$ mice was significantly higher than in wildtype.
Conclusions: APN deficiency aggravates tauopathy with increased hyperphosphorylated tau accumulation, microgliosis, and neuronal loss.

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SHIFT 01-615

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
2-3 April 2025

THE ROLE OF THE NLRP3 INFLAMMASOME IN MICROGLIAL SENESCENCE IN TAUOPATHIES

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Aims: Aging is the most important risk factor for the development of dementia. Senescent cells accumulate with age and present with an irreversible growth arrest and a senescence-associated secretory profile (SASP) including IL-1β, that might contribute to disease progression. Interestingly, increased numbers of senescent microglia are present in the brains of tauopathy mice and patients. Furthermore, activation of the NLRP3 inflammasome, leading to IL-1β secretion from microglia, was shown to drive tau accumulation in a tauopathy mouse model in an IL-1β-dependent manner. However, the contribution of the NLRP3 inflammasome to microglial senescence in the context of tauopathies remains unknown.
Methods: To investigate this, we use primary wildtype and *Nlrp3*-knockout murine microglia in which we induce a senescent-like cellular state including SASP formation by treating them with low concentrations of the tau protein. Furthermore, we assess senescence markers in brain slices of a tauopathy mouse model with and without a *Nlrp3*-knockout using immunohistochemical stainings.
Results: Here, we provide evidence that the tau protein can induce microglial senescence in vitro as evident by cell cycle arrest, loss of lamin B1 and formation of yH2AX. Additionally, we show that the NLRP3 inflammasome contributes to microglial senescence in vitro and in vivo as loss of NLRP3 rescues the occurrence of several senescence markers. However, release of the SASP is only partially ameliorated, but subsequently we identify a NLRP3-independent signaling pathway involving STAT3 to be a key driver of the SASP *in vitro*.
Conclusions: In conclusion, our study shows that NLRP3 as well as STAT3 are involved in microglial senescence. Investigating these mechanisms further can provide new insights into potential therapeutic applications related to NLRP3 or STAT3 inhibition in tauopathies.

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SHIFT 01-616

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
2-3 April 2025

THE MICROTUBULE SEVERING PROTEIN UNC-45A PATHOGENICALLY CONTRIBUTES TO NEURITE DYSTROPHY AND ALTERS THE MICROTUBULE LATTICE INTEGRITY BY PREVENTING MICROTUBULE LATTICE REPAIR

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Aims: Neurite swelling and disrupted microtubule (MT) integrity are key features of Alzheimer's disease (AD), neuropathies, and aging. In AD, amyloid plaques are characterized by loss of neuronal integrity. MT-protecting and -stabilizing proteins, such as Tau, doublecortin, and MAP2, are known to regulate the stability of neuronal MTs, and their abnormal expression or mislocalization has been linked to multiple neurodegenerative diseases and aging. The role of MT-destabilizing proteins is less well understood. In this study, we explored the localization of UNC-45A, the only ATP-independent MT-severing protein known and whose expression is abundant in MT-rich areas of the nervous system (PMID: 30322860, PMID: 31328624, PMID: 33262310, PMID: 34206743, PMID: 37858676) with respect to amyloid plaques in AD. We also determined the contribution of UNC-45A to neurite swelling and disrupted MT integrity in the presence of microenvironmental stimuli. We explored the mechanisms through which UNC-45A alters the MT lattice integrity, contributing to loss of MT mass.
Methods: UNC-45A expression was analyzed in tissues from the APP/PS1 mouse model of AD and in human AD specimens. The effects of UNC-45A on neuronal swelling was investigated via fixed and live-cell imaging techniques. The role of UNC-45A in controlling MT-lattice integrity was investigated using Total Internal Reflection Fluorescence (TIRF) microscopy.
Results: UNC-45A localizes in amyloid plaques in mouse and human tissues. At the cellular level, UNC-45A is localized in neuronal swellings and contributes to their formation. The presence of oxidative microenvironmental stimuli exacerbates its effect. Mechanistically, UNC-45A preferentially binds to defects on the MT lattice and dwells at these sites, preventing their repair.
Conclusions: UNC-45A pathogenically contributes to neurite dystrophy by preventing MT lattice repairs and may play a role in the loss of neuronal integrity in amyloid plaques

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SHIFT 01-623

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
2-3 April 2025

CIRCUIT-SPECIFIC TAU PATHOLOGY IN THE LOCUS COERULEUS AND ITS EFFECTS ON THE HIPPOCAMPUS

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Aims: The Locus Coeruleus is an early site of pathological Tau deposition in multiple neurodegenerative disorders but its role in these disorders is not well understood. We aim to establish a circuit-specific mouse model of Tau pathology in the Locus Coeruleus (LC-Tau) and to characterize the molecular and cellular phenotype in the hippocampus.
Methods: We used a cre-dependent viral vector to overexpress human Tau with the P301L mutation that can cause frontotemporal dementia. We injected this Virus into the LC of DBH- cre mice, where Cre-recombinase is selectively expressed in noradrenergic (NA) neurons (Tillage et al., 2020). We injected tau and control vectors in LC in 9- to 11-week-old mice and begin experiments 4 weeks post-injection.
Results: We confirm that viral injections lead to LC-specific overexpression of human Tau. Using TUNEL assay, we verified that the tau and control virus did not induce cell death in LC. Given that transgenic mouse models of Tauopathy report microglial activation as an early hallmark, we quantified microglial activation in LC-Tau and observed a significant increase in IBA1 intensity. Next, we used whole-cell patch-clamping to investigate electrophysiological changes in LC-Tau. Our data revealed that LC-Tau cells had a greater frequency of spontaneous excitatory post-synaptic currents. Interestingly, this effect was blocked by NE receptor antagonists, suggesting that LC Tau pathology leads to abnormal LC-NE signaling. Finally, we find a significant decrease in hippocampal NA concentrations using high-performance liquid chromatography followed by electrochemical detection.
Conclusions: We find that circuit-specific Tau pathology in the LC leads to dysregulated LC-NE signaling in the absence of cell death. We will further characterize the cellular consequences of this dysregulation in the hippocampus.

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SHIFT 01-624

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY
2-3 April 2025

FROZEN VS. FRESH: DECODING THE BEST SOURCE FOR HIGH-QUALITY SYNAPTOSOMES

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Aims: Synaptosomes are isolated synaptic terminals containing pre- and post-synaptic components. They are valuable for studying synaptic functionality and examining pathophysiological changes, such as those occurring in Alzheimer's disease, where synaptic dysfunction and loss are key features. Previous research suggests that synaptosome preparation from shock-frozen brain tissue yields synaptosomes with a lower respiratory rate, indicating reduced biological functionality compared to fresh tissue. However, detailed comparative studies on the impact of freezing on key isolation parameters are lacking. This study seeks to assess how fresh and frozen tissue impact synaptosome isolation.
Methods: Synaptosomes will be isolated from fresh and frozen brain tissue through mild homogenization under isotonic conditions, followed by differential and sucrose density gradient centrifugation. Comparative analyses to evaluate the quality of synaptosomes extracted from fresh and frozen brain tissue will include proteomic profiling, electron microscopy, western blotting, super-resolution microscopy, and a functionality assay. These analyses will focus on synaptic protein enrichment, contamination by non-synaptic structures, and the preservation of synaptic functionality and structural integrity.
Results: Preliminary proteomic results showed that synaptosome preparations from fresh and frozen mouse brain tissue shared 75% of their protein profiles. Synaptosomes isolated from fresh tissue exhibited higher contamination with mitochondrial matrix and membrane components, along with a lower presence of excitatory and presynaptic proteins. Contrarily, western blot analysis did not show significant differences in contamination levels of other cellular components between extractions. We are currently confirming these findings with a larger sample size.
Conclusions: Overall, this study aims to evaluate the efficacy of isolating synaptosomes from fresh versus frozen mouse brain tissue. Our study will enhance the understanding of how using fresh or frozen tissue affects synaptosome quality and to evaluate its broader implications for experimental practices.

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SHIFT 01-625

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

UNDERSTANDING THE FORMATION OF HETEROMERIC AMYLOIDS BETWEEN TAU AND MUSASHI PROTEINS IN ALZHEIMER'S DISEASE

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Aims: Objectives: Tauopathies are characterized by the accumulation of toxic tau species in the brain with oligomeric species being the most toxic form. Recent studies have also implicated RNA Binding Proteins, such as Musashi (MSI), in the onset and progression of several neurodegenerative diseases including Alzheimer's Disease (AD). Our lab has visualized co-localization between oligomeric tau and MSI1 and MSI2 in AD tissue, suggesting toxic crosstalk between tau and MSI proteins. In this study, we further investigated the relationship between MSI and Tau and the impact this relationship has on the formation of heteromeric amyloids.
Methods: Methods: We performed sarkosyl fractionation on human AD brain homogenates to better understand oligomer and fibril formation of MSI and Tau in diseased brains. Immunofluorescence and IHC were used to visualize these aggregates spatially in tissue. We also performed primary neuron and cell-based assays to investigate the interplay between MSI and Tau and the potential formation of heteroligomers and heterofibrils. We performed RBP/RNA immunoprecipitation of MSI1 in the presence of naïve and pathogenic mutant tau species to understand the impact of tau on MSI function.
Results: Results: This study shows a dynamic interplay between Tau and MSI in AD brains and cell models suggesting bidirectional influence on protein aggregation. Our results also show that the presence of pathogenic tau greatly impacts the functionality of MSI which may contribute to RNA dysregulation in diseased tissue.
Conclusions: Conclusions: Understanding the influence of RBPs on Tau aggregation and vice versa allows us to better understand disease pathophysiology and potential areas of therapeutic targets.

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SHIFT 01-626

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

SYNTHESIS OF RECOMBINANT PS396 AND PS404 PHOSPHO-TAU BY GENETIC CODE EXPANSION

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Aims: Accumulation of hyperphosphorylated tau is one of the main pathological hallmarks of Alzheimer's disease. However, the pathophysiological mechanisms triggered by specific tau phosphorylation sites remain elusive. To elucidate some of these mechanisms, we aimed to synthesize recombinant phospho-tau by genetic code expansion (GCE). GCE allows site-specific incorporation of non-canonical amino acids into tau during translation. It utilizes an archaeal translational machinery consisting of an aminoacyl-tRNA synthetase/$tRNA_{CUA}$ pair and incorporates non-canonical amino acids in response to a TAG stop codon in the protein-coding mRNA. Phosphoserine and phosphothreonine could be incorporated into proteins using this method. We therefore set forth to apply GCE for large-scale production of site-specifically post-translationally modified recombinant tau.
Methods: We synthesized plasmids encoding for the translational machinery, super-folder green fluorescent protein (sfGFP) and tau with site-specific TAG mutations. These plasmids were transformed into E. coli, followed by recombinant protein expression, extraction and purification. We imaged sfGFP-expressing E. coli at the Operetta CLS High-Content Analysis System and analyzed purified proteins with western blot.
Results: Initial results indicate successful incorporation of single phosphoserine in sfGFP at position N150 and tau at positions S396 and S404 with expected efficiency. Fluorescent imaging of sfGFP-expressing E. coli showed successful full-length synthesis of phospho-sfGFP. Western blot analysis with PHF1, anti-pS404 and anti-total tau antibodies confirmed the incorporation specificity and synthesis of full-length phospho-tau.
Conclusions: Our results indicate that GCE can be applied to incorporate phosphoserine into tau. Further optimization is ongoing to enable large-scale production of phosphorylated proteins, simultaneous incorporation of two phosphoserines into one protein, and incorporation of other phospho-amino acids. Future efforts will focus on applying GCE to other proteins and posttranslational modifications of interest to facilitate mechanistic studies of pathological mechanisms.

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SHIFT 01-627

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

IMPACT OF TREM2 RISK VARIANTS ON BRAIN REGION-SPECIFIC TAU PATHOLOGY IN ALZHEIMER'S DISEASE

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Aims: TREM2 risk variants, R47H and R62H, increase the risk of Alzheimer's disease (AD) by 2-4 fold. Previous studies suggest that TREM2 influences tau pathology by restraining its accumulation and related neurodegeneration. However, the effects of partial loss-of-function TREM2 variants on tau pathology remain unclear. This study aimed to investigate the impact of TREM2 risk variants, R47H and R62H, on tau hyperphosphorylation and aggregation across different brain regions.
Methods: Post-mortem human brain tissues from individuals with TREM2 common variants (CV), R47H, and R62H were examined. We utilized two approaches: 1) sarkosyl fractionation and western blotting to assess phosphorylated tau levels of different molecular sizes, and 2) immunohistochemistry followed by deep-learning-assisted morphological characterization of neurofibrillary tangles at different maturation stages and neuritic plaques in brain regions, including the somatosensory cortex(SSC) and mid-temporal gyrus(MTG).
Results: Our findings revealed that the R47H variant exhibited higher levels of sarkosyl-insoluble tau in the SSC compared to CV and R62H, while all variants showed similarly elevated tau levels in the MTG, possibly suggesting faster tau spreading during disease progression. R47H carriers also had an increased proportion of low molecular weight tau, indicating higher loads of truncated, aggregation-prone tau. Additionally, both R47H and R62H carriers demonstrated an increase in AT8+ neuritic plaques compared to CV.
Conclusions: These results suggest that TREM2 risk variants may accelerate tau pathology, potentially contributing to the increased AD risk by promoting tau hyperphosphorylation, aggregation, and spread across brain regions. This may provide a mechanistic explanation for the elevated AD risk in individuals carrying these TREM2 variants.

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SHIFT 01-628

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

TAU SEED AMPLIFICATION ASSAY FOR THE DETECTION OF MISFOLDED TAU IN 3R/4R AND 4R TAUOPATHY BRAIN SAMPLES.

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Aims: Pathological seeding-competent tau aggregates (tau-seeds) have been detected by tau seed amplification assay (tauSAA) in brain samples from 3R tauopathies such as Pick's disease (PiD), 4R tauopathies like progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD), and mixed 3R/4R tauopathies like Alzheimer's disease (AD). The type of recombinant tau used as substrate has varied greatly: K19 for PiD tau-seeds (Saijo et al., 2017), τ306/K19 (Kraus et al., 2019) or K12 (Manca et al., 2023) for increased detection of AD tau-seeds, and K18/K19 (Saijo et al., 2019) for increased detection of PSP/CBD tau-seeds. Additionally, 0N3R tau substrate was used for specific amplification of AD tau-seeds, as PSP tau-seeds did not amplify under those conditions (Frey et al., 2023). Our goal is to determine if a recombinant 3R tau substate can amplify AD, PSP, and CBD brain derived tau-seeds without systematic self-aggregation in control samples.
Methods: AD, PSP, and CBD middle frontal cortex samples collected at UCSD, were homogenized and evaluated at Amprion using tauSAA. Brain homogenates were analyzed at different dilutions to compare levels of amplification between tauopathy groups. Available contralateral formalin fixed frontal lobe samples were evaluated for phospho-tau by IHC using AT8 and GT38 antibodies. AD, PSP, and CBD post-mortem cerebrospinal fluid (PM-CSF) samples were also analyzed by tauSAA.
Results: Tau-seeds were detected in 3R/4R and 4R tauopathy brains, with higher analytical sensitivity in AD. Higher burden of phospho-tau and Braak tau stage were associated to higher levels of tau-seeds. AD, PSP, and CBD tau-seeds were detected in PM-CSF.
Conclusions: Recombinant 3R tau is a suitable substrate for 3R/4R and 4R tauopathies. Although PM-CSF samples are often contaminated with brain tissue, current results seem promising for detection of tau-seeds in antemortem CSF.

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SHIFT 01-629

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

COMPLEX INTERACTION PATTERNS BETWEEN TAU AND 14-3-3ZETA PROTEIN VARIANTS.

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Aims: After phosphorylation of 14-3-3ζ at Ser58 (pS58), it monomerizes and changes its properties [1,2,3]. Hyperphosphorylation of Tau protein, causes detachment of Tau from microtubules in neurons and leads to neurodegeneration.[4] Hyperphosphorylated Tau aggregates into neurofibrillary tangles (NFTs) - one of the hallmarks of Alzheimer's disease (AD). Interestingly, 14-3-3ζ proteins were also found colocalized in the NFTs [5]. Here, we compared the interaction properties of dimeric 14-3-3ζ WT and monomeric 14-3-3ζ pS58 with respect to Tau protein [6,7]. The interaction with Tau protein phosphorylated by protein kinase A (PKA) was inspected from various points of view.
Methods: The binding affinity, stoichiometry, and interacting residues were studied using native-PAGE, chemical cross-linking, tandem MS, and NMR spectroscopy.
Results: We revealed that phosphorylation of 14-3-3ζ at Ser58 decreases its affinity to Tau protein and changes binding stoichiometry. Both NMR and cross-linking results suggested that Tau is in contact with 14-3-3ζ proteins via the proline-rich domain and microtubule-binding domain. Moreover, cross-linking data showed that not only the binding channel of 14-3-3ζ protein is responsible for Tau binding, but also the outer 14-3-3ζ protein surface and exposed dimeric interface of monomeric 14-3-3ζ pS58 are involved [6].
Conclusions: In summary, we provide novel insight into the 14-3-3ζ/Tau interaction and its regulation by phosphorylation of both partners. **References:** 1. V. Obsilova et al. *Front. Mol. Biosci.*, **9**, (2022), 1-15. 2. A. Kozeleková et al. *Front. Chem.*, **10**, (2022), 1-17. 3. Z. Trošanová et al. *J. Mol. Biol.*, **434**, (2022), 167479. 4. T. Arendt et al. *Brain. Res. Bull.*, **126**, (2016), 238-292. 5. R. Layfield et al. *Neurosci. Lett.*, **209**, (1996), 57-60. 6. R. Crha et al. *Int. J. Biol. Macromol.* **2024**, 266, 130802 7. A. Lasorsa et al. *Biochemistry* **2023**, 62, 1631–1642

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SHIFT 01-630

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

TAU PROTEOFORM LANDSCAPE OF TRANSLATIONAL ORGANOID MODELS OF TAUOPATHIES

Andreas Huhmer[1], Zhengjian Zhang[1], S Guha[1], Vivek Budamagunta[1], Abdul-Rizaq Hamoud[1], Steven Tan[1], Maryam Jouzi[1], Greg Kapp[1], Taylor Bertucci[2], Sally Temple[2], Kara Juneau[1], Parag Mallick[1]
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Aims: The hyperphosphorylation and accumulation of abnormal forms of tau protein (MAPT) is a hallmark of Tauopathies and autosomal dominant mutations in the MAPT gene increase the risk of sporadic FTD associated tauopathies. We use human stem cell-derived brain organoids that include two known disease-associated MAPT mutations (V337M and IVS10+16) linked to hyperphosphorylation and aggregation of Tau and their mutant corrected isogenic controls to study the abnormal forms of Tau (proteoforms).
Methods: We apply a single-molecule detection technology to the discovery of Tau proteoforms. We demonstrate their detection using a multi-cycle method adopting commercially available protein-isoform and PTM-specific antibodies identifying the proteoforms and their relative abundance. First, to determine single-molecule binding, single protein nanoparticle-conjugates are deposited on the flow-cell. Second, an antibody specific for a Tau epitope of interest is added to analyze all single proteins. Third, bound antibody is imaged by fluorescence, localizing each antibody binding event to an individual protein at a specific location. Cycles of binding, imaging, and removal are repeated multiple times to probe for Tau epitopes of interest.
Results: Applying a panel of 8 epitope-specific probes (256 potential proteoforms) covering several Tau isoforms and phosphorylated proteoforms we quantify the relative amounts of Tau proteoform in the brain organoids of various maturation confirming the changes of relative amounts of Tau isoforms indicated by Western blot. The single-molecule nature of the platform also allows us to determine relative quantities of phosphorylated proteoforms emerging during organoid maturation, establishing a variant-specific Tau proteoform landscape between mutant organoids and corrected controls.
Conclusions: Results clearly demonstrate the unique capability of the platform to quantify biologically relevant Tau proteoforms accelerating our understanding of the role of Tau proteoforms in Tau aggregation.

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SHIFT 01-631

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

DELETION OF AN ACTIN REGULATOR AMELIORATES TAU HYPERPHOSPHORYLATION, GLIOSIS, AND MEMORY DEFICITS IN TAU P301S MICE.

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Aims: WAVE1 (Wiskott-Aldrich syndrome protein (WASP) and WASP-family verprolin-homologous protein 1) is a major regulator of Arp2/3 complex-mediated actin polymerization in the brain. Previously, we found a significant downregulation of WAVE1 in Alzheimer's brains (*Nature Medicine* 2015). We also observed the role of WAVE1 in the trafficking of amyloid precursor protein (APP)-containing vesicles and thereby Aβ production. Experimentally reducing WAVE1 gene expression dramatically reduced Aβ levels and restored memory deficits in APP/PS1 mice harboring APPswe and presenilin 1 ΔE9 mutations. However, the role of WAVE1 in regulating tau pathology has not been studied. We aim to examine the effects of WAVE1 reduction on Aβ-independent tau hyperphosphorylation and cognitive behavior in tau P301S mice.
Methods: We crossed tau P301S mice with WAVE1 KO mice to generate non-tau transgenic control mice and tau P301S mice, harboring WAVE1 KO (+/+, +/- or -/-) (6 groups). We used immunoblotting and immunohistochemistry methods to measure tau hyperphosphorylation, microgliosis and astrocytosis. We also performed Y-maze and Morris Water Maze tests to measure memory and cognitive function.
Results: We found that tau hyperphosphorylation at S202/T205 (AT-8) and T231 (AT-180) sites was significantly reduced in tau P301S mice harboring either heterozygous or homozygous WAVE1 KO compared to the levels in the P301S mice expressing WT WAVE1. WAVE1 heterozygous or homozygous KO also significantly reduced microgliosis and astrocytosis in tau P301S mice. WAVE1 heterozygous KO ameliorates memory and cognitive deficits in tau P301S mice.
Conclusions: Our studies suggest that WAVE1 is a potential therapeutic target for amyloid as well as tau pathology.

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SHIFT 01-632

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

CHARACTERISATION OF ALZHEIMER'S-DISEASE-RELEVANT TAU PROTEIN EXPRESSED IN HEK293 MAMMALIAN CELLS

Aneta Kozeleková[1,2,3], Gytis Kučinskas[1,2], Tomi Greňa[2], Marie Chovančíková[3], Petr Kašpárek[3], Martina Hložánková[3], Jozef Hritz[1,4]
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Aims: Hyperphosphorylation and abnormal posttranslational modification (PTM) of Tau were identified as key determinants connecting Tau and Alzheimer's disease (AD). Goals of our study were to 1) prepare Tau 2N4R protein in mammalian cells with AD-relevant PTMs, 2) characterise its structural, interaction and aggregation properties, and 3) compare them with Tau protein phosphorylated by selected kinases *in vitro*.
Methods: We transiently transfected HEK293 mammalian cells and purified the full-length Tau 2N4R protein using liquid chromatography. The PTMs within Tau were identified by trypsin digestion and LC-MS/MS analysis. Chemical cross-linking, PAGE and other biophysical methods were used in the interaction studies, and electron microscopy and atomic force microscopy to characterise Tau fibrils.
Results: We successfully prepared Tau in the HEK293 cells and identified approx. 20 phosphorylation sites with diverse extent of phosphorylation. The detected phosphorylation sites were comparable to those found in the brains of AD-patients. Interestingly, in contrast to Tau phosphorylated by protein kinase A (PKA) *in vitro*, Tau isolated from HEK293 and potentially AD-brains does not interact with 14-3-3ζ protein, a well-recognized Tau partner. Currently, we inspect aggregation properties of Tau from HEK293 cells.
Conclusions: Tau protein expressed in HEK293 cells contains similar phosphorylation sites as AD-Tau and its properties may differ from Tau protein selectively phosphorylated *in vitro*. Acknowledgement:This project has received funding from the European Union's Horizon Europe program under the grant agreement No. 101087124. We acknowledge CEITEC Proteomics Core Facility of CIISB, Instruct-CZ Centre, supported by MEYS CR (LM2023042, e-INFRA CZ (ID:90254)). We acknowledge Cryo-electron microscopy and tomography core facility CEITEC MU and Nanobiotechnology core facility of CIISB, Instruct-CZ Centre, supported by MEYS CR (LM2023042) and European Regional Development Fund-Project „UP CIISB" (No. CZ.02.1.01/0.0/0.0/18_046/0015974).

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SHIFT 01-633

Poster on Board - Shift 01
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
2-3 April 2025

EVALUATION OF HUMAN INDUCED PLURIPOTENT STEM CELL (HIPSC)-DERIVED TRI-CULTURE AS IN VITRO MODEL FOR ALZHEIMER'S DISEASE

Isabel Onofre, Carola Van Berkel, Leo Smit, Charles Leach, Shushant Jain
Ncardia, Leiden, Netherlands

Aims: Development of physiologically relevant models for Alzheimer's Disease (AD) remains a challenge with an unfilled gap in translatable human-based platforms. Ncardia developed human tri-culture models composed of neurons, astrocytes and microglia derived from iPSCs, resembling physiological conditions that allow modulation of neuroinflammation and neurodegeneration *in vitro* relative to AD.
Methods: First, we identified relevant triggers as α-beta (amyloid-beta) and TAU species capable of inducing cellular responses specific to AD pathology in cultures of microglia. Microglia cultures exposed to these triggers released higher levels of pro-inflammatory cytokines, exhibited higher and faster phagocytic activity, which was assessed by uptake of pHrodo Bioparticles and changed morphology to ameboid shape. Following this, we established a tauopathy model in the tri-culture system, by inducing phosphorylation (pTAU), misfolding and aggregation of TAU, using different recombinant mutant TAU (pre-formed fibrils) PFFs.
Results: This approach enabled a multi-parametric readout of neuronal and glial phenotypes including activation of microglia and astrocytes in the tri-culture, and release of pTAU and NfL (neurofilament light chain) in the supernatants. In this model we observed increased levels of phagocyted pTAU by microglia, mostly dependent on the phagocytosis of neurons expressing pTAU and also increased levels of release of IL-6, TNF-α, IL1-β and IL-18. Together, these observations support a neurodegenerative phenotype, typical of tauopathies in which secreted or engulfed pTAU activates microglia initiating the neuroinflammatory cascade.
Conclusions: Developing validated models that display microglia-neuron communications, provides insight on cellular interactions that play a role in recognizing apoptotic neurons and modulation of neuronal activity, which are crucial events in disease progression. Targeting these pathways in human models with a combination of clinically-relevant readouts allows the evaluation of therapeutics to rescue not only primary, but also secondary and tertiary neuro-pathologies.

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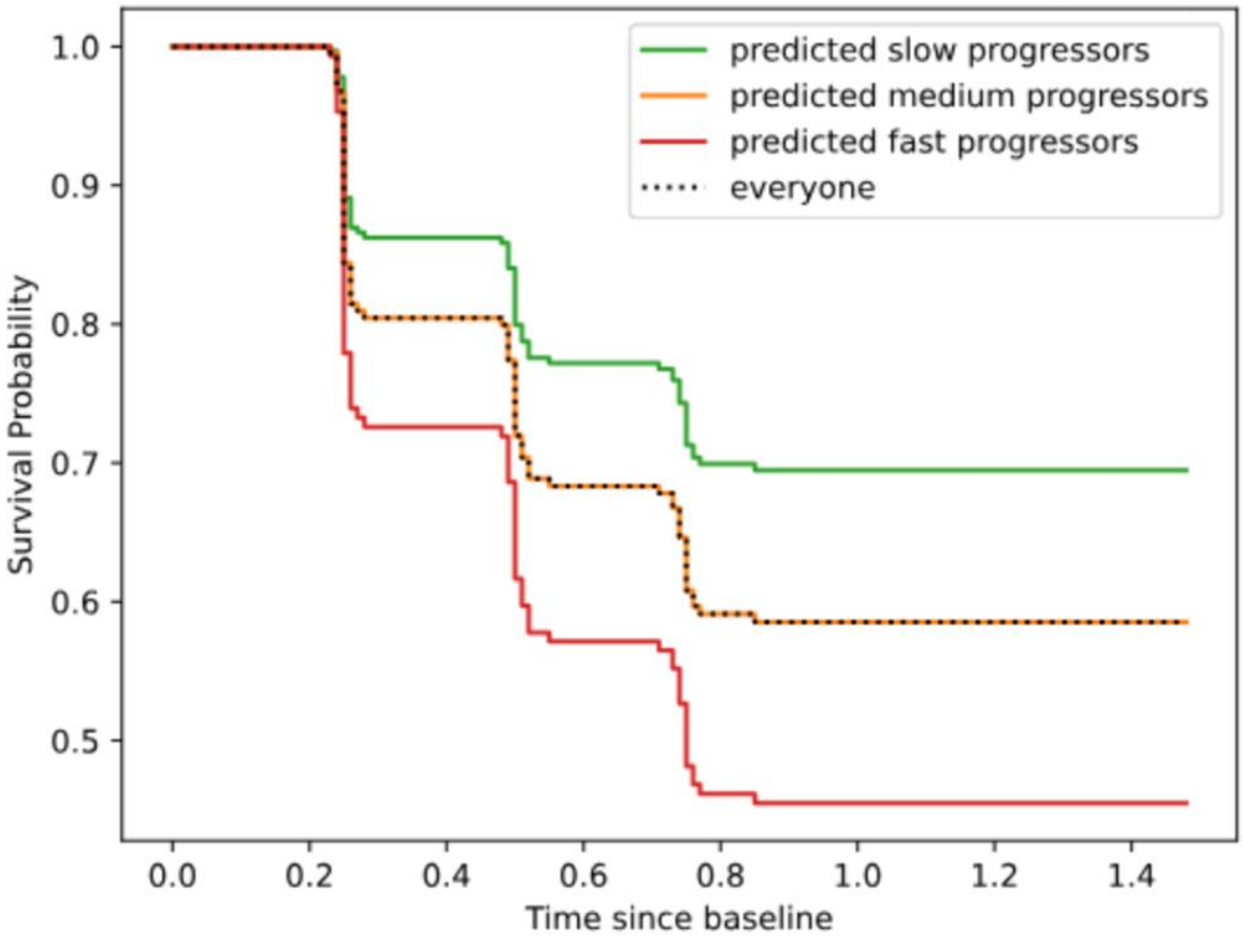
SHIFT 01-637

Poster on Board - Shift 01
TAUPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
2-3 April 2025

SIMULATION OF TIME-TO-WORSENING OUTCOME IN THE MOVES-PD STUDY: IMPACT OF PROGNOSTIC COVARIATE ADJUSTMENT

Nicolas Beaume[1], Graziella Mangin-Laignel[1], Stanley Durrelman[1], Pierre-Emmanuel Poulet[1], Adeebah Adams[2], Vincent Thuillier[3], Pascal Minini[3], Catherine Coulouvrat[3], Judith Peterschmitt[4]
[1]Qairnel, Paris, France, [2]Sanofi, Midrand, South Africa, [3]Sanofi, Gentilly, France, [4]Sanofi, Cambridge, United States of America

Aims: To assess a time-to-worsening outcome in MOVES-PD[a], a randomized Phase 2 trial evaluating venglustat in GBA1-associated Parkinson's disease and evaluate the effect of adjusting this outcome with prognostic covariates.
Methods: We defined an event as the increase of at least 5 points of the primary outcome (MDS-UPDRS II+III) from baseline, confirmed at the subsequent visit. We compared placebo and treatment arm using a Cox proportional hazards model adjusted for baseline MDS-UPDRS Part II+III, MoCA, LEDD, and GBA mutation severity. We used PD Course Map[b,c], a digital twin technology, to forecast the trajectory of the primary outcome based on screening and baseline data. Two prognostic scores were derived: Predicted Primary Outcome (PPO) and Parkinsonian Age at baseline (ParkAge). Participants were grouped into slow, medium or fast progressors (PPO), and early, medium and late patients (ParkAge). We used these discrete scores as covariates in the Cox model.
Results: The treated arm showed a higher risk of worsening compared to placebo (HR = 1.63; 95% CI = 1.06-2.51; p = 0.03), but no baseline covariates were significantly associated with the outcome. The model with discretized prognostic covariates has similar treatment effect but with a lower p-value (HR = 1.73; 95% CI = 1.13-2.67; p = 0.01), with significant differences in progression speeds (PPO, p=0.02) and disease stage at baseline (ParkAge,



p=0.04).

Conclusions: Time-to-worsening outcome proved more sensitive than continuous outcomes in MOVES-PD . Categorized prognostic covariates further enhanced sensitivity, underscoring the potential of this approach for designing future trials with time-to-event outcomes. This study was funded by Sanofi. References: [a]Giladi N et al. Lancet Neurol. 22 (2023) [b]Maheux E, et al. Nat Commun. 14 (2023) [c]Couronné R. et al. Mov. Disord. 35 (2020)

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SHIFT 01-638

Poster on Board - Shift 01
TAUPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
2-3 April 2025

TARGETING FAST PROGRESSORS IN CLINICAL TRIALS: A SIMULATION WITH MOVES-PD DATA USING PD COURSE MAP FOR FORECASTING PROGRESSION

Graziella Mangin-Laignel[1], Nicolas Beaume[1], Stanley Durrelman[1], Adeebah Adams[2], Pascal Minini[3], Vincent Thuillier[3], Catherine Coulouvrat[3], Judith Peterschmitt[4]
[1]Qairnel, Paris, France, [2]Sanofi, Midrand, South Africa, [3]Sanofi, Gentilly, France, [4]Sanofi, Cambridge, United States of America

Aims: To evaluate the reduction in sample size achievable through an enrichment strategy that uses prediction of disease progression.
Methods: We defined the event of interest as an increase of at least 5 points of the primary outcome (MDS-UPDRS Part II+III (OFF) sum score) from baseline, confirmed at the subsequent visit. We trained a classifier to predict the occurrence of the event from the baseline data of each participant in the MOVES-PD[a] trial. Input were pre-specified covariates and data derived from PD Course Maps[b,c], a digital twin technology forecasting disease progression from baseline. We computed the theoretical sample size for a trial akin to MOVES-PD that would include only patients with the highest risks of experiencing this event. We compared with the theoretical sample size without enrichment in fast progressors. Additionally, the results were compared to the maximum theoretical sample size reduction achieved by including only the true 50% fastest progressors.
Results: Restricting enrolment to the true fastest progressors would reduce the sample size by 25% while retaining 50% of the screened patients. The machine learning model achieved up to 15% sample size reduction, while retaining 16% of the screened patients in a cross-validation setting.
Conclusions: The PD Course Map shows promise as a strategy to reduce sample size by enriching the trial population with participants most likely to experience the event of interest during follow-up period. However, more stringent selection criteria necessitate screening a larger number of patients, warranting further evaluation. This study was funded by Sanofi. **References:** [a]Giladi N et al. Lancet Neurol. 22 (2023) [b]Maheux E, et al. Nat Commun. 14 (2023) [c]Couronné R. et al. Mov. Disord. 35 (2020)

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SHIFT 01-641

Poster on Board - Shift 01
TAUPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

EVIDENCE OF RECENT EVOLUTIONARY SELECTION AT ALZHEIMER DISEASE RISK LOCI IN AMERINDIAN POPULATIONS

Timothy Ciesielski[1], Neetesh Pandey[2], Farid Rajabli[3], Himiede Sesay[1], Razaq Durodoye[1], Rufus Akinyemi[4], Margaret Pericak-Vance[3], Jonathan Haines[5], Nilton Custodio[6], Rafael Samper-Ternent[7], Rebeca Wong[8], Giuseppe Tosto[9], Scott Williams[10]
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Aims: Many genetic variants associate with late-onset Alzheimer Disease (LOAD). As most of these variants are common, we are interested in their contribution to health and reproductive fitness across several life contexts. Illuminating these effects may inform the development of preventive interventions against dementia-causing effects later in life. To this end, we evaluated evidence of recent positive selection in or near LOAD variants in two highly-differentiated Amerindian populations.
Methods: We obtained whole-genome sequence data from 2,653 Mexicans and 638 Peruvians and used Selscan to obtain nSL values (which detects recent evolutionary selection based on Extension of Haplotype Homozygosity). We then identified SNPs with allele frequency normed |nSL| in the top one percent for Mexicans and Peruvians. Finally, we determined how many of these SNPs were in the gene lists from the largest most recent GWAS of LOAD. These ANNOVAR annotated lists include SNPs in the genes and regulatory regions for all genes implicated in by the index SNPs identified in the GWAS.
Results: Among the Mexicans, 13 LOAD-gene SNPs were in the top one percent of nSL scores. Among the Peruvians, 195 LOAD-gene SNPs were in the top one percent. Only one SNP was in the top 1% of scores in both Amerindian populations: rs6974672 (chromosome7:8121592). This SNP is in an intron for *ICA1*.
Conclusions: We identified evidence of recent positive selection at rs6974672 (*ICA1*) in Mexicans and Peruvians. Decreased *ICA1* expression is found in both Alzheimer mouse models and LOAD patients. It also alters amyloid precursor protein and metalloproteinases expression. More work is needed, but changing

environmental conditions could have caused this to be selected in these Amerindian populations over the last 10,000 years, while simultaneously increasing LOAD risk.

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SHIFT 01-642

Poster on Board - Shift 01
TAUPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
2-3 April 2025

THE PREVALENCE OF PARKINSONISM IN FTD SYNDROME AND ITS IMPLICATION TO LIFE SPAN : KOREAN MULTICENTER FTD STUDY

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Aims: To investigate the parkinsonism in each clinical syndrome of frontotemporal dementia(FTD) and its complication on survival time.
Methods: A total of 216 patients with FTD [82 behavioral variant FTD (bvFTD), 78 semantic variant primary progressive aphasia (svPPA), 43 non-fluent/agrammatic variant PPA (nfvPPA), 13 FTD-motor neuron disease (MND)] were enrolled from 16 centers across Korea. Behaviors and parkinsonism were assessed using the Frontal Behavioral Inventory and Unified Parkinson's Disease Rating Scale Part III, respectively.
Results: The parkinsonism is most common in bvFTD and significantly associated with survival. An overall median survival of FTD was 12.1 years. The survival time from onset was shortest for FTD-MND and longest for svPPA. The negative hehavioral symptoms were also associated with survival. In the nfvPPA group, the presence of dysarthria had a negative impact on survival.
Conclusions: These findings provide useful information to clinicians planning for care.

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SHIFT 01-643

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
2-3 April 2025

EXPLORATION VERSUS EXPLOITATION DILEMMA: NEUROCHEMICAL AND NEUROPHYSIOLOGICAL CORRELATES OF DECISION MAKING IN PARKINSON'S DISEASE: USING SOURCE IMAGED MAGNETOENCEPHALOGRAPHY AND SEMANTIC FLUENCY DATA

Dietta Chihade[1], Alex Wiesman[2], D Louis Collins[3], Victoria Madge[3], Ian Gold[3], Sylvain Baillet[3]
[1]McGill University, Neuroscience, Montreal, Canada, [2]Simon Fraser University, Biomedical Physiology & Kinesiology, Burnaby, Canada, [3]Montreal Neurological Institute-Hospital, Mcconnell Brain Imaging Centre, Montréal, Canada

Aims: Parkinson's Disease (PD) significantly impairs decision-making, particularly affecting the exploration-exploitation (EE) trade-off, which involves choosing between familiar, reliable options (exploitation) and riskier, potentially more rewarding ones (exploration). The death of neuromelanin-rich dopaminergic and noradrenergic cells in the substantia nigra and locus coeruleus underlies PD's motor and cognitive impairments, but the impact of noradrenergic signaling from the locus coeruleus on decision-making is poorly understood, highlighting the need for further research into these mechanisms.
Methods: Seventy-nine Parkinson's disease patients (mean age 66 years) underwent neuromelanin-MRI scans to assess locus coeruleus integrity, MEG to measure aperiodic-corrected alpha band activity over norepinephrine-sensitive cortical regions, and their semantic verbal fluency performance was evaluated using clustering and switching metrics.
Results: Although PD patients exhibited a shift toward exploitation in semantic search strategies during verbal fluency tasks, mediation analysis revealed that the small positive effect of locus coeruleus norepinephrine modulation on MEG alpha power spectral density ($\beta = 0.0199$, $p = 0.363$) was not statistically significant, indicating that while positive trends exist, these effects may not be robust.
Conclusions: The study found that levels of neuromelanin in the locus coeruleus (LC) do not predict semantic exploration-exploitation (EE) scores, nor is there an observed interplay between these scores and alpha wave activity measured by magnetoencephalography (MEG) in Parkinson's Disease (PD) patients. However, a relationship was identified between MEG alpha activity and the amount of neuromelanin in the LC, highlighting the need for further investigation into these processes and their impact on decision-making in PD.

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SHIFT 01-649

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

RELEVANCE OF ANTI-IGLON5 TESTING IN MOVEMENT DISORDER CLINICAL PRACTICE

Manfredi Carta, Benjamin Vlad, Bettina Balint
University Hospital Zurich, Department Of Neurology, Zurich, Switzerland

Aims: Anti-IgLON5 disease is a rare but treatable disease which frequently presents with movement disorders. It has been reported to mimic classic "idiopathic" degenerative diseases where immune involvement is typically not suspected, e.g. atypical parkinsonism including progressive supranuclear palsy (PSP) or multiple system atrophy (MSA), frontotemporal dementia (FTD) with stereotypies, and Huntington-like chorea. This study aimed to assess the seropositivity rate in patients with movement disorders that can be associated with anti-IgLON5 disease, excluding typical Parkinson's disease and essential tremor.
Methods: We conducted a retrospective analysis of records from 2022 to 2024 at a tertiary neurological clinic. Patients tested for IgLON5-antibodies were identified from laboratory records.
Results: We identified 53 movement disorder patients who underwent anti-IgLON5 testing in our laboratory. The phenotypes included PSP (n=20), MSA (n=4), corticobasal syndrome (n=2), stereotypies (n=5), chorea (n=2), undetermined parkinsonism (n=11), atypical-atypical parkinsonism (n=6), and "various" (n=3). Of these, 52 tested negative, and 1 PSP phenotype patient had an equivocal result pending further investigation.
Conclusions: Anti-IgLON5 seropositivity is rare, and in our cohort of patients without strong clinical indicators of the disease, testing yielded low results. Routine screening for IgLON5 antibodies in the absence of clear clinical indicators for anti-IgLON5 disease seems unlikely to provide relevant diagnostic value.

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SHIFT 01-650

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

NEUROLINCS: A LNCRNA CAPTURE PANEL TO BETTER CHARACTERIZE NEURODEGENERATIVE DISEASES AND PATIENT STRATIFICATION USING NOVEL LNCRNA SIGNATURE.

Nicolas Scalzitti[1], Dany Mukesha[1], Seval Kul[1], Miguel Casanova[2], Lucas Pham-Van[1], Çetin Kocaefe[1], Stéphanie Boutillier[2], Hüseyin Firat[2]
[1]Firalis, S.A., Huningue, France, [2]Amoneta Diagnostics, Huningue, France

Aims: Neurodegenerative diseases (ND), such as Alzheimer's disease (AD), are leading causes of mortality worldwide. Diagnosing these pathologies remains complex, requiring the development of more effective and less invasive methods. Long non-coding RNAs (lncRNAs) have recently emerged as potential biomarkers. This work aims to identify novel lncRNAs enriched in the brains (and/or blood) of patients with AD and other ND.
Methods: A pipeline was developed for the de novo reconstruction of transcripts and the identification of novel lncRNAs from 122 brain tissue data (Rush AD Encode) and 764 deep RNAseq from PBMC. Differential expression analysis was performed to identify lncRNAs enriched in AD patients compared to healthy controls (HC). Gene Ontology term enrichment and pathway analysis were conducted to elucidate the biological roles of these lncRNAs. In parallel, machine learning algorithms are being applied to build predictive models based on the signatures of these lncRNAs.
Results: We identified a subset of lncRNAs that are significantly enriched or differentially expressed in the brains and/or blood of patients with AD (or dementia), underscoring their potential as biomarkers. Functional analysis revealed their involvement in key biological processes linked to neurodegeneration such as AD or Parkinson's disease. Preliminary modeling approaches using these signatures demonstrated robust accuracy in distinguishing AD patients from HC. Based on these findings, the NEUROLINCS capture panel was created
Conclusions: The NEUROLINCS kit offers new insights into ND by quantifying brain-enriched lncRNAs. Our kit shows promise for diagnosing ND through lncRNA-based biomarkers. Future efforts will focus on refining machine learning models to enhance diagnostic and prognostic accuracy, paving the way for early intervention and personalized treatments. This approach could also extend to other brain disorders (e.g., depression, autism).

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SHIFT 01-651

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

PLASMA P-TAU217 VERSUS SERUM P-TAU217: ARE THEY EQUIVALENT? ASSESSMENT OF THREE COMMERCIAL ASSAYS

Ally Albert[1], Yijun Chen[2], Anuradha Sehrawat[1], Xuemei Zeng[3], Tara Lafferty[3], Michel Nafash[1], Marissa Farinas[1], Ann Malia[4], Rebecca Roush[4], Ann Cohen[4], Oscar Lopez[5], Thomas Karikari[1]
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Aims: Phosphorylated tau-217 (p-tau217) is a leading blood biomarker for Alzheimer's disease (AD). Despite its recognized value, the diagnostic performance of p-tau217 in matrices other than ethylenediaminetetraacetic acid (EDTA) plasma remains underexplored. This study assessed the diagnostic capabilities of p-tau217 in serum compared with plasma, using assay available on three different commercial platforms.
Methods: EDTA plasma and serum samples were concurrently collected from participants under a uniform blood collection protocol. The participants (n=50) were recruited from the University of Pittsburgh Alzheimer's Disease Research Center. The levels of p-tau217 in both sample types for all n=50 individuals were measured using the ALZpath and Lumipulse methods. A subset of n=43 participants were further evaluated with the Nulisa assay.
Results: Plasma and serum p-tau217 levels significantly differentiated AD-positive from AD-negative ($p<0.0001$) individuals across all platforms, with equivalent accuracies. Exceptionally strong correlations between matched plasma and serum p-tau217 measurements were found for all assays; ALZpath ($R=0.9135$, $p<0.0001$), Lumipulse ($R=0.9787$, $p<0.0001$), and NULISA ($R=0.902$, $p<0.0001$). However, the absolute levels of p-tau217 were higher in plasma than in serum for each platform, although the degree of variability in concentrations differed. For ALZpath, plasma p-tau217 was 1.483-fold higher than serum p-tau217 compared with 1.416-fold for NULISA. Conversely, for Lumipulse, serum p-tau217 was 1.149-fold higher than plasma p-tau217.
Conclusions: This study demonstrates that serum p-tau217 achieves robust diagnostic performance, comparable to plasma, across multiple assay platforms, supporting its use as a viable matrix for AD biomarker diagnostics. The significant correlation between serum and plasma measurements, across all assays, underscores their reliability and potential utility in clinical settings, especially in hospital systems where collection of serum is preferred over plasma.

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SHIFT 01-652

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
2-3 April 2025

TARGETING EARLY TAU PATHOLOGY IN ALZHEIMER'S DISEASE: ULTRASENSITIVE DETECTION OF SOLUBLE PRE-TANGLE AGGREGATES

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Aims: This research aims to conduct clinical validation of our pioneer novel approach for the amplification and quantification of minute amounts of aggregated human tau protein, focusing on a specific domain crucial for disease pathology.
Methods: Firstly, we will conduct comprehensive analytical validation of our recently discovered novel assay that amplifies minute amount of cerebrospinal fluid (CSF) tau protein and quantifies using a Single molecular array (Simoa) based immunoassay. Secondly, we will evaluate the clinical value of our assay in two human cohorts with longitudinal data and neuropathological examination. Finally,, we will adapt the assay for plasma and serum compatibility, validate it, and assess its clinical applicability.
Results: Our preliminary findings demonstrate the successful amplification of a very low amount of aggregated tau in CSF. This has led to a substantial enhancement in the detectability of tau aggregates, offering enhanced sensitivity.
Conclusions: Accurately quantifying tau aggregates remains challenging due to low abundance in body fluids. This novel method holds immense value for clinical research studies and clinical trials, allowing for the precise monitoring of treatment responses. Furthermore, the adoptation of this method to blood plasma and serum samples holds promise for non-invasive diagnostic tools, substantially enhancing our capacity to address the growing global burden of neurodegenerative diseases. In summary, our method stands as an innovative effort with far-reaching implications for the field of neurodegenerative disease diagnosis and treatment. A successful outcome of this project will provide clinicians and researchers with a powerful tool for early detection and precise monitoring of tau pathology, ultimately improving life quality of individuals affected by these devastating conditions.

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SHIFT 01-656

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

MONOCLONAL ANTIBODY DETECTS PHOSPHO-TAU P217 IN ALZHEIMER'S DISEASE TISSUE AND BIOFLUIDS

Arica Aiello[1], Lei Liu[2], Daniel Mulhern[1], Steven Mullenbrock[1], Mark Stump[1], Yujia Weng[1], Emily Estabrook[1], Kaitlin Macchi[1], Thorsten Wiederhold[1], Richard Cho[1]
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Aims: Measurement of fluid-based biomarkers largely leverages immuno-based technologies, including enzyme-linked immunosorbent assay (ELISA) assays, immunoassays with electrochemiluminescence detection (ECL), single molecule arrays, and immunoprecipitation mass spectrometry (IP-MS). To improve on these immunoassays, we sought to develop a highly specific and sensitive rabbit monoclonal antibody to pTau217.
Methods: The phospho-Tau (Thr217) (E9Y4S) rabbit mAb was generated, recombinantly cloned, and validated for target specificity by western blot, immunoprecipitation, peptide dot blot, and ELISA. Affinity and binding kinetics of E9Y4S were measured using the Octet RED96 System (Sartorius) and compared to an additional commercially available mAb to pTau217. ELISA was performed using PathScan® RP Phospho-Tau (Thr217) Sandwich ELISA Kit #59672, established using E9Y4S as the capture antibody, on both rodent and human tissue and biofluids. E9Y4S was also paired with another commercially available tau antibody, to measure p217 in AD and non-AD human CSF using other pair-based platforms like SMCxPRO (MilliporeSigma).
Results: E9Y4S was highly specific to pTau217 as evaluated by western, peptide dot blot, and immunoprecipitation using various mouse and human AD tissue. The binding kinetics revealed high avidity and kinetics to its target compared to a comparable commercially available antibody. We successfully used the pTau217 ELISA to detect elevated levels of pTau217 in plasma from the TauP301S transgenic mouse model and in human AD+CSF. We demonstrate that E9Y4S can distinguish between AD and non-AD human CSF using other pair-based platforms.
Conclusions: We have developed a highly sensitive and specific Phospho-Tau (Thr217) (E9Y4S) Rabbit mAb able to detect pTau217 by western blot, IP, and is compatible with pair-based assays like ELISA and ELISA-like platforms. E9Y4S detects pTau217 at the picogram level allowing for detection of pTau217 in biofluids.

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SHIFT 01-657

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

DEVELOPMENT OF A NOVEL IN-HOUSE BLOOD BIOMARKER PANEL FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

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Aims: Currently a definitive diagnosis for Alzheimer's disease (AD) is not readily available to the wider community as the gold standard markers of AD are either invasive and/or expensive. Therefore, there is an urgent need for a relatively low-cost blood test that can be readily used in clinical settings. This study aims to address this gap by developing a reliable and cost-effective in-house blood-based biomarkers panel for routine use in clinical labs for early detection of AD. Our team have shown that specific proteins in the blood, namely phosphorylated tau and Glial Fibrillary Acidic Protein (GFAP) as biomarker for early AD diagnosis. However, only a combination of selected blood biomarkers can reliably predict who is at risk of AD. We will first develop singleplex diagnostic Single Molecule Array (Simoa) blood assays for phosphorylated Tau: p-Tau217, pTau205, pTau208 as well as full-length of GFAP. A novel panel of the best 3 biomarkers will then be selected to establish panel for preclinical diagnosis of AD.
Methods: Monoclonal antibodies against the three pTau variants, N- and C-terminus GFAP were generated in collaboration with GenScript and undergone initial characterisation with controlled primary assessment of specificity and affinity (i.e immunostaining, immunoprecipitation-Western Blot, and immunoprecipitation-mass spectrometry) using various tissues such as cells expressing phospho-site-deficient (negative control), human recombinant proteins (positive controls), brain, and CSF from healthy and AD. Finally, these antibodies were developed for Simoa assay.
Results: We have successfully generated specific high affinity monoclonal antibodies against p-Tau217, p-Tau205, p-Tau208, and full-length GFAP, confirming that these antibodies have the necessary specificity and sensitivity for the Simoa platform.
Conclusions: The development of Simoa assays will be validated in a highly characterised Alzheimer cohort AIBL and a novel AD blood panel established.

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Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

CSF TOTAL-TAU AS PREDICTOR OF SURVIVAL IN SUSPECTED NON-ALZHEIMER DISEASE PATHOPHYSIOLOGY

Nils Briel[1,2], Marc Borsi[1,2], Simon Schreiner[1,2], Manfredi Carta[1,2], Claudio Togni[1,2], Tommaso Nicoletti[2,3], Tobias Weiss[1,2], Hans Jung[1,2]
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Aims: The 2018 Amyloid-Tauopathy-Neurodegeneration (ATN) research framework defines patients with negative A, but positive T and/or N biomarkers as "Suspected Non-Alzheimer Disease Pathophysiology" (SNAP, Jack et al. 2018). Previous studies have identified cerebrospinal fluid (CSF) total-tau as a predictor of worse survival outcomes in Alzheimer's disease (AD), Lewy body diseases, and aged individuals. We investigated the prognostic implications of a SNAP biomarker profile on survival outcomes in a real-world cohort.
Methods: We conducted a retrospective longitudinal monocentric study of survival outcomes of 52 patients with a CSF-defined SNAP biomarker profile who underwent lumbar puncture between 2019 and 2024. We collected CSF biomarker results and clinicodemographic variables including time-to-event intervals. Biomarkers were measured using the Fujirebio Lumipulse G600II system. We used the Youden index to dichotomize SNAP subgroups by CSF biomarkers and age, and assessed survival probabilities using Kaplan-Meyer curves and Cox proportional hazard models.
Results: Median follow-up times were 3 and 23 months in deceased cases and survivors, respectively. Deceased SNAP cases were younger (median: 70 vs. 75 years, $p<.04$) and had higher total-tau levels (median: 1,063 vs. 511 pg/mL, $p<.001$). Excluding 7 prion cases, the survival-conditioned cut-point for total-tau was 560 pg/mL, and higher values were significantly associated with a worse outcome (log-rank test, $p<.001$). Total-tau remained an independent predictor of survival in a Cox proportional hazards model (hazard ratio: 15.15, $p<.002$), adjusted for pTau-181, AB ratio, prion diagnosis, age, and sex.
Conclusions: This study extends the prognostic validity of CSF total-tau as a predictor of survival to SNAP, a biomarker-defined group of heterogeneous neurodegenerative diseases complementary to AD. Validation studies in larger and more diverse cohorts are warranted.

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SHIFT 01-659

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

THE PERFORMANCE OF CSF NPTX2 AS A BIOMARKER OF CLINICAL PROGRESSION IN ALZHEIMER'S DISEASE

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Aims: Neuronal pentraxin 2 (NPTX2) is a protein involved in synaptic function. Change in cerebrospinal fluid (CSF) NPTX2 has been correlated with cognitive decline in Alzheimer's disease (AD), suggesting a role for CSF NPTX2 as a biomarker of clinical progression. Here, we examine the relationship between CSF NPTX2, clinical data, and biomarkers from a Phase 2 study in early AD.
Methods: TANGO (NCT03352557) was a Phase 2 clinical study assessing the safety and efficacy of gosuranemab, an anti-tau monoclonal antibody, in participants with early AD. CSF was collected up to Week 78 from a subset of randomized TANGO participants (n=103). CSF NPTX2 was measured using the FujireBio Innotest immunoassay kit. Cognitive and functional measurements were collected using multiple clinical assessments. Correlation analysis was applied to data at the individual patient level.
Results: CSF NPTX2 levels at baseline had the strongest positive association with cognitive decline as measured by MMSE change from baseline over 78 weeks (correlation=>0.18, p-value <0.05 at all post-baseline timepoints. At Week 76, there was a modest association between change from baseline in CSF NPTX2 and the ADCS-ADL scale (p=0.05, Pearson correlation=0.23). There were no associations between change from baseline in CSF NPTX2 and changes in the other clinical scales measured in the TANGO study, including CDR-SB, iADRS, and ADAS-Cog13.
Conclusions: These preliminary results suggest CSF NPTX2 may be a useful biomarker for predicting cognitive decline in AD. Future analysis of CSF NPTX2 in amyloid positive MCI and mild AD subsets and its relationship with known biomarkers of AD (tau, phosphorylated tau, amyloid beta) will be explored to understand how this marker can be applied to early disease staging and monitoring of clinical progression.

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SHIFT 01-660

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

PRECISE AND SENSITIVE QUANTITATION OF PTAU-217 IN PLASMA AND CSF USING AN AUTOMATED WORKFLOW

Warren Higgs[1], Samantha Willis[2], Malcolm Connor[2], Joe Dunbar[3], Isabel O'Brien[3], Lee Honigberg[4], Yoav Noam[2]
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Aims: Growing evidence suggests a strong diagnostic utility for a phosphorylated isoform of the Tau protein (pTau-217) as a specific biomarker for Alzheimer's disease. However, many existing methods for detecting and quantifying pTau-217 in biofulids are time-consuming, expensive, and/or technically complex. Using a microfluidics immunoassay approach (Simple Plex/ Ella™) combined with a well-characterized monoclonal antibody against pTau217 (ALZpath), we set to establish and validate an automated assay to measure pTau217 in plasma and cerebrospinal fluid (CSF).
Methods: The Simple Plex pTau-217 ALZpath assay was established on microfluidic cartridges that measure up to 72 samples within 90 minutes, using as little as 25 ul sample volume. Analytical validation was performed to assess the performance characteristics of the assay, including dynamic range, precision, accuracy, and parallelism. The biomarker utility of the assay was assessed in a cohort of healthy controls and Alzheimer's disease (AD) patients.
Results: The microfluidic pTau-217 assay yielded a ~3.5 log dynamic range, as assessed by precision and dilutional linearity studies across a range of concentrations. Intra-assay precision was measured at less than 5% CV using both high- and low-level controls (n=16 replicates per control), and inter-assay precision averaged at 10.0% CV (n=174). Dilutional linearity experiments demonstrated good assay parallelism, recovering at 94-106% for plasma and 88-97% for CSF. Spike/recovery experiments demonstrated acceptable accuracy with mean recovery values of 86-94% (plasma) and 93-137% (CSF). Measurement of pTau217 in a cohort of AD and control donors demonstrated significant elevation of pTau217 in AD samples (p=0.007, Mann-Whitney test), consistent with previous reports.
Conclusions: This study supports the utility of an automated pTau-217 assay for fast, reliable, and sensitive quantitation in plasma and CSF samples of AD patients.

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Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
2-3 April 2025

ASSOCIATION OF CYTOKINE PROFILES AND NUCLEAR IMAGING IN B-AMYLOID–NEGATIVE CBS

Alexander Jäck[1,2], Carla Palleis[1,2,3], Wolfgang Wilfert[4], Alexander Bernhardt[1,2], Steffen Halbgebauer[5], Johannes Gnörich[6], Sabrina Katzdobler[1,2,3], Endy Weidinger[1,2], Hayrettin Tumani[5], Daniel Teupser[4], Nicolai Franzmeier[3,7], Günter Höglinger[1,2,3], Matthias Brendel[1,3,6], Johannes Levin[1,2,3]
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Aims: To identify reliable biomarkers for differential diagnosis and disease progression in neurodegenerative diseases, with a focus on neuroinflammation. This study aims to explore fluid biomarkers as accessible and less invasive alternatives to nuclear imaging, enabling the prediction of PET imaging results and advancing biomarker discovery.
Methods: CSF and serum samples were obtained from Aβ-negative CBS patients (n=22) and from symptomatic non-inflammatory controls (n=20). Cytokines were measured using a 48-Plex Cytokine Assay (Bio-Rad). Principal component analysis (PCA) was performed for dimensionality reduction to identify significant cytokine patterns. Demographic, clinical and imaging data, including global [^{18}F]GE-180-PET z-scores and TREM2 concentrations, were also retrieved from the CBS cohort database. Spearman's correlation analyses were conducted to evaluate associations between cytokine levels and the different clinical and imaging scores.
Results: Principal components were identified in CSF and serum, with two components explaining over 50% of the variance in the dataset. In CSF, PC2 significantly differentiated CBS patients from controls. However, no significant correlations were observed between the principal components and either TREM2 concentrations or the global TSPO z-score. Interestingly, TREM2 levels in CSF strongly correlated with the cytokines MIF and MIP-1α, while the global [^{18}F]GE-180-PET z-score showed negative correlations with IL-1α, IL-17A, and IL-16 in serum.
Conclusions: Principal component analysis identified distinct inflammatory patterns, with microglial- and monocyte-related components serving as key differentiators between CBS patients and controls. Notably, the microglial marker TREM2 showed a strong correlation with MIP-1α, a chemokine involved in CCR5-mediated immune trafficking. Additionally, lower serum levels of IL-17A were associated with higher TSPO-PET burden, supporting our previous findings that CBS patients with elevated TSPO-PET burden tend to experience slower disease progression.

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SHIFT 01-663

Poster on Board - Shift 01
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - TAU
2-3 April 2025

CONCORDANCE OF ANALYTICAL METHODS WITH VISUAL READING IN TAU PET IMAGING ACROSS NEURODEGENERATIVE DISORDERS

Yuna Gu[1], Jihwan Yun[2], Daeun Shin[1], Eun Hye Lee[1], Sang Won Seo[1], Alexis Moscoso Rial[3], Michael Schöll[4]
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Aims: This study evaluates the concordance of FDA-approved Tau PET visual reading with different quantification methods across neurodegenerative disorders. Establishing reliable quantification metrics is crucial for standardizing tau PET interpretation and improving its utility in both clinical and research applications. We aim to determine which analytical methods and brain regions best align with visual reading, while investigating relationships between these methods, plasma biomarkers, and cognitive changes.
Methods: We analyzed 289 participants (37 CU, 53 MCI, 85 DAT, 79 SVCI, 35 FTD) comparing three quantification pipelines (MCALT, FreeSurfer without/with PVC) across four brain regions (MTL, temporal meta-ROI, NEO, temporoparietal) against visual reading criteria. We assessed regional concordance rates with visual reading and examined correlations with plasma biomarkers and longitudinal MMSE changes.
Results: FreeSurfer without PVC showed the highest concordance with visual reading, particularly in temporal meta-ROI (AUC=0.93, concordance=84.94%, κ=0.703), outperforming others by preserving signal characteristics critical for visual assessment. Despite visual reading patterns focusing on posterolateral temporal and parietal regions, temporal meta-ROI emerged as the optimal quantitative correlate, capturing both early (entorhinal) and established (inferior/middle temporal) tau pathology patterns. Plasma p-tau217 demonstrated the strongest correlation with visual reading (AUC=0.828, Cohen's d=-1.097), and tau-positive cases predicted faster cognitive decline ($p<0.001$).
Conclusions: FreeSurfer without PVC and the temporal meta-ROI provide optimal quantitative correlates of visual reading across neurodegenerative disorders. The strong associations observed between visual assessments, quantitative metrics, plasma p-tau217, and cognitive decline support the use of this integrated approach in both clinical and research contexts. This framework bridges clinical visual assessments with advanced research applications in tau PET imaging, ultimately enhancing diagnostic accuracy, improving prognostic evaluation in neurodegenerative diseases.

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SHIFT 01-667

Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE AND RNAI THERAPY
2-3 April 2025

AAV-RNAI TARGETING MAPT FOR THE REDUCTION OF TAU PATHOLOGY IN ALZHEIMER'S DISEASE

Jessica Hogestyn[1], Yao Chen[2], Jie Bu[1], Erik Wischhof[1], Jordan Bresse[1], Tiffany Chan[1], Robert Jackson[2], Brenda Richards[1], Martin Goulet[1], Christian Mueller[1], Bradford Elmer[1]
[1]Sanofi, Waltham, United States of America, [2]Sanofi, Cambridge, United States of America

Aims: Tau reduction is a promising therapeutic approach with the potential to slow the progression of Alzheimer's disease. Adeno-associated viruses (AAVs) are well-validated gene delivery vectors with the ability to express therapeutic RNAi constructs for years in the brain. Here, we propose AAV delivery of an artificial miRNA (amiRNA) targeting the tau-encoding *MAPT* mRNA for sustained tau reduction with a single therapeutic injection.
Methods: *In silico* designed amiRNA sequences were screened for reduction of human tau protein in a *MAPT* overexpressing U2OS cell line. Candidates were then cloned into AAV vectors to evaluate reduction of *MAPT* mRNA, phosphorylated tau protein, and neurofilament light (NfL) in the Tau22 mouse model. Off-target mRNA reduction in human cells was evaluated using paired RNA and CLIP sequencing to identify mRNA sequences that were significantly downregulated in amiR^{Tau01}-treated cells with evidence of physical amiR^{Tau01} targeting within the RNA-induced silencing complex. Pharmacology was assessed in nonhuman primates (NHPs) using AAV.GMU01-amiR^{Tau01} administered by intra-cisterna magna administration, with *MAPT* knockdown assessed by RT-dPCR and RNAscope.
Results: amiR^{Tau01} significantly reduced pathological forms of phosphorylated tau and levels of the neurodegenerative biomarker NfL in the Tau22 tauopathy mouse model. In off-target analyses we identified amiR^{Tau01} doses that maintained clinically-relevant, >60% *MAPT* reduction without significantly impacting off-target genes. In NHP brain, we demonstrated clear amiR^{Tau01}-mediated *MAPT* knockdown in individual neurons, however, vector biodistribution was insufficient to drive *MAPT* reduction in bulk tissue.
Conclusions: Out of 22 initial designs, we identified amiR^{Tau01} as a potent, accurately processed, and highly specific amiRNA. Our findings warrant development of new AAV capsids with improved brain biodistribution to facilitate clinical development of this therapeutic candidate for Alzheimer's disease.

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SHIFT 01-670

Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
2-3 April 2025

IMMUNOTHERAPEUTIC TARGETING LYSINE280-ACETYLATED TAU FOR ALZHEIMER'S DISEASE WITH ADEL-Y01

Min-Seok Kim[1], Ha-Lim Song[1], Na-Young Kim[1], Yeon-Seon Mun[1], Dong-Hou Kim[2], Seung-Yong Yoon[1]
[1]ADEL, Seoul, Korea, Republic of, [2]University of Ulsan College of Medicine, Department Of Brain Science, Seoul, Korea, Republic of

Aims: Amyloid plaques and tau neurofibrillary tangles are the two pathologic hallmarks of Alzheimer's disease (AD). With recent approvals of anti-amyloid antibodies for AD, tau is the next pathology to target for therapeutic strategies against AD. Longest of tau isoform is 441 amino acids, and tau is target of various post-translational modifications and proteolytic cleavage, presenting a unique challenge of identifying the key pathogenic species which can seed and propagate tau spread. The hexapeptide ^{275}VQIINK^{280} of tau is a critical region for tau aggregation, and lysine280 is acetylated in various tauopathies including AD. Here, we link acetylated lysine280 to tau pathology and whether targeting acetylated lysine280 tau is effective means of targeting tau pathology in vivo and compared to other anti-tau antibodies.
Methods: We compared acetylated tau against wild-tau in the potential for tau pathology and amino acid substitution to evaluate the role of acetylated lysine280. We developed ADEL-Y01, an antibody that specifically targets acetylated lysine280 tau and tested efficacy in vitro and in vivo tauopathy model mice. Patient insoluble fraction-induced tau seeding inhibition was evaluated using FRET assay, compared to control IgG and other anti-tau antibodies.
Results: Acetylation, especially in the lysine280 is key for tau aggregation and seeding. ADEL-Y01 reduced tau pathology progression and increased neuronal viability in neuronal cultures and tau transgenic mice. Compared to other anti-tau antibodies, ADEL-Y01 showed greater inhibition of tau aggregation and seeding.
Conclusions: Our results demonstrate that acetylated lysine280 tau is a core species involved in tau aggregation and propagation. Among the numerous proposed epitopes of tau, acetylated lysine280 presents a promising target for the treatment of tauopathies. ADEL-Y01 is currently undergoing phase Ia/Ib clinical trial in the United States in collaboration between ADEL and Oscotec.

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SHIFT 01-671

Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

MODULATION OF MICROGLIAL TREM2 IN HUMAN DISEASE RELEVANT CNS MODEL

Agnes Cheong, Anna Mcgrath, Tejaswi Iyyanki, Clément Chatelain, Shameer Khader, Jing Ke, John Kane, Nellwyn Hagan
Sanofi, Cambridge, United States of America

Aims: TREM2 loss-of-function variants are strongly associated with neurodegeneration indications, such as Alzheimer's disease and frontotemporal dementia. Deficiency in *Trem2* in preclinical models of amyloidosis and tauopathy pathology results in excessive neuronal loss and memory impairment. Therapeutic boosting of TREM2 activation in AD mouse models reduces Aβ plaques and improves memory and learning and memory deficits over time. Currently, TREM2 agonist antibodies are in clinical development for patients with early AD. Therefore, it is crucial to understand the biology of TREM2 and establish models that allows for the assessment of TREM2 agonism on the effector function of microglia.
Methods: In this study, we established a disease relevant *in vitro* human iPSC tri-culture system (astrocytes, neurons and microglia) and stimulated the system with a small molecule TREM2 activator.
Results: Bulk RNA sequencing analysis reveals modulation on biological functions and disease pathways. As a complimentary approach, we performed targeted secretome profiling and observed modulation of various cytokines including TREM2 related clinically validated biomarker, IL1RN. Using transcriptomic fingerprinting connectivity analysis, we showed that TREM2 SM partially reversed disease signatures derived from tissue samples of patients with neurodegenerative diseases.
Conclusions: Together, this study demonstrates that the small molecular activator modulates TREM2-related cellular function under basal and disease conditions *in vitro*. In future studies, we will continue to utilize the human cell-based *in vitro* CNS model system as a tool for understanding cellular changes relevant to disease progression.

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SHIFT 01-672

Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

CSF1R INHIBITION OF MICROGLIA PLUS GAMMA STIMULATION OFFER PROTECTIVE EFFECTS IN ALZHEIMER'S DISEASE MOUSE MODEL

Md Rezaul Islam, Chinnakkaruppan Adaikkan, P. Lorenzo Bozzelli, Zhuyu Peng, Matt Sears, Cameron Parro, Ping-Chieh Pao, Na Sun, Taehyun Kim, Karim Abdelaal, Mia Sedgwick, Manolis Kellis, Li-Huei Tsai
MIT, Cambridge, United States of America

Aims: Depleting CSF1R-sensitive microglia reduces inflammation and improves synaptic integrity in mouse models of Alzheimer's disease (AD). However, the effects of CSF1R-sensitive microglial depletion on synaptic and neural functions in AD remain largely unknown. Here, we utilized the 5XFAD mouse model to characterize the effect of CSF1R-sensitive microglial removal by Plx3397 treatment.
Methods: We introduced microglia depletion using CSF1R inhibitor (Plx3397, an FDA-approved drug) in the 5xFAD mouse model of AD and assessed its impact on both molecular and cognitive phenotypes. This drug treatment was further combined with/without patterned sensory gamma stimulation, and we describe the downstream effects using an integrated approach combining *in vivo* neuronal network activity recording across different cortical layers, immunohistochemistry, mouse behavioral experiments and in depth analyses of single-cell transcriptomics data.
Results: Plx3397 administration in 5xFAD mice aberrantly altered neural activity, resulting in a reduced percentage of neurons phase-locked to gamma oscillations. This neural decoupling was closely associated with gene expression changes related to synapse organization. To investigate whether entraining neurons could improve the neural circuit alterations induced by Plx3397, we increased gamma phase-locking of neurons through non-invasive patterned sensory light stimulation. Notably, driving gamma oscillations and rhythmicity in neurons improved neural functions and transformed gene expression profiles, leading to neuroprotective effects and enhanced learning and memory in Plx3397-treated 5xFAD mice. These findings suggest that while CSF1R inhibitors like Plx3397 show promise for disease modification, their effectiveness might be enhanced when combined with non-invasive sensory stimulation to offer neuroprotection and improve cognitive function in Alzheimer's disease.
Conclusions: These findings suggest that CSF1R inhibitors, such as Plx3397, which show great promise for disease modification, may require combination with non-invasive sensory stimulation to offer neuroprotection and improve AD cognitive function.

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SHIFT 01-673

Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / MICROGLIA
2-3 April 2025

TARGETING MICROGLIA TO PREVENT NEURODEGENETATION AND TAU SPREADING

Yixia Jin[1,2,3], Uxía Fraga-Bouzas[1,2,3], Irene Pallás[1,2,3], Guy Brown[4], Carlos Saura[5], Mar Puigdellívol[1,2,3]
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Aims: Intraneuronal tau aggregates are closely linked to neuronal loss and cognitive impairments in tauopathies. Increasing evidence suggests that microglia contribute to neurodegeneration, synaptic loss, and tau propagation. Our study aims to elucidate the role of microglial UDP and ADP receptors in the progression of tauopathy and evaluate their therapeutic potential.
Methods: P301S Tau transgenic mice were used to assess the effects of blocking microglial UDP and ADP receptors to tau progression. Histological analyses were conducted to examine changes in tau pathology and behavioral tests were performed to assess cognitive functions. Moreover, a neuronal-microglial co-culture system is being set up for mechanistic insights.
Results: Inactivation of a microglial UDP receptor in P301S Tau mice preserved neuronal integrity and cognitive function, accompanied by reduced tau pathology in cerebral cortex, indicating that the blockade of microglial phagocytosis can mitigate neuronal loss and tau pathology in neurodegeneration. Similarly, pharmacological blockade of a microglial ADP receptor involved in chemotaxis led to cognitive improvements and a reduction of tau-positive neurons in the hippocampus of a model with tauopathy. Preliminary, observations from the *in vitro* co-culture system suggest that microglia contribute to the loss of tau-positive neurons via UDP and ADP receptors.
Conclusions: Our findings support the therapeutic potential of targeting specific microglial purinergic receptors to prevent the phagocytosis of viable tau-containing neurons in tauopathy. Further research is needed to clarify the underlying mechanisms.

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SHIFT 01-675

Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

ABEMACICLIB CONTROLS TAU PATHOLOGY AND IMPROVES COGNITIVE IMPAIRMENTS IN ALZHEIMER'S DISEASE VIA INHIBITING TAU KINASE AND ACTIVATING AUTOPHAGY

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Aims: This study aims to evaluate abemaciclib, an FDA-approved breast cancer drug, as a potential Alzheimer's disease (AD) treatment. By using AD patient-derived brain organoids and animal models, the research seeks to validate a novel drug screening platform and elucidate abemaciclib's effects on AD pathology, particularly tau-related processes, and its impact on cognition. The study also aims to uncover new mechanisms of action for abemaciclib in the context of AD. By repurposing this drug and exploring its effects on AD pathology, we suggest a promising new therapeutic approach for AD treatment.
Methods: The study employs a logical network-based drug screening platform using AD patient-derived brain organoids to identify promising drug candidates. Abemaciclib, the selected candidate, is then evaluated in animal models to verify its effects on AD pathology and cognition. The research combines in vitro and in vivo experiments to examine abemaciclib's impact on tau pathology, neuronal cell death, and cognitive function. The study also investigates the underlying mechanisms of abemaciclib's action in AD, exploring effects beyond its known CDK4/6 inhibition. This comprehensive approach allows for thorough evaluation of abemaciclib's potential as an AD therapeutic, from initial screening to mechanistic studies.
Results: Abemaciclib significantly reduced hyperphosphorylated tau proteins in AD patient-derived brain organoids. Moreover, oral administration of abemaciclib to AD model mice reduced tau pathology and prevented neuronal cell death, resulting in improved cognitive functions. We discovered that abemaciclib has new roles in inhibiting the well-known tau kinases CaMKII and GSK3β and decreasing hyperphosphorylated tau proteins. Furthermore, abemaciclib promoted autophagic degradation of pathological tau proteins.
Conclusions: Overall, these findings show that abemaciclib is effective in alleviating AD pathology and suggest it as a potential therapy for the disease.

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SHIFT 01-677

Poster on Board - Shift 01
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TAU, PHOSPHORYLATION, TRUNCATION
2-3 April 2025

THERAPEUTIC POTENTIAL OF NIACIN IN PS19 TAUOPATHY MICE

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Aims: We aimed to investigate whether the activation of HCAR2 with the FDA-approved formulation of Niacin (Niaspan®) is a potential therapeutic approach to reduce tau pathology.
Methods: PS19 mice were treated at 9 months of age when they exhibit a severe pathological phenotype. We investigated the therapeutic effect of Niacin by administering daily oral gavage (100 mg/kg) for 30 days or niacin-enriched diet for three months and assessed motor tasks, microglia phenotype, synaptic markers, and levels of tau species.
Results: HCAR2 expression was significantly induced in hippocampal microglia. Treatment with Niacin rescued motor coordination deficits but did not affect clasping reflex nor inflammatory markers. Interestingly, niacin treatment reduced neuronal loss suggesting improvement of synaptic integrity. Genetic deletion of HCAR2 in PS19 mice accelerated the onset of behavioral deficits, exacerbated expression of hyperphosphorylated tau, and worsened microgliosis.
Conclusions: Our results indicate that hippocampal HCAR2 expression is increased in 9-month-old PS19 mice. Moreover, treatment with Niaspan® improved motor coordination but did not affect the clasping reflex nor inflammatory markers. These results indicate that niacin may be acting via microglial HCAR2 to attenuate disease severity. Additional studies are necessary to determinate the exact mechanisms of this process. Overall, this work could support the repurposing of marketed niacin-formulations as a potential therapy for AD.

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SHIFT 01-678

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / ANIMAL MODELS
2-3 April 2025

PHENOTYPIC CHARACTERIZATION OF THE TRANSGENIC HUMAN TDP-43Q331K MOUSE MODEL OF AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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Aims: TAR DNA binding protein 43 (TDP-43) encoded by the TARDBP gene, is a major pathological protein involved in the pathogenesis of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia. Although multiple preclinical research models of ALS exist, to date, mouse models with TDP-43 pathology have not been characterised in detail. Therefore, we performed an extensive phenotypic characterisation of the transgenic human TDP-43Q331K model to assess its suitability for preclinical efficacy studies.
Methods: Transgenic TDP-43 mice expressing human TDP43 with Q331K mutation and mice expressing the wild-type (WT) mouse TDP-43 protein were examined at three different ages (4, 6 and 8 months). Motor function was assessed by a battery of tests (spontaneous behaviour, inverted grid, weight-lifting test, rotarod, CatWalk test, and grip strength). Sciatic nerve electrophysiology was performed by testing compound muscle action potential (CMAP). Spinal cord tissue was isolated for histopathology analyses. Neurofilament light (NfL) chain was analyzed from plasma samples.
Results: Compared to WT, TDP-43QQ331K mice had significantly lower muscle weight. Mutant TDP-43 mice show significantly lower activity duration during dark phase, significantly lower on-shelter visit during the dark phase at 6 and 8 months, and significantly longer shelter visits at all timepoints. Principal component analysis of multiple variables showed consistent phenotypes at different ages, with a progressively larger effect size over time. Muscle strength as measured via inverted grid was significantly lower at 6 and 8 months and at all time points in the weights-lifting test and rotarod. Reduction of CMAP amplitude suggests loss of functional motor axons. TDP-43 mutant mice show higher concentrations of plasma NfL at 7 and 9 months.
Conclusions: Motor deficits in TDP-43Q331K mice mimic the human disease pathophysiology, indicating the suitability of this model for preclinical studies.

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SHIFT 01-679

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
2-3 April 2025

NEURONAL MODELS OF THE AGING-ASSOCIATED LOSS OF PROTEOSTASIS LEADING TO PROTEINOPATHY

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Aims: Aging is the major risk factor for the development of neurodegenerative diseases, including Alzheimer's disease (AD) and frontotemporal lobar degeneration (FTLD). These conditions are characterized by a generic failure of the proteostasis network, with specific proteins loosing solubility, gaining propensity to misfold and aggregate into neurotoxic species and inducing many others to aggregate. Among them, the transactive response DNA-binding protein 43 (TDP-43) is recognized as the major neuropathological hallmark of FTLD with TDP-43 inclusions (FTLD-TDP) and other TDP-43 proteinopathies, and also reported to accumulate in the brain of AD patients in addition to amyloid-β (Aβ) and tau proteins. The aim of this study was to set up two neuronal models of brain aging characterized by the progressive decline of protein homeostasis.
Methods: The first model was obtained by treating cultured neuronal cells overexpressing human full-length TDP-43 with sub-threshold concentrations of autophagy and proteasome inhibitors. The second one is a model of protein comorbidity between tau and TDP-43, obtained by co-expressing them in neuronal cells and investigating their pathological synergy.
Results: We show that cells overexpressing human full-length TDP-43 undergo a progressive pathogenic accumulation of cytoplasmic self-assemblies visualized by confocal microscopy upon chronic exposure to autophagy and proteasome inhibitors. We also demonstrate that the concomitant overexpression of tau and TDP-43 worsens TDP-43 pathology, inducing a time-dependent impairment of neuronal viability and DNA damage.
Conclusions: In conclusion, these results suggest the employment of our experimental approaches as good model systems to mimic the aging-associated functional decline of the proteostasis machinery. They also suggest the association between TDP-43 and tau pathologies, demonstrating the existence of a pathogenic synergy resulting in increased TDP-43 cytoplasmic accumulation and neurotoxicity.

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SHIFT 01-681

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

SOURCES OF DOUBLE-STRANDED RNA (DSRNA) IN NEURODEGENERATIVE DISEASE WITH TDP-43 PATHOLOGY.

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Aims: Neuroinflammation is a pathologic hallmark of multiple neurodegenerative conditions. Recent work implicates immunogenic cytoplasmic double stranded RNA (cdsRNA) in the pathogenesis of several neurodegenerative diseases that share TDP-43 pathology, including C9orf72-FTD/ALS and Alzheimer's disease (with TDP-43 pathology present in roughly 50% of all cases). Our prior studies showed that cdsRNA triggers Type I interferon-mediated immune signaling, causing cell death in cultured human neurons as well as in a mouse model of neuronal dsRNA expression. We also previously showed that dsRNA is spatially coincident with pTDP-43 inclusions in neurons of patients with C9orf72-FTD/ALS and Alzheimer's disease with TDP-43 pathology. However, the origin of cdsRNA in these diseases was previously unknown. The current study aims to identify where in the genome pathologic dsRNA originates, with preliminary analyses focused on C9orf72-FTD/ALS.
Methods: Using a dsRNA-specific antibody, we performed dsRNA immunoprecipitation and sequencing (dsRIP-Seq) in control and C9orf72-FTD/ALS human brain tissue to detect dsRNA-forming transcripts.
Results: We identified a number of nuclear and mitochondrial transcripts giving rise to dsRNA specifically in C9orf72-FTD/ALS. Additionally, we found that dsRNA in C9orf72-FTD/ALS is enriched in repetitive sequences arising from certain families of transposable element.
Conclusions: This work identifies genomic sources of dsRNA in C9orf72-FTD/ALS and establishes a pipeline for the isolation and characterization of dsRNA from human brain tissue. Further characterization of dsRNA across various neurodegenerative conditions may yield important insights into shared neuroinflammatory mechanisms and identify common therapeutic targets.

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SHIFT 01-682

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

MODELLING OF TDP-43 PROTEINOPATHY IN HUMAN CORTICAL ORGANOTYPIC SLICE CULTURE.

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Aims: Amyotrophic lateral sclerosis and frontotemporal dementia are caused by the accumulation of TDP-43 protein in neuronal cells resulting in progressive neurodegeneration. The translocation of TDP-43 from the nucleus to the cytoplasm into stress granules is a key step leading to compromised TDP-43 function. Our objective is to develop a TDP-43 proteinopathy model using adult human cortical organotypic slice cultures from patients undergoing neurosurgical procedures and perform mechanistic studies in cell culture model. This model will enable us to study the molecular mechanism of TDP-43 accumulation in neurons and, in future, allow testing of novel therapeutic interventions.
Methods: Human slice cultures were prepared according to McLeod et al. **(**Brain, 2023) and cultured for up to 21 *days in vitro* (DIV). SH-SY5Y cells were cultured in DMEM complete media. Viral transduction of human TDP-43 was conducted using adeno-associated virus and human synapsin promoter (AAV2-hSYN1-EGFP or AAV2-hSYN1-EGFP-hTARDBP).
Results: Immunohistochemistry for TDP-43 in human slice cultures at baseline (DIV0) showed that 40-70% of the total number of cells (~400-700/1000 cells per slice; n=3 cases) expressed TDP-43. Co-Staining with NeuN showed that 70-90% (~250-350/400) NeuN positive neuronal cells expressed TDP-43. Human slice cultures at DIV21 showed a small decrease in the expression of TDP-43 in comparison to DIV0, however, the nuclear to cytoplasmic ratio of TDP-43 was unaltered. Viral transduction of SH-SY5Y cells with hTDP-43 caused an increase in the intensity of nuclear expression of TDP-43 (228% ± 50%, n=3) compared to those transduced with control (EGFP) only virus.
Conclusions: Initial data suggests human slice cultures are viable up to 21 DIV and express stable nuclear TDP-43 under baseline conditions. We are now assessing the impact of environmental stressors on TDP-43 cytoplasmic translocation and stress granule formation.

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SHIFT 01-683

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

ASSESSING FUNCTIONAL CONSEQUENCES OF RISK-ASSOCIATED SORT1 VARIANTS IN FRONTOTEMPORAL DEMENTIA

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Aims: Mutations in the GRN gene encoding progranulin (PGRN) have been identified as a major genetic factor in familial frontotemporal dementia (FTD) due to pathological reductions in PGRN levels. PGRN binds to neuronal sortilin receptors, which aid in the uptake and clearance of PGRN. Multiple rare nonsynonymous variants in the sortilin gene (SORT1) have been associated with an increased risk of FTD, and 11 variants were observed exclusively in patients. Functional studies are needed to clarify the mechanisms by which these genetic variants may contribute to the development of FTD. Our aim is to investigate the functional consequences of these SORT1 variants by investigating their impact on several key aspects of sortilin function.
Methods: HEK293MSR cells were transiently transfected with sortilin variants generated through site-directed mutagenesis. To assess the functional properties of the variants, we conducted shedding assays, cell surface biotinylation, dimerization studies, and PGRN uptake assays. Furthermore, we developed an optimized assay to investigate PGRN-sortilin interactions. Results were visualized using Western blotting.
Results: Several SORT1 risk variants located across different structural domains of sortilin affect distinct molecular mechanisms of sortilin in vitro. The variant we identified as most significantly affected has a high pathogenicity score. Interestingly, despite its altered PGRN binding and uptake, this variant is not located within the predicted PGRN binding site. This suggests that disruptions in sortilin mechanisms beyond direct ligand binding may disturb the PGRN-sortilin axis and possibly contribute to disease pathogenesis.
Conclusions: These SORT1 risk variants do not exhibit the same functional alterations of sortilin, suggesting that the mutations influence different aspects of sortilin mechanisms. This implies that sortilin-related pathogenicity in FTD may arise from multiple distinct pathways, rather than a single generalized mechanism.

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SHIFT 01-684

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

C9ORF72 DIPEPTIDE REPEATS CO-CONDENSE WITH HSP90 AND DISRUPTING ITS DYNAMICS IN ALS

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Aims: Hsp90α, a pivotal canonical chaperone, is renowned for its broad interaction with numerous protein clients to maintain protein homeostasis, chromatin remodeling, and cell growth. Recent studies indicate its role in modifying various components of membraneless organelles (MLOs) such as stress granules and processing bodies, suggesting its participation in the regulation of protein condensates. Our goal is to determine whether Hsp90α can undergo phase separation and understand how this condensation is regulated.
Methods: A high-throughput protein phase separation profiling assay was used to characterize the condensation of Hsp90α. We utilized LC-MS/MS to identify the components of reconstituted Hsp90α condensates, and fluorescence microscopy imaging to analyze the condensates in vitro. Fluorescent after photo bleaching assay was used to characterize the dynamic of condensates.Additionally, we employed bio-layer interferometry to investigate protein-protein interactions.
Results: In this study, we discovered that Hsp90α has an intrinsic ability to form dynamic condensates in vitro. Using LC-MS/MS, we identified proteins from cell lysates that preferentially integrate into Hsp90α condensates. Notably, we found an enrichment of RG motif repeats in the client proteins of Hsp90α condensates, many of which are associated with various membrane-less organelles (MLOs). Furthermore, all three domains of Hsp90α were shown to undergo phase separation, with numerous solvent-exposed negatively charged residues in these domains being critical for driving Hsp90α condensation through multivalent weak electrostatic interactions. Additionally, various clients, including TDP-43 and hnRNPA1, as well as poly-GR and PR dipeptide repeats, were found to have differential effects on the dynamic behavior of Hsp90α condensates
Conclusions: We found that GR and PR dipeptide repeats enhance Hsp90α condensation and significantly impair the internal dynamics of condensates. This may trap Hsp90α in solid-like condensates, disrupting its normal functions and protein homeostasis.

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SHIFT 01-686

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

A NOVEL ASSAY TO DETECT PLASMA NEURON-DERIVED EXTRACELLULAR VESICLE PHOSPHO-TAR DNA-BINDING PROTEIN 43 AS A BIOMARKER FOR ALS

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Aims: In motor neurons of patients with amyotrophic lateral sclerosis (ALS), TAR DNA-binding protein 43 (TDP-43) is mislocalized to the cytoplasm, where it becomes hyperphosphorylated and aggregated. Phosphorylated TDP-43 (pTDP-43) has been implicated in pathological changes observed in motor neurons of patients with ALS. Here, we developed an assay to assess pTDP-43 levels in plasma neuron-derived extracellular vesicles (NDE) as a potential biomarker for ALS/FTD spectrum disorder.
Methods: We developed a pTDP-43 Luminex sandwich immunoassay with anti-pTDP-43 and anti-TDP-43 as capture and detection antibodies, respectively. NDEs were enriched from plasma samples of patients with ALS and healthy individuals using ExoSORT.
Results: We confirmed pTDP-43 expression in NDEs from plasma and conditioned media from induced pluripotent stem cell (iPSC) motor neurons by western blot. Compatibility of the antibody pair with plasma NDEs was confirmed through dilution linearity (parallelism), with low variability both within and between plates. Assay specificity was demonstrated through reduced signal in the absence of phosphatase inhibitors, immunodepletion by an independent anti-TDP-43 antibody, and TDP-43 knockdown cells. Plasma levels of pTDP-43 from six patients with newly diagnosed ALS were significantly higher compared to healthy individuals (n=18), (486±112 medium fluorescence intensity (MFI) vs. 365±103MFI; P=0.046). Furthermore, the pTDP-43 levels in ALS patients increased by 1.6 fold (P=0.09) to 754±163MFI with disease progression over a six-month period.
Conclusions: pTDP-43 is detectable in plasma NDEs. Our newly developed Luminex assay shows a significant increase in plasma pTDP-43 from ALS patients compared to healthy individuals, which further increases with disease progression. Additional studies in a larger cohort are needed to establish the value of NDEs-pTDP-43 as a diagnostic and disease monitoring biomarker in ALS.

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SHIFT 01-687

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

BLOOD AND CEREBROSPINAL FLUID NEUROFILAMENT LIGHT CHAIN IN A BI-COMPARTMENTAL MODEL FOR THE DIFFERENTIATION OF PERIPHERAL AND CENTRAL NERVOUS SYSTEM AXONAL DAMAGE

Steffen Halbgebauer[1], Veronika Klose[1], Badrieh Fazeli[1], Paula Klassen[1], Christoforos Alexudis[1], Nerea Gómez De San José[1], Zeynep Elmas[1], Franziska Bachhuber[1], Markus Otto[2], G. Bernhard Landwehrmeyer[1], Albert Ludolph[1], Hayrettin Tumani[1]
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Aims: CSF and blood neurofilament light chain (NfL) concentrations are used as neuroaxonal damage markers for (differential-) diagnosis neurological diseases. In different diseases NfL can be released from central and/or peripheral neurons. In this study we aimed to set up a bi-compartmental NfL model to help in the discrimination between central (CNS) and peripheral nervous system (PNS) neurodegeneration.
Methods: We analyzed NfL in corresponding CSF and serum samples from 384 control patients seen at the University Hospital Ulm. For the evaluation of the model NfL levels of amyotrophic lateral sclerosis (ALS) (n=10), multiple sclerosis (MS) (n=10), Guillain–Barré syndrome (GBS) (n=9) and idiopathic intracranial hypertension patients (n=12) were analyzed.
Results: Serum and CSF NfL levels were associated with each other with a spearman r of 0.68 (95%CI: 0.62-0.73), p<0.0001. We used this association to establish a bi-compartmental CSF and serum NfL model allowing to graphically differentiate between peripheral or central origin of neurodegeneration. For this we also defined different areas in the graph (A-D). MS NfL levels were found to be in the upper part of area A which illustrates "normal" NfL levels. The ALS patients fell all into the area B with high CSF and serum levels. GBS patients were partly found in area C with high serum and lower CSF values. IIH patients on the other hand were close to the border to area D, depicting high CSF and lower serum NfL levels. However, no patient was found directly in area D.
Conclusions: CSF and serum NfL levels show a strong association with each other which allowed us to create a bi-compartmental model. This model could be applied for clinical issues regarding overlapping symptoms of CNS and PNS derived neurological diseases.

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TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

PLASMA OLIGOMERIC TDP-43 LEVELS FOR DIAGNOSIS OF SEMANTIC DEMENTIA

Haemin Jeong[1], Hyojung Park[1], Ji Sun Ryu[1], Taehwi Yoon[1], Hyo Rim Ko[1], Dawon Lee[1], Sungmin Kang[1], Sangyun Kim[2]
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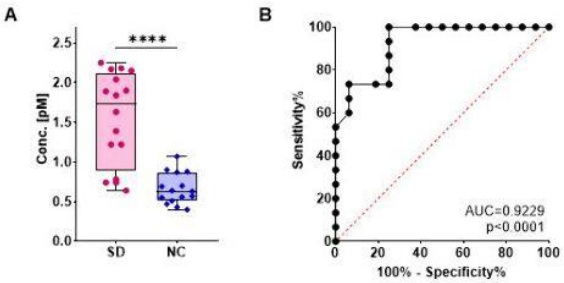
Aims: Background: The hallmark pathology of semantic dementia (SD) is the abnormal accumulation of TDP-43 (TAR DNA-binding protein 43) protein in the neural tissue, particularly in the frontal and temporal lobes. This accumulation leads to significant atrophy and degeneration of brain regions associated with language and semantic processing. Nevertheless, there is currently no specific diagnostic method for SD using body fluids such as plasma.
Methods: Method: We developed a recombinant monoclonal antibody, 1T47, that recognizes the full length of TDP-43 with a phage display. Antibody 1T47 was used for the construction of a new sandwich ELISA method for the detection of TDP-43 oligomers in plasma. Total TDP-43 in plasma was quantified by commercial TDP-43 ELISA kit. Plasma from 36 SD patients and 25 healthy controls were measured by the new method.
Results: Result: Oligomeric TDP-43 levels in plasma were significantly higher in SD patients compared with healthy controls ($p<0.001$). However, total TDP-43 in plasma was not statistically significant between the SD patients and healthy controls. Using this new TDP-43 sandwich ELISA, plasma oligomeric TDP-43 distinguished SD from healthy controls (AUC=0.921).
Conclusions: Conclusion: Our newly developed assay for detecting oligomeric TDP-43 differentiates between SD and HC groups with high sensitivity and specificity.



Group	Semantic Dementia(SD)	Normal Control(NC)
Mean	1.549	0.658
Std. Deviation	0.5875	0.1948

Area under the ROC curve Analysis	
AUC	0.923
Significance level P	<0.0001
Sensitivity	75.00
Specificity	100.00

Oligomeric TDP-43 detection in human plasma. Plasma oligomeric TDP-43 concentrations were significantly higher in semantic dementia (SD) patients compared to normal controls (NC) ($p < 0.0001$). The ROC analysis of oligomeric TDP-43 demonstrated a high level of diagnostic accuracy for diagnosing SD and normal controls (AUC = 0.923, sensitivity = 75%, specificity = 100%).

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TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

THE EDINBURGH COGNITIVE AND BEHAVIOURAL ALS SCREEN IN A KAZAKH AMYOTROPHIC LATERAL SCLEROSIS POPULATION

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Aims: This study aimed to validate the effectiveness of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) adapted version and assess cognitive and behavioural impairments in the Kazakh Amyotrophic Lateral Sclerosis (ALS) population.
Methods: We enrolled 43 patients with definite or probable ALS, evaluated using Gold Coast criteria. Participants were administered adapted version of the ECAS, which evaluates language, verbal fluency, executive functions, memory, and visual-spatial abilities. Cognitive and behavioural statuses were classified according to ECAS categories. ROC curve analyses were conducted to determine the sensitivity and specificity of the ECAS.
Results: The distribution of patients across diagnostic categories was as follows: ALS without impairment (23%), ALS with mild cognitive impairment (38%), ALS with mild behavioural impairment (11%), ALS with mild cognitive/behavioural impairment (19%), and ALS with frontotemporal dementia (9%). Cognitive impairment was more prevalent in bulbar forms of ALS (89.8%) compared to spinal ones (49.8%) ($p < 0.012$). ROC curve analysis revealed an area under the curve (AUC) of 0.94 (94% CI: 0.86–1.03). Sensitivity and specificity of the ECAS 84.7% and 90.6%, respectively.
Conclusions: Cognitive impairment frequently occurs in ALS patients, especially in those with bulbar onset. Cognitive and behavioral impairments in ALS adversely affect both quality of life and survival, making regular screening for these deficits advisable. The ECAS is an efficient and reliable tool for detecting cognitive and behavioural impairments in ALS, as indicated by its excellent AUC and high sensitivity and specificity.

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SHIFT 01-691

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

TARGETING G-QUADRUPLEX NUCLEIC ACIDS IN THE C9ORF72 GENE

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Aims: Aberrant hexanucleotide repeat expansions (HRE) in the first non-coding region of the C9orf72 gene are the leading cause of Amyotrophic Lateral Sclerosis (ALS).[1] HRE drives ALS pathogenesis by both the repeat RNA-forming foci, that sequester RNA-binding proteins (RBPs) impairing their functions,[2] and through toxic dipeptide repeat proteins (DPRs) generated by repeat-associated non-ATG (RAN) models.[3] The cytotoxicity of these processes is linked to the tendency of the mRNA-HRE to fold into parallel G-quadruplexes (G4s), [4] high-order nucleic acid (NA) secondary structures involved in regulating many biological functions.[5] Thus, disrupting these G4s can offer attractive and uncharted opportunities in light of pharmacological advantages against ALS.
Methods: We developed new small molecules specifically targeting C9orf72 mRNA-G4s to explore this therapeutic avenue. These new tools aim to sequester G4 structures, preventing pathogenic interactions with RBPs, and degrade HRE to interfere with RAN translation. This innovative approach, acting on the two key processes related to C9orf72-HRE toxicity, could prove mRNA-HRE G4s as effective therapeutic targets.
Results: Given the success of antisense oligonucleotides in previous studies,[6] we also designed a phosphorodiamidate morpholino oligomer (PMO) complementary to HRE to force duplex NA structures disrupting G4 folding (Figure 1a). Additionally, the unfolding of multimeric HRE-G4s has been proven by in-house G4-unfolders through biophysical studies (Figure

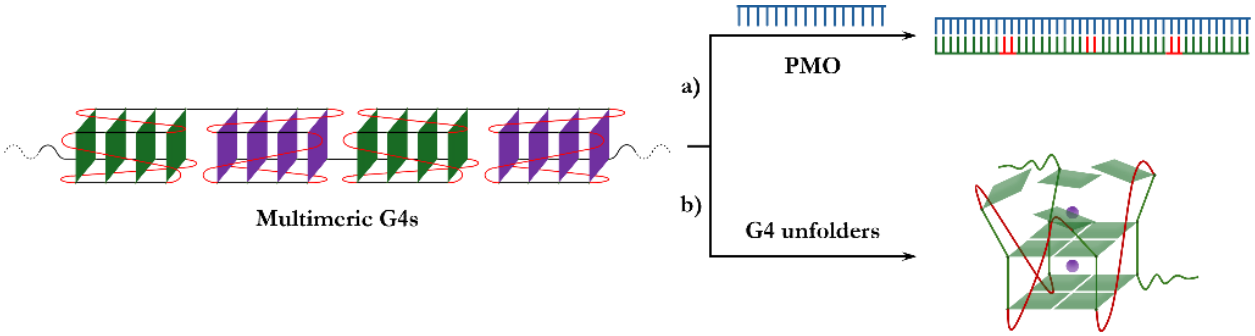

Figure 1: Schematic representation of the two approaches used for this purpose

1b).[7]
Conclusions: The functional target and degradation of C9orf72 mRNA-G4s by new G4-unfolders should prevent the pathogenic interaction with RBPs and inhibit RAN translation. Together, PMOs overcome some of the drawbacks of ASOs. The higher affinity to complementary NA allows the use of shorter hybridization

probes to achieve high sequence

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specificity.

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SHIFT 01-692

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

TRODUSQUEMINE PREVENTS THE FORMATION OF TDP-43 INCLUSIONS AND THEIR ASSOCIATED NEUROTOXICITY

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Aims: The mislocalization of TAR DNA-binding protein 43 (TDP-43) from the nucleus to the cytoplasm with the formation of aberrant inclusions is a common feature of neurodegenerative conditions such as amyotrophic lateral sclerosis (ALS) and frontotemporal lobar degeneration (FTLD). The natural aminosterol trodusquemine (TRO) have been reported to modulate the aggregation and to suppress the toxicity of α-synuclein (αS) protein and amyloid-β peptide ($A\beta_{42}$), representing putative drug candidates against Parkinson's disease and Alzheimer's disease, and possibly other neurodegenerative conditions.
Methods: In this study we evaluated the effect of TRO in modulating TDP-43 aggregation both *in vitro* and in NSC-34 motorneuron-like cells. Moreover, we monitored whether TRO was able to suppress TDP-43 accumulation and neurotoxicity in neuronal cells taking advantage of super resolution STED microscopy, Raman spectroscopy *in situ* and photometric assays.
Results: We showed that TRO binds with high affinity to purified full-length (FL) TDP-43, promoting its phase separation and modulating its aggregation. We also found that TRO dramatically affects TDP-43 accumulation and pathology in NSC-34 cells following the overexpression of human NLS1 TDP-43 YFP in NSC-34 cells, and restoring cell viability. Moreover, TRO induces a structural reorganization of neuronal TDP-43 inclusions.
Conclusions: This study provides evidence that TRO can prevent the pathological effects induced by TDP-43, putting forwards its potential as a new therapeutic candidate in TDP-43-associated proteinopathies. *This study was supported by MUR (PRIN2022PNRR, project P20225ZPYH to R.C.).*

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SHIFT 01-693

Poster on Board - Shift 01
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

SORTILIN INHIBITION WITH VES001 AND ELEVATION OF PROGRANULIN AS A NOVEL THERAPEUTIC APPROACH IN FTD-GRN AND OTHER NEURODEGENERATIVE DISEASES

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Vesper Bio, Copenhagen, Denmark

Aims: Progranulin (PGRN) deficiency is associated with several neurodegenerative diseases, including frontotemporal dementia where around 10% of cases are caused by mutations in the progranulin gene (*GRN)* known as FTD-GRN. FTD-GRN patients have 50% PGRN levels relative to healthy controls and these reduced levels are associated with distinct and overlapping pathological processes, including gliosis, complement activation, TDP-43 accumulation, and neurodegeneration. Sortilin controls PGRN levels and facilitates apoptotic signalling stemming from the sortilin-$P75^{NTR}$ complex. Vesper Bio has developed novel small molecule sortilin inhibitors for oral administration and is investigating the therapeutic potential in different neurodegenerative diseases. Vesper Bio aims to develop the first sortilin inhibitor for oral administration to treat FTD-GRN, and lead candidate, VES001, is currently Phase 1 clinical trials. The aim for VES001 is to normalize PGRN levels.
Methods: Characterization of VES001 included, among other outcomes, target and non-target affinity, the half-maximal inhibitory concentration, and PK/PD studies in different animal and cell models.
Results: VES001 is highly selective for sortilin and shows high affinity across multiple species. A micro-dialysis rat study showed VES001 elevated PGRN 2-2.5-fold in plasma, CSF, and hippocampus ISF. The vehicle groups did not show changes in PGRN.
Conclusions: Sortilin inhibition with oral small molecule VES001 increases PGRN in different compartments and holds promise as a novel therapeutic approach to attenuate neuroinflammation and neurodegeneration for different neurodegenerative diseases, including FTD-GRN.

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SHIFT 01-697

Poster on Board - Shift 01
VASCULAR DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
2-3 April 2025

EARLY DIETARY REVERSAL PREVENTS SPATIAL DISCRIMINATION DEFICITS AND CORRESPONDS WITH ALTERED BRAIN AND BODY CYTOKINE PROFILES RESULTING FROM SUSTAINED HIGH FAT DIET

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Aims: Obesity is a risk factor that can increase the likelihood of Alzheimer's disease (AD). Studies indicate that dietary reversal may be sufficient to rescue or prevent some but not all aspects of neuropathology. In this study, the role of dietary reversal on body weight, peripheral and central cytokine levels, and memory impairment was investigated using male mice raised on a high-fat diet.
Methods: Twenty male mice were placed on a high-fat diet (HFD; 60%kcal fat) at 6w of age (Jackson C57BL/6J DIO, #380050). At 14w, the diet for half of the mice was switched to standard mouse chow (STD; 14%kcal fat) for the remainder of the study. Mouse weights were collected weekly as a measure of metabolic health. Observable health was assessed using the frailty index tests. Spatial discrimination and spatial working memory were assessed by novel spatial recognition (NSR) and spontaneous alternation (SA), respectively, in the Y-maze apparatus. Following observational and behavioral assessments, blood samples were collected at baseline, one month, and two months post-diet change. Brain tissue was collected at the conclusion of the study.
Results: Diet reversal regulated weight gain trajectories, preserved physical health, and altered several plasma cytokine levels compared to sustained HFD over time and at the terminal endpoint. Additionally, HFD induced spatial discrimination deficits in the NSR, but spared working memory deficits in the SA tasks across the 2mo period.
Conclusions: These findings demonstrate that high fat diet reversal can preserve cognitive and metabolic health and is associated with alterations in peripheral and central neuroinflammatory markers. Interestingly, certain brain and peripheral cytokine alterations persisted to at least 8 weeks of dietary reversal, the implications of which are under investigation.

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SHIFT 01-701

Poster on Board - Shift 01
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

MICROSCALE VESSEL QUANTIFICATION IN ENTORHINAL SUBFIELDS IN AGING AND EARLY STAGE ALZHEIMER'S DISEASE

Emma Rosenblum[1], Smriti Chadha[1], Josue Llamas Rodriguez[1], Matthew Frosch[2], Jean Augustinack[1]
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Aims: The entorhinal cortex succumbs to a specific and differential vulnerability for tau pathology at early Braak stage. We previously demonstrated that vascular density (e.g. arteriole) in MRI correlates positively with tau pathology. Baseline quantitative data on vascular size (arterioles, branching arterioles, capillaries) is needed in this at-risk region. Immunostaining with laminin, a basement membrane protein, offers a method to assess and measure the vessel lumen in histology.
Methods: We obtained four human parahippocampal samples, mean age 74.8± 11.8 years, three males, one female, three left hemispheres, one right hemisphere. Samples were limited to preclinical Braak stages 0-II, based on tau severity with no cognitive impairment. Selected entorhinal subfields ER, EI and ECs were chosen to evaluate given their differential tau vulnerability. Vessels were categorized based on morphology but also lumen size, which was measured and quantified per subfield/per sample. Sections were digitized at 10x with the Keyence BZX800. Lumen diameter measurements were collected on randomly selected vessels using the Adobe Photoshop measure tool.
Results: Laminin immunostaining revealed varying types of vessels, and we categorized *three* classifications based on size but also morphology: large (arteriole or venule), small (capillary) and diseased (string) vessels. The median lumen widths were: large vessels 31.09 µm, capillaries 9.19 µm, and string vessels 2.40 µm. Lumen width was not significantly different among subfields or between preclinical Braak and Braak stages. All structures were observed in all subfields in all samples.
Conclusions: These data provide not only a baseline for vessel size in susceptible subregions but also may help define vessel health quantitatively in the aging brain. Vessel abnormalities – whether it be structurally, functionally, disease-related, or specific location – may influence the local neuronal-vascular environment.

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SHIFT 01-702

Poster on Board - Shift 01
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

COMPARISON BETWEEN THE MINI-MENTAL STATE EXAMINATION AND THE MINI-MENTAL STATE EXAMINATION-2 IN KOREAN PATIENTS WITH VASCULAR MILD COGNITIVE IMPAIRMENT AND VASCULAR DEMENTIA

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Aims: To compare the usefulness of the Mini-Mental State Examination-2 and Korean version of the Mini-Mental State Examination to determine which test is more sensitive in discriminating between normal cognitive aging and patients with vascular mild cognitive impairment and vascular dementia in a Korean population.
Methods: Sixty-six patients with VaMCI, 46 patients with VD, and 75 healthy older adults were recruited. All participants consented to examination with the MMSE-2, the MMSE, and other detailed neuropsychological assessments. Discriminant analysis of each test was used to evaluate and compare their correct classifications and sensitivity and specificity of each test was compared using receiver operating characteristic analysis.
Results: The result of discriminant validity of MMSE-2 showed that 80.2% of cases correctly identified in a discriminant analysis of patients with VaMCI (81.8%), patients with VD (80.4%), and healthy older adults (78.7%). The result of discriminant validity of K-MMSE showed that 71.1% of cases correctly identified in a discriminant analysis of patients with VaMCI (63.6%), patients with VD (80.4%), and healthy older adults (72.0%). The AUC of the the MMSE-2:SV, and the MMSE-2:EV were larger than the AUC of the K-MMSE when comparing with healthy older adults and patients with MCI. However, the AUC of the K-MMSE was larger than the MMSE-2:BV. The AUC of the MMSE-2:SV was larger than the AUC of the K-MMSE, but the AUC of the K-MMSE was larger than the MMSE-2:BV and the MMSE-2:EV when comparing with patients with VaMCI and VD.
Conclusions: The MMSE-2 (SV & EV) are more sensitive to detect early cognitive decline than the K-MMSE or the MMSE-2:BV, but as the dementia progresses, the K-MMSE or the MMSE-2:BV may be more useful than the MMSE-2 (SV & EV).

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SHIFT 01-703

Poster on Board - Shift 01
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
2-3 April 2025

COMPARING MYELIN DEGENERATION WITH CHANGES IN IRON AND FREE WATER LEVELS IN MONOGENIC CEREBRAL SMALL VESSEL DISEASE

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[1]Institute for Stroke and Dementia Research, LMU University Hospital, Ludwig Maximilian (LMU) University, Munich, Germany, [2]Seoul National University, Seoul, Korea, Republic of, [3]Institute for Stroke and Dementia Research (ISD), Munich, Germany, [4]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [5]The Sahlgrenska Academy, University of Gothenburg, Mölndal and Gothenburg, Institute Of Neuroscience And Physiology And Department Of Psychiatry And Neurochemistry, Mölndal and Gothenburg, Sweden, [6]German Center for Neurodegenerative Diseases (DZNE), Munich, Germany, [7]University of Basel, Medical Image Analysis Center, Basel, Switzerland, [8]University of Basel, Department Of Biomedical Engineering, Basel, Switzerland, [9]University Hospital, LMU Munich, Institute For Stroke And Dementia Research, Munich, Germany

Aims: White matter alterations such as MRI-visible white matter hyperintensities (WMH) are core brain abnormalities in cerebral small vessel disease (cSVD). Myelin is of critical importance for information transfer and is a putatively altered in cSVD: However, the MRI-based assessment is complicated by co-occurring pathologies including iron alterations and oedema (free water). We leveraged multimodal imaging and advanced post-processing including X-separation to differentiate myelin alterations from those in iron and free water in patients with monogenically caused cSVD (CADASIL).
Methods: We included 60 CADASIL patients and 20 matched cognitively unimpaired controls (CN). We assessed on T2*-weighted scans negative susceptibility (i.e. myelin, χ-negative), positive susceptibility (i.e. iron, χ-positive), and on diffusion weighted images FW in T2-FLAIR defined white matter hyperintensities (WMH), normal appearing white matter (NAWM), and the penumbra around WMH. We performed voxel-based analysis and conducted region of interest analyses with one-sample *t*-tests utilizing difference scores to account for subject specific WMH location. Difference scores were corrected for age, sex, education, χ-positive, and FW when appropriate. We used ridge-regression to associate trail-making test scores with MRI markers and covariates.
Results: Voxel-based analysis yielded significantly lower χ-negative, lower χ-positive and increased FW in CADASIL patients (Fig. 1). WMH showed the strongest alterations, but differences persisted within the penumbra of WMH as well as globally in the NAWM (Fig. 2). Lower χ-negative showed a moderate association with higher levels of iron but not FW (Fig. 3). Only χ-negative was associated with trail-making test scores in the global WM, NAWM, and WMH (*p*-values ≤ .032, pR^2 ≥

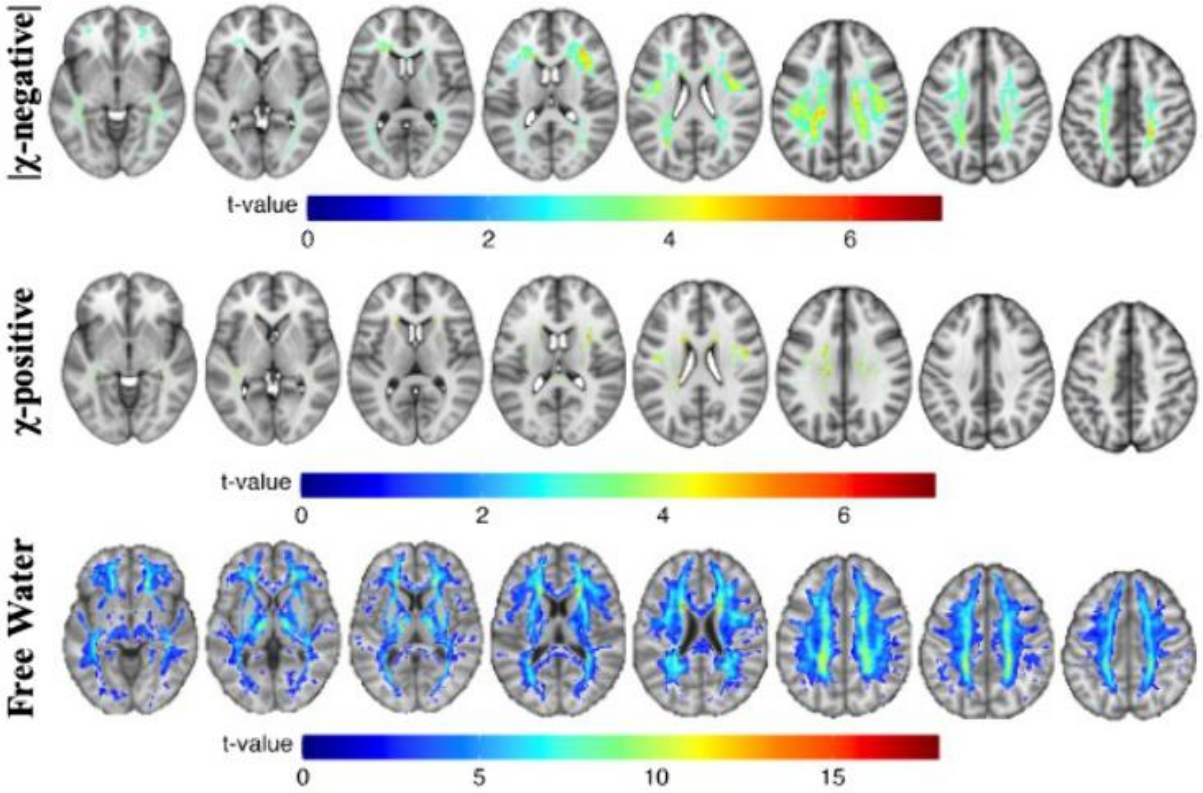

Figure 1. Significant voxel-wise difference between CADASIL and cognitively unimpaired controls for χ-negative (i.e. myelin, CADASIL < CN), χ-positive (i.e. iron, CADASIL < CN) and free water (CADASIL > CN). Only voxels remaining significant after FDR correction (α=0.05) and a voxel extend threshold of ten are plotted. Testing the opposite contrasts did not yield any significant results.

0.08).

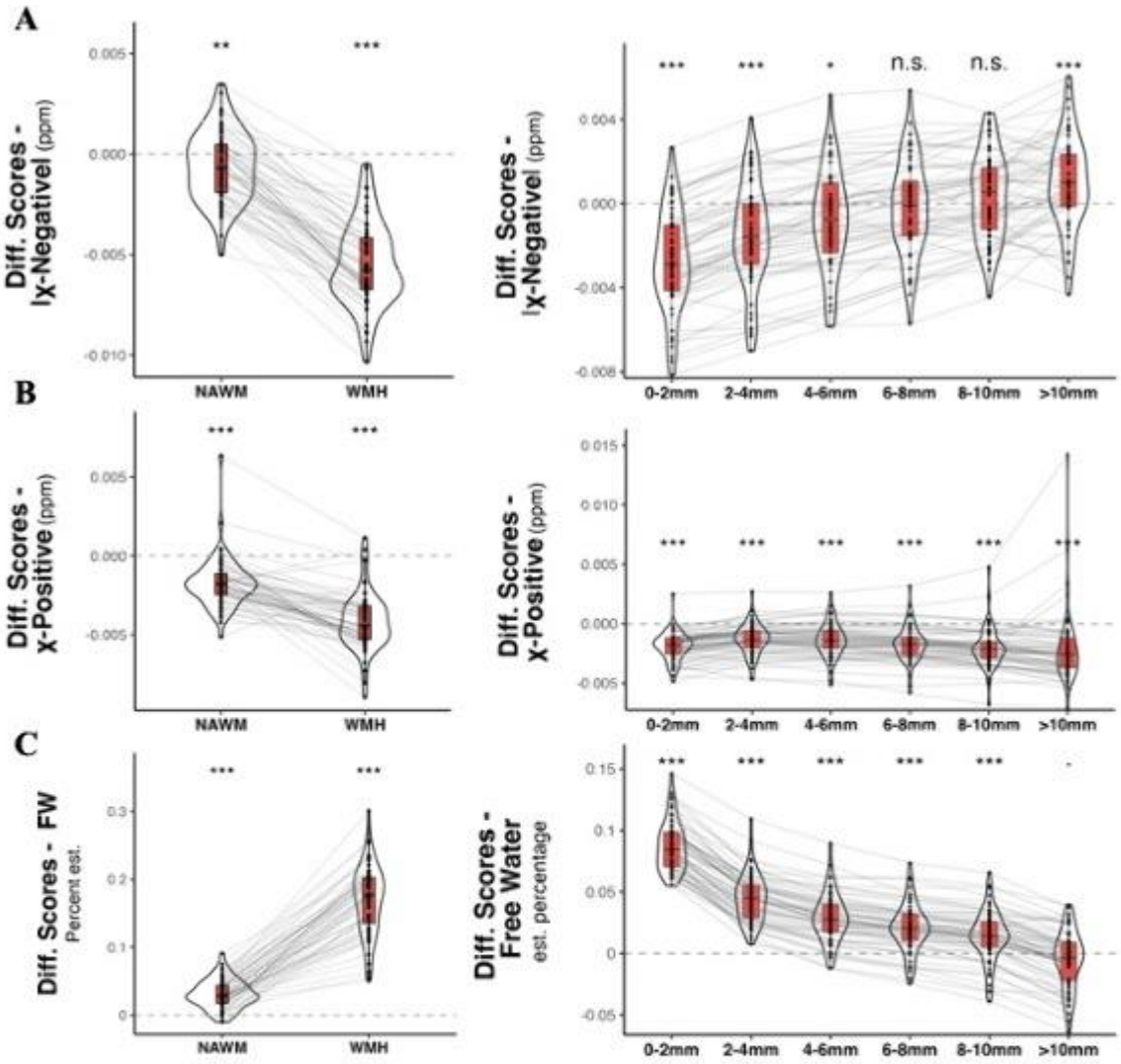

Figure 2. Violin plots with box plots for A) χ-negative (i.e. myelin), B) χ-positive (i.e. iron) and C) free water. Every line represents one subject. The left column shows NAWM and WMH areas, the right the WMH penumbra. The Penumbra is confined to the white matter and lacunes have excluded from all areas. One-sample *t*-tests ($\mu = 0$) were used to test significance. Difference scores were corrected for age, sex, education, for free water in the case of the susceptibility marker, while FW and χ-negative was furthermore corrected for χ-positive.

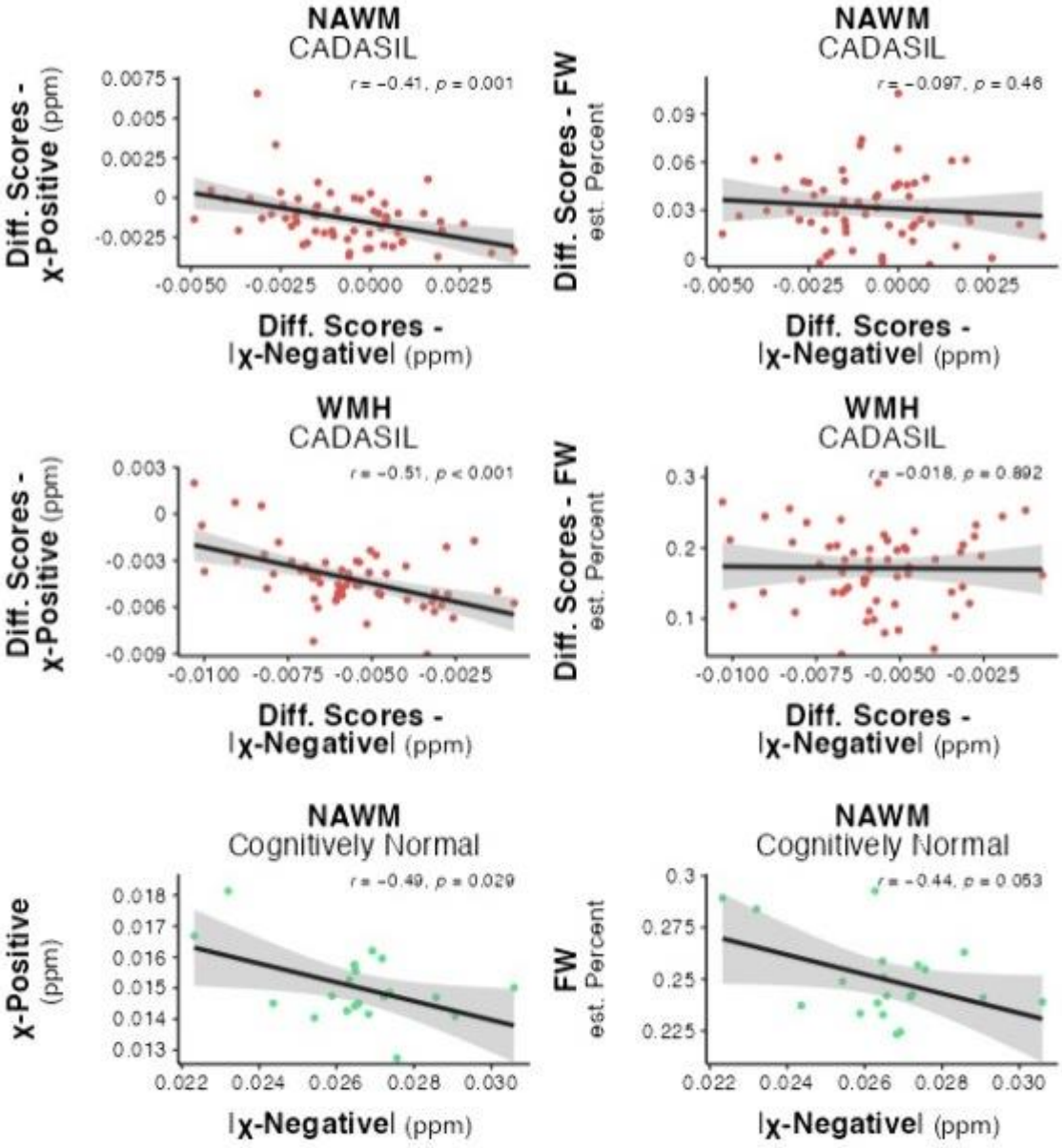

Figure 3. Scatterplots with regression line and 95% CI (shaded area) for the associations of χ-negative with χ-positive (left column) and free water (right column). Top row is NAWM in CADASIL, middle row WMH in CADASIL in bottom row NAWM in CN. As CN exhibited only few WMH, those were not assessed.

Conclusions: We demonstrate that myelin alterations are present in both WMH and NAWM in cSVD, which cannot be explained by increased free water pools (possibly oedema) or iron changes.

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SHIFT 01-705

Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

INHIBITION OF P38A AS A TREATMENT FOR OBESITY-INDUCED NEURAL DYSFUNCTION

Caleb Bailey, Meggie Coleman, Hilaree Frazier, Linda Van Eldik, David Braun
University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America

Aims: One of the strongest modifiable risk factors for later-life dementia is obesity. Though the incidence of Alzheimer's disease has declined in recent years, the rising obesity prevalence threatens to undo much of this progress. High fat obesogenic diets are known to impair cognition in association with increased oxidative stress, neuroinflammation, cerebrovascular dysfunction, and synaptic loss. One promising therapeutic candidate in this regard is the stress-responsive kinase p38α, which is a major sensor of oxidative stress and regulator of inflammatory responses throughout the body. In the brain, inhibition of p38α in various disease contexts directly ameliorates the types of pathologies caused by high fat diet. Here, we investigate the effects of the brain-penetrant p38α inhibitor, MW150, in mitigating the effects induced by the administration of obesogenic high fat diet in male and female mice.
Methods: Male and female mice were placed on high fat diet (60 kcal% fat) beginning at 6 weeks of age. After 12 weeks on diet, animals underwent pre-treatment MRI and blood draws prior to beginning 4 weeks of treatment with the p38 inhibitor MW150 (2.5 mg/kg 3x per week, IP). In addition to MRI, western blot and MSD ELISAs were used to assess alterations in peripheral and central nervous system metabolism, inflammation, and neuronal damage.
Results: MW150 had no effect on overall weight but significantly altered the systemic metabolic profile induced by high fat diet. This corresponded with a reduction in proinflammatory cytokine production, gliosis, and neuronal damage in a region-specific manner.
Conclusions: Inhibition of p38α by MW150 may be a useful approach to ameliorate central nervous system pathology caused by chronic high fat diet.

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SHIFT 01-706

Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

SARS-COV-2 INFECTION AGGRAVATES BRAIN SENESCENCE AND SENESCENCE-ASSOCIATED SECRETORY PHENOTYPE IN ENDOTHELIAL NITRIC OXIDE SYNTHASE DEFICIENT MOUSE MODEL OF VASCULAR DEMENTIA.

Saifudeen Ismael, Meenakshi Umar, Blake Ouvrier, Gregory Bix
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Aims: SARS-CoV-2 causes various neurological sequelae in COVID-19 survivors including cognitive dysfunction. Endothelial dysfunction, a key mechanism in COVID-19 illness, is also a major risk factor for vascular dementia (VaD). Reduced nitric oxide (NO) bioavailability is a likely pathogenic factor of endothelial dysfunction in COVID-19 patients, and eNOS levels decline with advancing age, a risk factor for both COVID-19 morbidity and VaD. In addition, SARS-CoV-2 is known to induce cellular senescence and senescence-associated secretory phenotype (SASP) activation. We hypothesize that endothelial nitric oxide synthase (eNOS) deficiency worsens SARS-CoV-2-associated senescence and SASP activation and accelerates the early onset of VaD in eNOS-deficient mice.
Methods: 6-month-old eNOS+/- (pre-cognitively impaired experimental VaD)/WT-male-mice were infected with $1X10^4$-pfu mouse-adapted (MA10) SARS-CoV-2 intranasally. Viral copy numbers and nuclear capsid were also quantified in lungs and brain. Immunofluorescence and qPCR were used to analyze markers of brain senescence and SASP activation 3-day-postinfection.
Results: eNOS+/- infected mice exhibited more disease-associated weight loss (~15%) than WT-infected mice (~5 %). While infected WT and eNOS+/- had comparable pulmonary viral load, neither had detectable virus in the brain. Quantitative PCR analysis showed increase in SASP markers such as CCL2, IL-1β and IL-6 and senescence markers such as p53 and p21 ($eNOS^{+/-}$ >> WT). Similarly, immunofluorescent analysis showed increased Iba1 (microglia marker) fluorescent intensity in the cortex of infected mice ($eNOS^{+/-}$ >> WT).
Conclusions: eNOS+/- deficiency, a clinically relevant model of VaD, worsens acute SARS-CoV-2-associated morbidity, neuroinflammation and brain senescence despite comparable pulmonary viral load (to WT-infected animals) and absence of virus in the brain. While the potential effects of SARS-COV-2 on cognitive decline in this model will be assessed in future studies, this is the first experimental evidence demonstrating a link between eNOS and senescence-associated with COVID-19.

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SHIFT 01-707

Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

NEUROPROTECTIVE EFFECT OF FISETIN AND SEMAGLUTIDE AGAINST LIPOPOLYSACCHARIDE-INDUCED NEUROINFLAMMATION IN SH-SY5Y-DERIVED NEURONAL-LIKE CELLS

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Aims: Cardiovascular diseases (CVDs), especially stroke, are the main cause of morbidity and mortality worldwide. Risk for CVDs is further aggravated by ageing and the rising incidence of unhealthy lifestyle-related cardiovascular risk (CVR) factors. CVDs may cause permanent brain injury, possibly due to chronic (neuro)inflammation, which can be attenuated by healthier lifestyles, namely the neuro-/cardioprotective Mediterranean diet (MedDiet) or CVR-lowering drugs (*e.g.*, Semaglutide). We aimed to assess the neuroprotective role of the MedDiet-related Fisetin and of Semaglutide against lipopolysaccharide (LPS)-induced inflammation in an SH-SY5Y cell-derived neuronal model.
Methods: We first selected the best experimental approaches, by evaluating the effect of increasing exposure times (6-48h) and concentrations (0.1-50 µg/mL) of LPS, Fisetin (50-250 nM), and Semaglutide (0.5-2.5 nM) on the viability of differentiated SH-SY5Y neurons, using the dual resazurin/SRB assay. Then, we measured IL-1β levels by ELISA.
Results: We observed that ~30% of the SH-SY5Y cells were differentiated into a neuronal-like phenotype. Administration of 50 µg/mL LPS for 24h decreased metabolic activity and cell mass of differentiated SH-SY5Y neurons (by 25% and 53%, respectively), while increasing extracellular IL-1β levels (by 325%). Under these conditions, treatment with Fisetin or Semaglutide increased metabolic activity (by 15% and 8%, respectively) and cell mass (by 15% and 23%, respectively), thus mitigating LPS-induced cell death.
Conclusions: Our preliminary results indicate that treatment with Fisetin or Semaglutide may protect against LPS-induced neuroinflammation and death. Further studies are crucial to uncover the mechanisms underlying neuroprotection by MedDiet-related compounds and CVR-lowering drugs. Funded by EU Horizon Europe CHAngeing - Excellence Hubs-HORIZON WIDERA-2022-ACCESS-04-01 (grant agreement #101087071); Portuguese Fundação para a Ciência e a Tecnologia (FCT): UIDB/04539/2020, UIDP/04539/2020, LA/P/0058/2020 (CIBB); European Social Fund: 2021.04707.BD (DM), EU HORIZON-CSA-WIDERA-2022-ACCESS-04 Excellence Hubs/CHAngeing/II0347.01 (KM, AID).

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SHIFT 01-708

Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

NEUROPROTECTIVE EFFECT OF FISETIN AND SEMAGLUTIDE AGAINST PALMITIC ACID EXPOSURE IN DIFFERENTIATED NEUROBLASTOMA-DERIVED SH-SY5Y NEURONS

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Aims: Stroke, a main cardiovascular disease (CVD), is a major global cause of morbidity and mortality. Chronic neuroinflammation can play a pivotal role in the pathophysiology of stroke-related brain damage. The rising prevalence of unhealthy lifestyle-linked cardiovascular risk (CVR) factors (*e.g.*, obesity) may predispose individuals to stroke. Diet-derived palmitic acid (PA) may enhance neuroinflammation and CVD risk, while healthier lifestyles (*e.g.,* the neuro-/cardioprotective Mediterranean diet (MedDiet)) or CVR-lowering drugs (namely Semaglutide) may exert a neuroprotective effect herein. We aimed to assess the neuroprotective effect of the MedDiet-related fisetin and Semaglutide against PA-induced inflammation in an SH-SY5Y cell-derived neuronal-like model.
Methods: We tested the impact of increasing concentrations and exposure times of PA, and the effect of fisetin and Semaglutide on the viability of differentiated SH-SY5Y neuronal-like cells, using the dual resazurin/SRB assay. Then, we used colorimetric techniques to measure cholesterol, free fatty acids (FFA), and TBARS levels (a lipid oxidation marker) in cellular extracts.
Results: We observed that administration of 500 µM PA for 24h reduced the metabolic activity and cell mass of differentiated SH-SY5Y neurons ($P<0.001$ and $P<0.001$, respectively). Under these conditions, neuronal cholesterol, FFA, and TBARS levels were decreased by fisetin ($P=0.05$, $P<0.001$, $P=0.005$, respectively) and Semaglutide ($P=0.03$, $P=0.001$, $P=0.001$, respectively).
Conclusions: Our preliminary results suggest that fisetin and Semaglutide may protect against PA-induced neuronal damage and death. However, more studies are needed to clarify the mechanisms underlying the neuroprotective effect of MedDiet-related molecules and CVR-lowering drugs. Funded by EU Horizon Europe CHAngeing - Excellence Hubs-HORIZON WIDERA-2022-ACCESS-04-01 (grant agreement #101087071); Portuguese Fundação para a Ciência e a Tecnologia (FCT): UIDB/04539/2020, UIDP/04539/2020, LA/P/0058/2020 (CIBB); European Social Fund: 2021.04707.BD (DM), EU HORIZON-CSA-WIDERA-2022-ACCESS-04 Excellence Hubs/CHAngeing/II0347.01 (KM, AID).

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SHIFT 01-709

Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

VASCULAR PROTECTIVE EFFECTS OF SGLT2 INHIBITION IN AD/ADRD

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Aims: Recent evidence highlights a significant association between cerebral hypoperfusion and Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD). Our previous studies have shown that SGLT2 inhibitors can reverse cerebral vascular dysfunction and cognitive impairments in diabetes-related ADRD rats. This study aims to investigate the impact of SGLT2 inhibition on cerebral vascular function and AD pathology in an AD rat model without hyperglycemia.
Methods: TgF344-AD rats were orally administered luseogliflozin (20 mg/kg/day) for 3 months. Cognitive function was assessed using an eight-arm water maze. Cerebral vascular function was evaluated by measuring the myogenic response of the middle cerebral artery with pressure myography and cerebral blood flow autoregulation using laser-Doppler flowmetry. Bulk RNA-seq analysis was conducted on primary cerebral VSMCs isolated from AD rats to examine their transcriptomic profile.
Results: SGLT2 inhibition improved learning and memory in AD rats. Impaired myogenic responses and cerebral blood flow autoregulation observed in AD rats were normalized with SGLT2 inhibition. Bulk RNA-seq analysis of primary cerebral VSMCs revealed that SGLT2 inhibition restored disrupted molecular pathways essential for VSMC contractility and vascular function.
Conclusions: These findings suggest that SGLT2 inhibition is a promising therapeutic approach for addressing vascular dysfunction in AD.

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SHIFT 01-710

Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

TARGETING CD38 WITH FLAVONOID COMPOUNDS FOR FUTURE THERAPEUTIC DEVELOPMENT: A COMPUTATIONAL-BINDING ANALYSIS

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Aims: CD38 is an enzyme that is expressed in various tissues. It is involved in the degradation of nicotinamide adenine dinucleotide (NAD^+). It also plays a role in intracellular calcium signaling and regulating cellular migration. CD38 has been implicated in various pathophysiological conditions such as chronic lymphocytic leukemia, multiple myeloma, cardiovascular diseases, and aging disorders including Alzheimer's disease, making CD38 a novel potential pharmacological target. The aim of this study is to investigate the interaction between flavonoid compounds apigenin and its congeners and CD38 for future therapeutic development.
Methods: Crystal structures of CD38 molecules (4F46) was obtained from the RCSB Protein Data Bank, alongside the three-dimensional structure of apigenin (4',5,7-trihydroxyflavone), 7,8-dihydroxyflavone, 3,6-dihydroxyflavone, 5,7-dihydroxyflavone, and 4',5-dihydroxyflavone from the NCBI PubChem database. Docking simulations were utilized to simulate binding modes and affinities between the flavones and CD38.
Results: Apigenin shows potential interactions with specific amino acid residues of CD38. In chain A, it interacts with LEU123, TRP125, LEU145, SER220, THR221, PHE222, and GLU226, with a binding energy of -8.33 kcal/mol. In chain B, it interacts with TRP125, LEU145, ASP155, TRP189, THR221, and GLU226, with a binding energy of -8.01 kcal/mol. Four congeners of apigenin also interact with CD38 in a similar fashion, with slightly different binding energies.
Conclusions: Molecular docking studies indicate that apigenin, a known CD38 inhibitor, forms non-covalent bonds with CD38 molecules. Notably, four congeners of apigenin are predicted to bind to both chain A and chain B of the CD38 molecule with similar or slightly lower affinities, suggesting potential inhibition of the enzyme's activity. This makes CD38 an attractive pharmacological target for various conditions, including Alzheimer's disease.

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SHIFT 01-711

Poster on Board - Shift 01
VASCULAR DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
2-3 April 2025

GLIA-LIKE CELLS FROM LATE PASSAGE MESENCHYMAL STEM CELLS CAN TREAT THE SEQUELAE OF ISCHEMIC STROKE BY BOOSTING NEUROPLASTICITY

Eun Ji Lee[1], Jeong-Min Baek[1], Yejin Ryu[2], Seon Ju Lee[2], Min-Ju Kim[1], Hyunhee Park[3], Hyuk Sung Kwon[2], Hyun-Jung Yu[4], Seong-Ho Koh[2]
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Aims: In our prior study, we developed human mesenchymal stem cells (hMSCs) into glia-like human mesenchymal stem cells (ghMSCs), which acquire a glial shape and secrete growth factors. These cells showed promising results in acute ischemic stroke models. This research investigates the effectiveness and mechanisms of ghMSCs transplantation in chronic cerebral infarction using a rat model.
Methods: Middle Cerebral Artery Occlusion (MCAO) was performed on 8-week-old SD rats to establish the model. Two weeks post-MCAO operation, 15μl containing $2x10^5$ ghMSCs or vehicle was injected into the peri-infarct striatum using stereotactic surgery. Behavioral functions were assessed using the Sticky Tape test and the Inclined Plane test, and MRI scans were conducted before and after transplantation. Rats were sacrificed four weeks post-surgery for molecular analysis.
Results: MRI results showed a significant reduction in infarction volume in the ghMSC-treated group. Behavioral tests indicated improved sensorimotor functions: the Inclined Plane test showed significant increased tolerance angles, and the Sticky Tape test showed faster tape removal times, though not statistically significant. Molecular analysis revealed higher levels of PSD-95, synaptophysin, and neural plasticity markers (MAP2, NeuN, GAP43) in the ghMSC-treated group, indicating enhanced neuroplasticity. Additionally, ghMSCs treatment activated pAkt and BrdU signaling, associated with cell survival, and increased CXCR2 expression and CXCL8 secretion, suggesting mechanisms for neural recovery and hemiplegia improvement.
Conclusions: Our findings suggest that ghMSCs can effectively address chronic cerebral infarction sequelae in animal models, highlighting their potential for treating chronic neurological conditions and paving the way for innovative stem cell therapies.

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SHIFT 01-712

Poster on Board - Shift 01
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
2-3 April 2025

ASSOCIATION OF CAIDE AS A MODIFIABLE RISK FACTOR WITH PROGRESSION TO DEMENTIA CONCERNING AMYLOID AND TAU PATHOLOGY

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Aims: Dementia prevention efforts addressing multiple modifiable risk factors are promising. However, the influence of these factors on dementia progression, particularly in the presence of beta-amyloid or phosphorylated tau (p-tau) pathology, remains unclear.
Methods: Methods: This study aimed to investigate the impact of modifiable risk factors (including vascular risk factors and smoking) on dementia progression in 611 individuals with mild cognitive impairment (MCI) from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database. Vascular risk factors were summarized using the Cardiovascular Risk Factors, Aging, and Dementia (CAIDE) score, categorized into higher or lower risk levels. Smoking status (yes/no) was determined based on medical history and current symptoms. Analyses were stratified by beta-amyloid and p-tau biomarker status: beta-amyloid negative (A-) and positive (A+), p-tau negative (T-) and positive (T+), and both beta-amyloid and p-tau negative (A-T-) and positive (A+T+). Cox proportional hazard models were adjusted for age, sex, education, baseline MMSE score, baseline hippocampal volume, and ApoE4 carrier status.
Results: Results: The median follow-up time was 48 months (30-78 months), and progression to dementia was 36.2%. In the whole sample, 12.2% were smokers, and 36.8% were in the CAIDE high-risk group. A higher CAIDE score was linked to an increased risk of all-cause dementia progression across most MCI subgroups: adjusted hazard ratios (aHR) [95% CI] were 3.1 [1.43; 6.53] for the A- group, 1.7 [1.20-2.27] for T+, 2.6 [1.06-6.59] for A-T-, and 1.6 [1.15-2.22] for the A+T+ subgroup. Smoking was associated with a higher risk of dementia progression in the A+ MCI subgroup (aHR = 1.6 [1.07-2.34]).
Conclusions: Conclusion: Addressing modifiable risk factors holds significant potential to reduce dementia risk even after Alzheimer's pathology onset, with biomarker information potentially enhancing prevention strategies.

Posters on Board

Shift 02

4 – 5 April 2025

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SHIFT 02-001

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / ANIMAL MODELS: RODENTS
4-5 April 2025

THERAPEUTIC POTENTIAL OF NON-INVASIVE TRANSCUTANEOUS AURICULAR VAGUS NERVE STIMULATION IN A PARKINSON'S DISEASE MODEL

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the loss of dopaminergic neurons, leading to impaired motor functions. Current treatments focus on symptom management, with a critical need for therapies that may modify disease progression. Recent studies suggest that vagus nerve stimulation could provide neuroprotection in PD models. However, the majority of studies have focused on invasive vagus nerve stimulation. Therefore, this study aims to evaluate the therapeutic potential of non-invasive Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) in PD models.
Methods: A PD model was developed in mice through five consecutive intraperitoneal injections of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). taVNS was administered concurrently with MPTP administration and applied once daily for 12 days. Motor function was assessed using the cylinder and rotarod tests. Tyrosine hydroxylase (TH) staining in the striatum (ST) and substantia nigra pars compacta (SNpc) was conducted to quantitatively evaluate dopaminergic neuronal prevention.
Results: The tans group demonstrated significant improvements in the cylinder and rotarod tests compared to the MPTP group. In this group, TH-immunoreactivity in both the ST and SNpc suggested dopaminergic neuronal preservation, indicating neuroprotective effects of taVNS.
Conclusions: These results suggest that taVNS may enhance motor function and promote dopaminergic neuronal preservation in a PD mouse model. These findings support taVNS as a promising therapeutic approach for PD. Further studies focusing on the mechanisms underlying these effects, particularly regarding the modulation of neuroinflammation, will be crucial to fully understand the therapeutic potential of taVNS.

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SHIFT 02-002

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / ANIMAL MODELS: RODENTS
4-5 April 2025

ACCELERATING THE PARKINSON´S DISEASE PHENOTYPE IN LINE 61 MICE WITH D-GALACTOSE

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Aims: Aging and the resulting senescence are major risk factors for many neurodegenerative diseases, including Parkinson's disease (PD). Modelling age-related conditions is challenging, as the natural aging process is time-consuming and costly. While the use of transgenic animals has reduced the time required to observe PD-related symptoms, many models still depend on aging to fully develop the disease phenotype, making PD studies resource-intensive. Systemic administration of D-galactose (d-gal) has emerged as a reliable method to artificially induce senescence in vitro and in vivo, and it is therefore widely used in aging and anti-aging therapy studies.
Methods: Two- and six-month-old Thy1-a-syn "Line 61" mice are treated daily with 200 mg/kg of d-gal via their drinking water for 20 weeks and 10 weeks, respectively. Behavioral assessments include the pasta gnawing, grip strength, and passive avoidance test. Gastric emptying and the small intestinal transit time are measured, and organs collected to analyse beta-galactosidase activity and cytokine levels.
Results: Although analyses are ongoing, this study introduces a novel approach to accelerate the development of PD phenotype in Line 61 transgenic mice.
Conclusions: Accelerating aging in transgenic animal models could offer a promising tool to evaluate challenges in neurodegenerative research by reducing study duration and allowing researchers to investigate PD interventions more efficiently.

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SHIFT 02-003

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / ANIMAL MODELS: RODENTS
4-5 April 2025

CHARACTERIZATION OF THE TRANSGENIC PINK1/PARKIN DOUBLE KNOCK-OUT RAT MODEL OF PARKINSON'S DISEASE

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Aims: The objective of this study was to characterize the Pink1/Parkin double knock-out (dKO; Envigo/Inotiv) rat model of Parkinson's disease until 6 months of age.
Methods: Male Pink1/Parkin dKO and wild-type (WT) littermate (n=12/group) rats were characterized at 2, 3 and 6 months of age with the open field test and kinematic gait analysis, and neurofilament light chain (NfL) levels were analyzed from CSF and plasma. At 3 and 6 months of age, brain volumetric and metabolite analysis were performed by magnetic resonance imaging (MRI and MRS). DAT-PET imaging was performed at 5 months. Weakness symptoms were assessed by cage-side observations.
Results: By 6 months of age, all Pink1/Parkin dKO rats manifested moderate to severe hind-leg weakness. Open field conducted at 6 months showed reduced total locomotion and rearing frequency but increased movement velocity. Gait analysis at 2, 3 and 6 months showed significant differences in gait overall scores. Notable findings apart from overall speed-related parameters were compromised inter-limb coordination, increased movement jerkiness, reduced hip height and smaller ankle and knee angles in the Pink1/Parkin dKO rats. Whole brain volume was increased at 6 months, as well as cortex volume at 3 and 6 months in Pink1/Parkin dKO rats. Glucose levels were reduced in the brain at 2 and 6 months and taurine at 3 and 6 months. Creatine (Cr) and, Cr+phospho-Cr and glutamine levels were significantly lower only at 3 months. Dopamine transporter levels were non-significantly reduced at 5 months. NfL levels were elevated both in plasma and CSF from 3 months of age.
Conclusions: By 6 months of age, the Pink1/Parkin dKO rats showed Parkinson's-relevant features in several of the readouts used, providing a tool to explore therapeutic strategies for Parkinson's disease.

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SHIFT 02-006

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / A-SYNUCLEIN
4-5 April 2025

ALPHA-SYNUCLEIN STRAIN-BASED SCREENING IDENTIFIES INCREASED BCL-XL EXPRESSION IN PARKINSON'S DISEASE

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Aims: Parkinson's Disease (PD) is a growing neurodegenerative disorder driven by an aging population. Characterised by the accumulation of alpha-synuclein in dopaminergic neurons, PD leads to dopaminergic neuron death, causing motor and non-motor symptoms. It is now recognised that alpha-synuclein can form distinct strains, each with unique pathogenic properties. Additionally, recent research has highlighted the involvement of non-neuronal cells in PD progression. We aimed to explore the role of non-neuronal cells in the context of alpha-synuclein strains to unveil novel protein targets associated with disease pathogenesis.
Methods: Human brain-derived pericytes were treated with five alpha-synuclein strains (Fibrils, Fibrils-65, Fibrils-91, Fibrils-110 and Ribbons), before RNAseq identified differentially expressed genes (DEGs) involved in significant biological pathways. Using fluorescent immunolabelling, we investigated the analogous proteins of DEGs in alpha-synuclein strain-treated human brain-derived pericytes and post-mortem middle temporal gyrus tissue microarrays.
Results: RNAseq analysis resulted in 321 unique DEGs (Fibrils: 82, Fibrils-65: 56, Fibrils-91: 56, Fibrils-110: 42, Ribbons: 34 and 51 changed with multiple strains). 55 analogous proteins were selected based on the magnitude of their RNAseq fold change and their overlap with the Developmental Studies Hybridoma Bank database. Seven proteins were successfully labelled *in vitro* with increased BCL-XL expression observed in treated human pericytes ($p = 0.009$). *In situ, multiplex* immunohistochemistry resulted in seven proteins being robustly expressed in pericytes: ABCF1, ASAH1, BCL-XL, CSNK2A1, MEGF11, MTHFD1, and PUM2. Notably *in situ* pericytic BCL-XL expression was also increased in PD ($p = 0.001$) by 20%.
Conclusions: Differential BCL-XL expression in pericytes highlights its involvement in PD pathogenesis via vascular-related functionality. Further mechanistic studies will determine if altering BCL-XL expression can modify strain-specific PD processes.

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SHIFT 02-007

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES
4-5 April 2025

INVESTIGATING THE ROLE OF LRRC37A2 IN IPSC-ASTROCYTES AND PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder characterized by both motor and non-motor symptoms. Emerging evidence suggests that the *LRRC37A2* gene may influence PD risk, but its cellular function remains largely unstudied due to its exclusion from many genetic analyses. Located at the 17q21.31 '*MAPT*' locus, a region prone to genomic instability, *LRRC37A2* is subject to copy number variations (CNVs) across haplotypes. Increased *LRRC37A2* expression and CNVs are associated with reduced PD risk. This study aims to explore the role of *LRRC37A2* in astrocyte function, focusing on its regulation of cellular migration, inflammation, and its potential impact on neuronal health. We also aim to understand how *LRRC37A2* contributes to PD risk variability among different genetic ancestries.
Methods: Transcriptomic and functional analyses were used to investigate *LRRC37A2* expression in astrocytes derived from induced pluripotent stem cells (iPSCs) to assess its role in modulating PD risk across ancestries. Whole-cell patch clamp electrophysiology was employed to study the effects of *LRRC37A2* expression on astrocyte function and neuronal health, focusing on glutamate processing and ion channel activity.
Results: Increased *LRRC37A2* expression in astrocytes is linked to a protective effect against PD, driven by cell-autonomous modulation of the inflammatory response. Ongoing electrophysiological studies are examining its role in regulating glutamate homeostasis and ion channel conductance, both critical for neuronal function.
Conclusions: *LRRC37A2* appears to play a protective role in PD by modulating astrocyte activity and influencing inflammation. It may also account for PD risk variability across populations. Further studies will clarify its molecular mechanisms and therapeutic potential.

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SHIFT 02-008

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / LRKK2, PARKIN, PINK1, DJ-1 AND OTHER PD REALTED GENES
4-5 April 2025

LRRK2 INHIBITION MODULATES CELL DEATH INDUCED BY LYSOSOMAL STRESSORS IN THE MOUSE MACROPHAGE-LIKE RAW 264.7 CELL LINE

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Aims: Activating mutations in Leucine Rich Repeat Kinase 2 (LRRK2) strongly increase the risk for developing Parkinson's disease (PD). The mechanistic path from LRRK2 mutations to PD is not established, but LRRK2 modulation of lysosomal function appears likely to be involved. Accumulating evidence indicates that regulation of lysosomal trafficking is an important function of LRRK2, and genes enriched in lysosomal function including LRRK2 are enriched in PD genome-wide association studies (Chang et al. 2017). Recent literature (Eguchi et al. 2018, Herbst et al. 2020, Bonet-Ponce et al. 2020) has reported that lysosomal damage induced by lysosomotropic agents such as LLOMe and chloroquine can activate LRRK2, which we have replicated. Thus, we sought to further the mechanistic understanding of the LRRK2 effects on lysosomal damage in macrophages.
Methods: To determine if LRRK2 activity can modulate the impact of lysosomotropic agents, we assessed the effect of LRRK2 inhibition on LLOMe-induced cell death in the macrophage-like mouse cell RAW 264.7, which has high endogenous LRRK2 expression. This was measured with a variety of confocal imaging and microplate-reader-based assays. In addition, lysotracker-based measurement of lysosomal integrity, and RNAseq analysis of transcriptional footprints was performed to investigate the mechanisms underlying LRRK2 inhibitor modulation of lysosomal damage.
Results: Selective LRRK2 kinase inhibitors concentration-dependently attenuated LLOMe-induced RAW 264.7 cell death. The effect is lysosome specific as LRRK2 inhibition did not affect cell death induced by a variety of other cell death inducers that did not directly affect lysosomes. Transcriptional profiling identifies cholesterol metabolism pathway as important for the effects.
Conclusions: Our data suggests that LRRK2 inhibition can attenuate cell death in macrophages induced by lysosomal damage.

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SHIFT 02-009

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4-5 April 2025

PROTEOME CORRELATES OF ALPHA-SYNUCLEIN PROTEIN LEVEL AND GLUCOCEREBROSIDASE ACTIVITY IN PARKINSON'S DISEASE HUMAN BRAIN

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Aims: The identification of disease mechanisms underlying Parkinson's disease (PD) is complicated by the heterogeneous nature of the disease within brain tissue. Notably, both clinical and neuropathological descriptors, such as the α-synuclein (αSyn)-based Braak staging, poorly correlate with proteome changes in specific disease-affected regions. Quantifiable disease-associated descriptors, such as αSyn protein accumulation and loss of enzymatic activity of β-glucocerebrosidase (GCase), are observed in the brains of patients. This study aims to identify proteome correlates of biochemically-quantified αSyn levels and total GCase enzyme activity in the human brain of PD patients.
Methods: We quantified serine129-phosphorylated (pSer129) αSyn, aa122-truncated αSyn (CTT122- αSyn), and "total" (most proteoforms) αSyn using AlphaLISA and measured total and GBA1-specific GCase activity in frozen human *post-mortem* brain samples from the locus coeruleus (LC, n=74), substantia nigra (SN, n=54), and gyrus temporalis medius (GTM, n=114) of patients with either PD, PD dementia (PDD), incidental Lewy body disease (iLBD), and controls. In the GTM (n=114), we conducted parallel high-resolution shotgun proteomics (TIMS-TOF). Correlation analyses were performed between the quantified protein intensities and the biochemical measures of αSyn and GCase activity.
Results: Initial analysis identified GTM proteomic alterations correlating with either an increase in "total" and pSer129- αSyn proteoforms or with a decrease in GCase activity, or both, notably of those pathways involved in protein degradation and lipid metabolism. Comparisons across PD, PDD, and iLBD samples showed progressive proteomic dysregulation and identified pathways linked to disease progression in the early stages of disease development.
Conclusions: This data provide new insights into the molecular mechanisms underlying PD, offering valuable insight into the pathways involved in the early stages of disease. Additionally, our data emphasizes the importance of biochemically-resolved proteomic analyses in deciphering the mechanisms of neurodegeneration.

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SHIFT 02-010

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4-5 April 2025

INTEGRATING LONG-READ RNA-SEQUENCING WITH MASS SPECTROMETRY DATA IN PARKINSONS WITH TX2P

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Aims: The availability of long-read RNA sequencing technologies is leading to the identification of numerous novel transcripts. Many are predicted to encode novel proteins with implications for genetic variant interpretation and gene function understanding. Currently, there is no efficient means of integrating transcriptomic data with mass spectrometry data to determine whether these transcripts undergo translation in human tissues.
Methods: We developed TX2P, a pipeline that automates the integration of long-read RNA sequencing workflows with existing mass spectrometry data. For transcripts within an input GTF/GFF file, TX2P predicts open reading frames and peptide sequences. It searches for predicted peptides in mass spectrometry data using the tool MetaMorpheus. TX2P identifies proteomic support for transcripts across multiple datasets with statistical validation and uses Docker for cross-platform compatibility.
Results: We used long-read RNA sequencing from 12 Parkinson's disease cases and 12 controls to identify 25897 novel transcripts of interest. This transcriptomic data is integrated with mass spectrometry data from multiple studies to identify novel transcripts with mass spectrometry support for translation.
Conclusions: By efficiently integrating transcriptomic and proteomic data at scale, TX2P enhances the biological value of novel transcript discovery in complex genes and improves our understanding of the genetic architecture of brain diseases, including Parkinson's disease and synucleinopathies.

SHIFT 02-013

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

CHARGED BIOPOLYMERS INDUCE DISTINCT STRUCTURES IN A-SYNUCLEIN FIBRILS

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Aims: The deposition of α-synuclein (α-syn) fibrils is a key pathological hallmark of Parkinson's disease (PD) and other synucleinopathies. The diverse structural polymorphs of α-syn fibrils are thought to contribute to the varied clinical manifestations of these disorders. Factors such as lipids, chaperones, protein partners, post-translational modifications (PTMs), and metabolites influence pathological α-syn aggregation. Its lysine-rich N-terminal and negatively charged C-terminal enable interactions with polycations and polyanions like heparin, nucleic acids, and polyamines, affecting fibrillation kinetics. However, the specific impact of different biopolymers on α-syn fibril structure remains unclear, which we address in this study.
Methods: A Thioflavin-T (ThT) fluorescence assay was used to monitor α-syn fibrillation kinetics in the presence of various biopolymers. Negative-staining TEM characterized the fibril quantity and morphology, while cryo-EM offered high-resolution structural analysis of α-syn fibrils formed with different biopolymers.
Results: We found that both cationic and anionic biopolymers, such as polyphosphate (polyP), polyuridine (polyU), and polyamines (putrescine, spermidine, and spermine), accelerate α-syn aggregation at low stoichiometry. Structural analysis showed that different biopolymers distinctly influence the polymorphs of α-syn fibrils. Polyamines alter fibrillation kinetics without affecting overall fibril structure, while polyU and polyP affect both kinetics and fibril morphology in unique ways. PolyU induced diverse fibril morphologies, whereas polyP led to untwisted fibrils. These findings highlight the critical role of biopolymer type in shaping α-syn fibril structure.
Conclusions: We conducted a thorough investigation of how various charged biopolymers, including polycations and polyanions, affect the aggregation process and the resultant structures of α-syn fibrils. This implies that the intricate and critical roles of different charged biopolymers in the process of α-syn fibril formation and thereby enhancing our understanding of the structural variations in α-syn fibrils across different pathological conditions.

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SHIFT 02-014

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

PHOSPHORYLATED MECP2 (PS423-MECP2) ACCUMULATES IN LEWY BODIES AND LEWY NEURITES OF PARKINSON'S DISEASE AND INCIDENTAL LEWY BODIES

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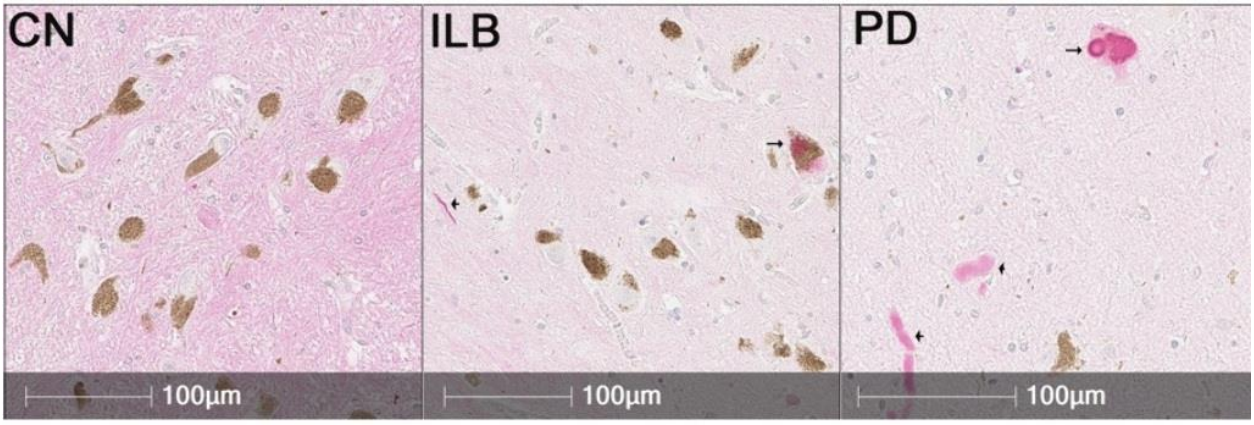
Aims: Methyl-CpG-binding protein 2 (MECP2) is a global epigenetic repressor. Mutations of the gene are the cause of the synaptic pathology in Rett syndrome. We previously demonstrated that neuronal activity-dependent phosphorylated MECP2 (pS423-MECP2) co-accumulates with hyper-phosphorylated Tau in hippocampus of sporadic Alzheimer's disease cases. Here we investigate whether pS423-MECP2 accumulates in the substantia nigra (SN) of autopsy-confirmed Parkinson's disease (PD) brains and non-PD brains with incidental Lewy bodies (ILB).
Methods: We developed and validated a rabbit pS423-MECP2 specific polyclonal antibody and carried out immunohistochemistry (IHC) using magenta label to differentiate it from brown neuromelanin color of dopamine neurons on postmortem SN specimens from 10 PD cases, 10 controls with ILB (ILB), and 10 matched normal controls without ILB (CN). We used HALO 3.3 to quantify the positive signals of pS423-MECP2 and neuromelanin in SN.
Results: pS423-MECP2 was present in Lewy bodies and Lewy neurites of ILB and PD (Fig 1), while pS423-MECP2 was absent in Lewy body from CN. pS423-MECP2 was significantly increased in ILB and PD (4.5 and 12.3-fold, respectively). In contrast, neuromelanin in PD specimens was reduced by 43.2% compared to CN and ILB specimens. Fig 1. Arrows point out Lewy bodies and arrowheads Lewy neurites.



Conclusions: pS423-MECP2 accumulates within Lewy bodies and Lewy neurites and its level increases in ILB and PD.

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4-5 April 2025

MODELLING MULTIPLE SYSTEM ATROPHY DISEASE THROUGH BRAIN ORGANOIDS' GENERATION

Manuela Magni[1], Emanuele Frattini[2], Elena Vezzoli[3], Letizia Bertolasi[2], Ilaria Trezzi[2], Fabio Biella[4], Marco Brevi[2], Gaia Faustini[5], Arianna Bellucci[5], Stefano Bogetto[2], Andrea Falqui[6], Alessio Di Fonzo[2]
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Aims: Multiple System Atrophy (MSA) is a progressive neurodegenerative disorder due to the loss of various neuronal populations, including the GABAergic and the dopaminergic systems. The neuropathological hallmarks of MSA consist of alpha-synuclein aggregations in oligodendrocytes and neurons. No disease-modifying therapy is available for this disorder, resulting in a reduced life-span of affected patients with a median survival of 6-9 years. This is largely due to the lack of reliable human models capable of reproducing key features of the disease and that could be tested for drug-development applications. Here, we aim to generate advanced 3D models of MSA derived from patients by developing brain region-specific organoids with midbrain and striatum identities. These innovative cultures have proven particularly useful to mimick the embryonic organogenesis and for disease-modeling purposes. However, their application to the study of MSA has yet to be explored.
Methods: iPSC lines were differentiated into midbrain organoids with our already established method and into striatum organoids with an unpublished GABAergic-patterning protocol developed in our laboratory. Samples were collected at different time-points.
Results: Organoids showed a correct spatial and temporal progression in the expression of genes involved in the development of both midbrain and striatum, mimicking the embryogenesis of the human brain. These models display several cell populations, particularly enriched in neurons (GABAergic, dopaminergic, glutamatergic) and glia (astrocytes, oligodendrocytes).
Conclusions: Both midbrain and striatum organoids showed a correct spatial and temporal progression in the expression of genes involved in the in-vivo development of both midbrain and striatum. Moreover, striatal organoids of the MSA subject reproduced a higher expression of α-synuclein and a reduced content of neurons as seen in patients' brains, therefore showing potential to reproduce, at least in part, the typical human neuropathology.

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SHIFT 02-016

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

DIAGNOSTIC ACCURACY OF ALPHA-SYNUCLEIN SEEDING AMPLIFICATION ASSAYS IN DIFFERENT BIOSPECIMENS FROM LEWY BODY DEMENTIA VERSUS ALZHEIMER'S DISEASE

Oskar Hoffmann Mcwilliam[1], Remarh Bsoul[2], Ausrine Areskeviciute[2], Eva Løbner Lund[2], Gunhild Waldemar[1,3], Steen Hasselbalch[1,3], Anja Simonsen[1], Marie Bruun[1], Christian Von Buchwald[3,4], Kasper Aanæs[4], Christian Korsgaard Pedersen[4], Ida Schlosshauer Brandt Andersen[4], Magne Bech[4], Kristian Frederiksen[1,3]
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Aims: Diagnosing dementia with Lewy bodies (DLB) poses significant challenges, particularly in differentiating DLB from Alzheimer's disease (AD). Seeding aggregation assays (SAA) offer an accurate method to measure pathological alpha-synuclein by utilizing its ability to induce misfolding in other alpha-synuclein proteins.
This study aims to evaluate the sensitivity, specificity, and diagnostic accuracy of alpha-synuclein SAA for DLB versus AD in cerebrospinal fluid (CSF), skin, olfactory mucosa, and urine, while also assessing the influence of DLB symptoms on aSyn SAA positivity.
Methods: We recruited patients with DLB and AD from The Copenhagen Memory Clinic. CSF, two skin punch biopsies taken paramedian from C7, one nasal swab from each side at agger nasi, and urine samples, were collected and tested using SAA with recombinant aSyn.
Patients were assessed cognitively with the Montreal Cognitive Assessment (MoCA) and for motor and non-motor symptoms with the MDS-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) I-III.
Results: We included 31 patients with DLB patients (mean age 72 years, 13% female) and 25 patients with AD (75 years, 44% female). There was a significant sex difference ($p=0.01$) but no significant differences in age ($p=0.08$) or in MoCA ($p=0.16$) between DLB and AD. MDS-UPDRS I-III scores were higher in DLB ($p<0.0001$).
The sensitivity, specificity, and diagnostic accuracy of alpha-synuclein SAA were 82%, 92%, and 87% in CSF; 77%, 92%, and 85% in skin; 40%, 88%, and 62% in olfactory mucosa; and 17%, 100%, and 59% in urine.
Conclusions: The diagnostic accuracy of alpha-synuclein measurement in skin and CSF using SAA was high, demonstrating its potential utility in diagnosing DLB. Measurements in urine and olfactory mucosa were less reliable and may not yet be clinically relevant for DLB diagnosis.

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SHIFT 02-017

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

CONTROLLING POLYMORPHISM TO REPLICATE DISEASE-RELEVANT ALPHA-SYNUCLEIN STRUCTURES

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Aims: Synucleinopathies are associated with the intracellular deposition of aggregates of aSyn, which at the molecular level involves many individual alpha-synuclein molecules forming long fibrils in a beta-rich, highly repetitive, and tightly packed amyloid fold. Recent breakthroughs in direct imaging single-particle CryoEM analysis have revealed a much greater structural diversity and complexity of such amyloids than previously thought. It is now clear that the same protein (including aSyn) can form several distinctly different amyloid folds, known as polymorphs, depending on the environment during aggregation. Until now, none of the alpha-synuclein polymorphs found in human brain samples could be reliably reproduced or amplified in vitro. Our objective is to produce disease-relevant structures and, more broadly, to gain a deeper understanding of and exert greater control over the driving forces of amyloid polymorphism.
Methods: In addition to the many established methods for amyloid characterization, we are using the latest CryoEM techniques to elucidate near-atomic resolution structures.
Results: Among the many polymorphic structures of aSyn fibrils, the ordered protein region typically comprises various ranges of residues 1-100, while the C-terminal part remains disordered. It has also been shown that even small changes in the alpha-synuclein sequences, such as a single point mutation or post-translational modification (PTM), can alter the distribution of polymorphs or even give rise to new folds. We have recently shown a pH-dependence on aSyn polymorphism and are currently exploring other aspects guiding polymorphism.
Conclusions: Many therapeutic approaches against aggregation rely on detecting aggregates by targeting unique features on the amyloid fibril surface. Given the recent findings on polymorphism, we hope to foster greater awareness of this fundamental reality of aSyn beyond the field of structural biology, potentially leading to new or adapted therapeutic strategies.

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SHIFT 02-018

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

LEWY BODY PATHOLOGY AND SEEDING-COMPETENT ALPHA-SYNUCLEIN ALONE DO NOT DRIVE MOLECULAR OR CELLULAR CHANGES IN DOPAMINERGIC NEURONS

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc). Lewy body pathology (LBP) has long been considered a primary correlate of DA neuron loss. Recent findings suggest that seeding-competent forms of alpha-synuclein (αSyn) could serve as an additional biomarker, and possibly as a pathological substrate, for Lewy body disease progression and neuronal loss. However, the pathological significance of these αSyn changes remains unclear, with important implications for developing disease-modifying therapies.
Methods: We analyzed serial post-mortem SNc tissue sections from age- and sex-matched control cases (CON, n=6), PD cases at Braak stage>3 (PD, n=9), cases with Alzheimer's disease pathology (AD, n=5), and cases with AD pathology with LB co-pathology (AD/LBP, n=5). Analyses included spatial transcriptomics, spatial proteomics (LC-MS), and αSyn seeding aggregation assays (SAA) from consecutive tissue sections in all cases.
Results: In control and AD cases, no detectable LBP was observed, whereas all PD and AD/LBP cases showed the presence of Lewy bodies in the SNc. Importantly, both PD and AD/LBP cases demonstrated seeding-competent αSyn, indicated by a positive SAA result, while all control and AD cases were SAA-negative. Transcriptomic and proteomic analyses revealed significant cellular and molecular differences, along with DA neuron loss, when comparing PD to CON cases, and PD to AD cases. In contrast, no transcriptomic differences or significant neuron loss were detected between AD and AD/LBP cases.
Conclusions: Our findings suggest that LBP and seeding-competent αSyn may not be primary drivers of the cellular and molecular changes associated with DA neuron pathology. Instead, these results support the hypothesis that an alternative, yet unidentified disease mechanism may underlie DA neuron degeneration and cell death in PD.

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SHIFT 02-019

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

INVESTIGATING A-SYNUCLEIN AGGREGATION IN PARKINSON'S DISEASE USING INTRACRANIAL FN075 INJECTIONS IN MICE

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Aims: Alpha-synuclein aggregation plays a critical role in the degeneration of nigral dopaminergic neurons in Parkinson's disease (PD). Misfolded alpha-synuclein forms toxic oligomers, disrupting cellular functions such as mitochondrial activity and protein clearance, leading to nigral dopaminergic cell loss. In this study, we examine the *in vivo* effects of FN075, a small peptidomimetic molecule promoting alpha-synuclein aggregation *in vitro*, in mice.
Methods: FN075 was administered intracranially into the substantia nigra of C57BL/6J mice to simulate PD-like synucleinopathy. Vehicle-injected animals were used as controls. The functional effects of FN075 on nigrostriatal dopamine transmission were evaluated at 3 and 6 months using *in vivo* amperometry. The brains were then dissected and processed both for immunohistochemistry, with antibodies directed towards tyrosine hydroxylase and α-synuclein, and for protein misfolding cyclic amplification (PMCA). Additionally, behavioral effects were monitored repeatedly using the cylinder test, sticker test, and grip test.
Results: FN075-treated animals demonstrated impaired striatal dopamine release, motor dysfunction, and nigral dopaminergic cell loss.
Conclusions: These results establish FN075 as a valuable tool for modeling PD pathology and testing potential therapeutic interventions targeting alpha-synuclein aggregation.

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SHIFT 02-020

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

SEEDING ACTIVITY AND EPITOPE MAPPING OF GLIAL ALPHA-SYNUCLEIN INCLUSIONS IN ALPHA-SYNUCLEINOPATHIES

Marcelina Wojewska, Maria Otero-Jimenez, Simona Jogaudaite, Steve Gentleman, Javier Alegre-Abarrategui
Imperial College London, Department Of Brain Sciences, London, United Kingdom

Aims: Glial alpha-synuclein (**α-syn**) inclusions are not only limited to Multiple System Atrophy (**MSA**) but are also infrequently observed in Parkinson's disease (**PD**), and dementia with Lewy bodies (**DLB**). This project aims to characterise the regional involvement as well as epitope mapping of microglial, astrocytic, and oligodendrocytic inclusions across the α-synucleinopathies. Furthermore, we aim to elucidate the correlation with seeding capacity and clinical features.
Methods: Immunohistochemistry and immunofluorescence uses α-syn antibodies mapping to different epitopes alongside cell-specific markers. The cohort is composed of 64 MSA cases, 36 PD cases and 17 DLB cases from the Imperial Parkinson's UK tissue bank. Seeding is investigated using brain tissue and cerebrospinal fluid via the α-syn real-time quaking-induced conversion (**RT-QuIC**) assay.
Results: Microglial and astrocytic α-syn were observed particularly in the neocortex of DLB cases. Astrocytic α-syn was absent in MSA cases but microglial α-syn was seen predominately in the cerebellum. Apart from in MSA, oligodendrocytic α-syn was also seen in PD and DLB chiefly in the cerebellum and the brainstem. Lewy body type neuronal pathology was revealed by antibodies covering the length of α-syn but astrocytic and microglial pathology was only picked up by antibodies targeting amino acids 39-96 indicating either possible truncation, or inaccessibility of the N and C terminus. The α-syn was localised to an endo-lysosomal location within activated astrocytes and microglia as determined by HLA-DR, glutamine synthetase, and LAMP1, suggesting internalisation rather than *de novo* formation. Seeding data of regions with differential involvement of glial pathology will be provided.
Conclusions: Our data suggests that glial pathology is a secondary phenomenon, highlighting the multi-cellular involvement underlying the pathogenesis of α-synucleinopathies. Further investigation is needed to determine whether these inclusions ameliorate or accelerate the disease process.

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SHIFT 02-021

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

DIFFERENT CHARGED BIOPOLYMERS INDUCE A-SYNUCLEIN TO FORM FIBRILS WITH DISTINCT STRUCTURES

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Aims: The aggregation of α-synuclein (α-syn) into amyloid fibrils, a key process in the development of Parkinson's disease (PD) and other synucleinopathies, is influenced by a range of factors such as charged biopolymers, chaperones, and metabolites. However, the specific impacts of different biopolymers on α-syn fibril structure are not well understood.
Methods: In this work, we used Thioflavin-T (ThT) fluorescence assay, negative-staining transmission electron microscopy (NS-TEM) and cryo-electron microscopy (cryo-EM) to conduct a comprehensive investigation into the kinetic and structural impact of various biopolymers on α-syn fibril formation.
Results: In our work, we found that different polyanions and polycations, such as polyphosphate (polyP), polyuridine (polyU), and polyamines (including putrescine, spermidine, and spermine), markedly altered the fibrillation kinetics of α-syn *in vitro*. Utilizing cryo-electron microscopy (cryo-EM), we further examined the structural configuration of α-syn fibrils formed in the presence of these biopolymers. Notably, we found that while polyamines do not change the atomic structure of α-syn fibrils, polyU and polyP induce the formation of distinct amyloid fibrils, exhibiting a range of structural polymorphs.
Conclusions: Our work offers valuable insights into how various charged biopolymers affect the aggregation process and the resultant structures of α-syn fibrils, thereby enhancing our understanding of the structural variations in α-syn fibrils across different pathological conditions.

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SHIFT 02-022

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / A-SYNUCLEIN AGGREGATION
4-5 April 2025

DESIGN OF IG-LIKE BINDERS TARGETING A-SYNUCLEIN FIBRIL FOR MITIGATING ITS PATHOLOGY

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Aims: The accumulation and propagation of pathological α-synuclein (α-syn) fibrils are central to the pathogenesis of Parkinson's disease (PD) and other synucleinopathies. Consequently, targeting α-syn has become a primary focus for therapeutic intervention in these diseases, with particular emphasis on targeting pre-existing α-syn fibrils that form in advanced disease stages. We develop novel immunoglobulin-like (Ig-like) binders that specifically target the C-terminal of α-syn fibrils, disrupting their interactions with various cell surface receptors to mitigate their neuropathology.
Methods: We explored the potential of isolated Ig-like domains derived from α-syn receptors as protein binders for α-syn fibrils to inhibit their pathology using cell surface binding assays, neuron propagation assays, and quantitative polymerase chain reaction. Additionally, we employed NMR spectroscopy, bio-layer interferometry, immunogold TEM, and AlphaFold modeling to elucidate the molecular mechanisms underlying the interaction between Ig-like binders and α-syn. Finally, through structure-based design, we significantly improved the binding affinity and inhibitory activity of these Ig-like binders.
Results: We discovered two Ig-like domains derived from α-syn receptors, the D1 domain of LAG3 and the V domain of RAGE, effectively block cell surface binding, prevent neuronal propagation, and reduce microglial inflammatory responses of α-syn fibrils. We further identified two new Ig-like binders, the D1 domain of CD4 and the D1 domain of CAR, which bind the C-terminal of α-syn fibrils with high affinity and alleviate its neuropathology. Furthermore, we developed a mutant version of CARD1 with enhanced binding affinity to α-syn fibrils, thereby increasing its inhibitory activity against α-syn fibril pathology.
Conclusions: Our work presents new strategies for designing Ig-like binders that specifically capture the C-terminal region of α-syn fibrils to mitigate its neuronal propagation and inflammation, offering a promising therapeutic approach to slow PD progression.

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SHIFT 02-024

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
4-5 April 2025

TRUNCATION-DEPENDENT LYSOSOMAL LOCALIZATION OF NEURONAL ALPHA-SYNUCLEIN IN PARKINSON'S DISEASE HUMAN BRAIN

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Aims: The accumulation of α-Synuclein (αSyn) within neurons is a hallmark of synucleinopathies, such as Parkinson's disease (PD), and may stem from impaired protein degradation. Lysosomes have been proposed as a key site for αSyn degradation, but direct evidence of their association in vivo and ex vivo has been limited. This study aimed at investigating the lysosomal localization of αSyn and its post-translational modifications in the soma of human post-mortem nigral neurons and iPSC-derived PD neurons.
Methods: We analysed formalin-fixed, paraffin-embedded brain tissue from neuropathologically-verified donors diagnosed with either PD, PD with Dementia (PDD) and incidental Lewy body disease (iLBD) with Braak αSyn stage ≥ 4. Substantia nigra (SN) sections were assessed using an extensive panel of αSyn and lysosomal marker antibodies via IHC and advanced confocal and super-resolution STED microscopy.
Results: We demonstrate, for the first time, widespread localization of αSyn within lysosomes in dopaminergic neurons of the SN. This lysosomal αSyn is morphologically distinct from cytosolic Lewy bodies (LBs) and pale bodies and appears either independently or in association with intracellular LBs. When present, LBs are consistently accompanied by ring-shaped lysosomal structures. Interestingly, lysosomal αSyn is truncated, lacking the C-terminal region beyond residue 103, suggesting defective lysosomal processing. Our findings reveal two distinct pools of intracellular αSyn: a lysosome-associated, C-terminally truncated form, and a non-lysosomal form with an intact C-terminus, primarily phosphorylated at Ser129.
Conclusions: Our data indicate that lysosomal accumulation of αSyn might precede LB formation, implying that impaired lysosomal processing of αSyn might be an early event during the pathogenesis of PD. These findings highlight the potential role of modulating lysosomal proteases as a therapeutic strategy for preventing αSyn accumulation and disease progression.

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SHIFT 02-025

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
4-5 April 2025

ROLE OF AUTOPHAGIC CLEARANCE IN AMYLOID BETA-ALPHA SYNUCLEIN CO-PATHOLOGY

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Aims: There remains a large gap in knowledge about the pathological overlap of Alzheimer Disease (AD) and Parkinson's Disease (PD). My project seeks to understand the underlying mechanisms behidn this co-pathology. **Aim 1: Determine how inhibition of autophagy contributes to the increased dysfunction seen in co-pathology Aim 2: Examine how α-syn membrane interactions contribute to worsening Aβ pathology**
Methods: I employed SH-SY5Y cells to study the effects of autophagy compounds and Aβ oligomers and α-synuclein fibrils. I analyzed protein amounts by ELISA and Western blot. I also used microdialysis to measure levels and half life of Aβ and α-synuclein in WT and APP/PS1 mice.
Results: I found significant increases in secreted and intracellular Aβ when exposed to α-synuclein pre-formed fibrils.Additionally, fibril exposure seemed to significant increase autophagic flux in the cells. Mice experiments are currently underway.
Conclusions: While experiments are still underway, because of the effect of α-syn to increase levels of amyloid-beta, and to modulate autophagy markers, it seems likely that α-syn and amyloid-beta interact through an autophagy-dependent pathway.

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SHIFT 02-026

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AUTOPHAGY, LYSOSOMES, UBIQUITIN, PROTEASOME
4-5 April 2025

P73-MEDIATED REGULATION OF AUTOPHAGY: A NEW THERAPEUTIC TARGET IN PARKINSON'S DISEASE AND RELATED SYNUCLEINOPATHIES

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Aims: α-Synucleinopathies are characterized by abnormal accumulation of α-synuclein aggregates in neurons, nerve fibers, and glial cells, including Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA). Autophagy is a lysosome-dependent mechanism for cellular degradation. It targets aberrant protein aggregates, damaged organelles, and other defective intracellular components to preserve cellular homeostasis. Research suggests that autophagy plays a crucial role in the etiology of neurodegenerative diseases, particularly α-synucleinopathies. Numerous in vitro and in vivo investigations have indicated aberrant autophagy in neurodegenerative diseases, including our finding that α-synuclein impedes autophagic flow in a Parkinson's disease cellular model. P73 is a transcription factor involved in stress response, tumor suppression, apoptosis, and autophagy, similar to p53. Recently, we have demonstrated, using RNA sequencing, that p73 and its several isoforms are impacted by the overexpression of α-synuclein. Notably, ΔNp73, a truncated variant of p73 at the N-terminus, exhibits inverse expression levels compared to p73 following α-synuclein overexpression. Based on our prior research, we postulated that α-synuclein regulates p73 expression in α-synucleinopathies to restrict autophagic flow.
Methods: To elucidate the function(s) of p73 in autophagic flux within a PD cellular model, p73 expression was either inhibited using p73 siRNA or restored through p73 adenovirus.
Results: indicate that autophagy-related proteins, including p62 and LC3-II, are affected by p73 protein levels. Furthermore, α-synuclein aggregates diminished with the restoration of p73.
Conclusions: According to these findings, p73 might play a role in maintaining autophagic flux, potentially inhibiting the progression of neurodegenerative diseases.

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SHIFT 02-028

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4-5 April 2025

MOLECULAR BASIS OF AMYLOID AGGREGATION OF TPPP/P25 IN PARKINSON'S DISEASE

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Aims: TPPP/p25 is a microtubule-associated protein and serves as a Golgi outpost for myelin sheath elongation in the oligodendrocyte of brain. TPPP/p25 resists to aggregate under normal condition, but forms massive protein aggregates in the brains of PD and MSA patients. However, the molecular mechanism of TPPP/p25 amyloid aggregation and its relationship to the disease remains elusive.
Methods: In this study, combined with biophysical and biochemical approaches, including solution nuclear magnetic resonance (sNMR) spectroscopy, Thioflavin T (ThT) fluorescence kinetics assay and negative-staining transmission electron microscopy (NS-TEM), we investigated the molecular mechanism of TPPP/p25 fibrillation. Moreover, we determined the cryo-EM structure of TPPP/p25 fibrils prepared *in vitro* and identified the cytotoxicity of TPPP/p25 fibrils in neuron.
Results: In this work, we reveal that TPPP/p25 employs a self-lock mechanism for maintaining its native conformation against amyloid aggregation. Further cryo-EM study demonstrates that the well-folded core domain (termed as CORE) locked in its native state of TPPP/p25 undergoes dramatic conformational change to form a novel fold of TPPP/p25 fibril structure which exhibits potent neurotoxicity. More importantly, we found a PD-associated mutation in the CORE of TPPP/p25 can significantly destabilize the native conformation of Core and promote its amyloid fibrillation.
Conclusions: Collectively, our work elucidates the molecular basis of the amyloid aggregation of TPPP/p25 and how this process is regulated by disease-associated mutation, which highlights its pathological role in synucleinopathies.

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SHIFT 02-029

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
4-5 April 2025

IDENTIFYING A NOVEL ROLE FOR THE PD/DLB-LINKED VPS13C IN NUTRIENT SENSING

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Aims: VPS13C is a lipid transfer protein localized at membrane contact sites (MCS) between the endoplasmic reticulum (ER) and late endosomes/lysosomes (LE/Lys), as well as between the ER and lipid droplets (LDs). Its recruitment to these MCS depends on interactions with organelle-specific membrane proteins: VAPB on the ER, RAB7 on LE/Lys, and an unidentified partner on LDs. Interest in VPS13C has increased following the discovery of mutations in its gene linked to Parkinson's Disease (PD) and Dementia with Lewy Bodies (DLB). However, the precise mechanisms by which these mutations contribute to Lewy Body Diseases (LBD) remain elusive.
Methods: To expand our understanding of the cell physiological role of VPS13C, we identified its interactome, through employing immunoaffinity purification of endogenous VPS13C followed by mass spectrometry. Our approach prioritized interactors relevant to organellar homeostasis, providing a starting point to elucidate how loss of function of VPS13C may contribute to neurodegeneration.
Results: Within the interactome, we identified an association between VPS13C and GATOR2, a key complex regulating mTorC1 activation. Super-resolution imaging and co-immunoprecipitation (Co-IP) confirmed that VPS13C colocalizes with subunits of this complex at the cell periphery in response to nutrient availability, and which was paralleled by mTORC1 recruitment; these events being dependent on VPS13C expression. Surprisingly, VPS13C exerts this role in recruiting the nutrient sensing machinery at plasma membrane domains in protruding membrane ruffles, and not on lysosomes. We further scrutinized this by identifying additional effector proteins in these plasma membrane domains.
Conclusions: These findings suggest a novel role for VPS13C in activating peripheral mTORC1 signaling, which is as well disrupted by mutations in VPS13C linked to DLB.

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SHIFT 02-030

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
4-5 April 2025

PHOSPHORYLATION AT TYROSINE 204 IS A MARKER OF ABL1 ACTIVATION

Carla Bento, Lizzie Glennon, Anthony Dossang, Alpesh Shah, Navi Kandola, Don Murphy, Tomoko Smyth, Heather Weir, Nicola Wilsher, David Norton, Amanda Price, Nicola Wallis, Elena Di Daniel
Astex Pharmaceuticals, Cambridge, United Kingdom

Aims: Oxidative stress and mitochondrial dysfunction play a role in dopaminergic neuron degeneration in Parkinson's Disease (PD). The tyrosine-protein kinase ABL1 is activated by oxidative stress and has been shown to phosphorylate PD proteins such as α-Synuclein, Parkin and PARIS. Clinical trials for ABL1 inhibitors in PD patients are ongoing. Traditionally, ABL1 activation is determined by phosphorylation at tyrosine Y245 or Y412; however, low endogenous expression in mouse brain and sub-optimal sensitivity of commonly used assays limit their use as biomarkers. We investigated phosphorylation at Y204 residue as an alternative.
Methods: Phosphorylation of specific ABL1 tyrosine residues were determined by western blotting, immunofluorescence, and plate-based immunoassays (ELISA, MSD and SIMOA). HEK293 cells overexpressing ABL1, SH-SY5Y cells, or iPSC-derived dopaminergic neurons were subjected to oxidative stress or activation of upstream PDGFR/Src family kinases using recombinant platelet-derived growth factor (PDGF) and treated with ABL1 inhibitors. Wild-type and BCR-ABL (KCL22) xenograft-bearing mice were used to assess ABL1 activity *in vivo*.
Results: ABL1 phosphorylation at Y204 was induced in response to oxidative stress and PDGFR signalling *in vitro* and reduced by treatment with ABL1 inhibitors both *in vitro* and *in vivo*. A custom-made SIMOA assay successfully detected phosphorylation of Y204 at endogenous levels in mouse brain.
Conclusions: ABL1 Y204 phosphorylation mirrors the well-documented phosphorylation event at Y412 that occurs upon protein activation, and is modulated by ABL1 inhibitors, thus offering utility as a biomarker for ABL1 activation. The ultra-sensitive SIMOA assay here developed for Y204 phosphorylation can facilitate detection of ABL1 activation at low levels and in samples of limited size. This assay will have utility in the evaluation of Astex proprietary ABL1 inhibitors that have been designed using our fragment and structure-based drug discovery approaches.

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SHIFT 02-032

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / DOPAMINERGIC, CHOLINERGIC
4-5 April 2025

EVALUATION OF COGNITIVE FUNCTION IN 4- AND 6-MONTHS OLD LINE 61 MICE

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Aims: Parkinsons's diseases (PD) most recognized pathology is the occurrence of unvoluntary movement in patients. However, cognitive decline is also a major characteristic of PD in some patients, with severity and frequency increasing as the disease progresses to later stages. The Line 61 (Thy1-a-syn) mouse is a well-studied model for PD, overexpressing human alpha-synuclein and exhibiting many hallmarks observed in humans. Although cognitive deficits have been reported in this model, severity and age varies between research groups. Here, we thus perform a series of behavioral tests to evaluate the cognitive phenotype of Line 61 animals compared to non-transgenic (ntg) littermates at 4 and 6 months of age.
Methods: Line 61 and ntg-littermates are repeatedly tested at 4 months of age and again at 6 months of age, evaluating their cognitive state using Y-maze and Morris water maze. Additionally, the passive avoidance test is performed exclusively at 6 months of age, as this test can only be performed once. The general health status is tracked using Irwin testing including wire hanging for motor defects.
Results: Previously collected data indicate a cognitive decline in Line 61 mice, suggesting long- and short-term memory deficits. Results of this study will characterize the longitudinal cognitive phenotype of these mice.
Conclusions: This study will shed further light on the cognitive aspect of PD in Line 61 mice and help to combat this disease by providing a treatment window for drug interventions.

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SHIFT 02-033

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / DOPAMINERGIC, CHOLINERGIC
4-5 April 2025

IN VITRO DIFFERENTIATION OF DOPAMINERGIC NEURONS FROM HUMAN ESC: PARKINSON'S DISEASE IN VITRO MODEL

Malika Bsibsi[1], Catalina Gomez-Puerto[1], Cyntha Van Der Berg[1], Berke Gurkan[1], Kimberly Lo[1], Mark Musters[1], David Ketskemety[1], Sophie Vermond[1], Amit Chouhan[2], Dario Magnani[2], Cindy Loomans[1], Stefan Kostense[2], Marijn Vlaming[1]
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Aims: Dopaminergic neurons are the main source of dopamine in the mammalian central nervous system and play an important role in brain functions including voluntary movement and behavioral processes. The loss of dopaminergic neurons is associated with one of the most prominent human neurological disorders, Parkinson's disease. Therefore, dopaminergic neurons are considered a potential therapeutic target to treat the disease.
Methods: Charles River has implemented a robust dopaminergic neuron differentiation protocol that is amenable to compound screening and involves the use of small molecules. For characterization, we collected samples at different timepoints during the differentiation procedure to assess gene and protein expression and compared these to commercially available induced pluripotent stem cell derived dopaminergic neurons (iCell DopaNeurons).
Results: As expected, expression of pluripotency markers NANOG, OCT4 and SOX2 was high at the pluripotency stage (day 0, D0) and immediately dropped in the first few days of the differentiation procedure. Early development of dopaminergic neurons was confirmed by detecting expression of Nestin, LMX1A, FOXA2, OTX2 and NURR1 from D16 onwards. Additionally, cells were predominantly neurons based on βIII-Tubulin expression. Expression of mature dopaminergic neuronal markers TH and EN1 was low expressed at day 20, when compared to the iCell Dopaneurons from Fuijifilm, suggesting the lack of fully mature dopaminergic neurons phenotype. Ongoing studies are focused on characterizing the functional phenotypes of the differentiated dopaminergic neurons and iCell DopaNeurons WT and PD GBA N370S, 11344 (mutant) using Microelectrode Arrays (MEA).
Conclusions: Taken together, we successfully demonstrated that human embryonic stem cells be differentiated into early-stage dopaminergic neurons with the potential of further maturation. This in vitro model can be used in the discovery of novel targets and drugs for therapeutic intervention for Parkinson's disease.

SHIFT 02-034

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

TH17 CELLS INDUCE DOPAMINERGIC NEURONAL DEATH VIA LFA-1/ICAM-1 INTERACTION IN A MOUSE MODEL OF PARKINSON'S DISEASE

Zhan Liu
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Aims: T helper (Th)17 cells, a subset of $CD4^+$ T lymphocytes, have strong pro-inflammatory property and appear to be essential in the pathogenesis of many inflammatory diseases. However, the involvement of Th17 cells in Parkinson's disease (PD) that is characterized by a progressive degeneration of dopaminergic (DAergic) neurons in the nigrostriatal system is unclear. Here, we aimed to demonstrate that Th17 cells infiltrate into the brain parenchyma and induce neuroinflammation and DAergic neuronal death in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- or 1-methyl-4-phenylpyridinium (MPP^+)-induced PD models.
Methods: Blood–brain barrier (BBB) disruption in the substantia nigra (SN) was assessed by the signal of FITC-labeled albumin that was injected into blood circulation via the ascending aorta. Live cell imaging system was used to observe a direct contact of Th17 cells with neurons by staining these cells using the two adhesion molecules, leukocyte function-associated antigen (LFA)-1 and intercellular adhesion molecule (ICAM)-1, respectively.
Results: Th17 cells invaded into the SN where BBB was disrupted in MPTP-induced PD mice. Th17 cells exacerbated DAergic neuronal loss and pro-inflammatory/neurotrophic factor disorders in MPP^+-treated ventral mesencephalic (VM) cell cultures. A direct contact of LFA-1-stained Th17 cells with ICAM-1-stained VM neurons was dynamically captured. Either blocking LFA-1 in Th17 cells or blocking ICAM-1 in VM neurons with neutralizing antibodies abolished Th17-induced DAergic neuronal death.
Conclusions: These results establish that Th17 cells infiltrate into the brain parenchyma of PD mice through lesioned BBB and exert neurotoxic property by promoting glial activation and importantly by a direct damage to neurons depending on LFA-1/ICAM-1 interaction.

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SHIFT 02-035

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

INVESTIGATING INFLAMMASOME PROTEIN ASC-ALPHA-SYNUCLEIN COMPLEX-TRIGGERED INFLAMMATORY RESPONSES IN MURINE MICROGLIA

Karan Thakur[1,2], Christine Péladeau Ladouceur[1], Klaudia Baumann[1], David Cai[1], Ewa Baumann[1], Gerard Agbayani[1], Julianna Tomlinson[3], Michael Schlossmacher[2,3], Jagdeep Sandhu[1,4]
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Aims: Neuroinflammation is a core component of Parkinson's disease (PD) which is characterized by the accumulation of misfolded α-synuclein (αSyn) protein aggregates that can activate the NLRP3 inflammasome in microglia. The inflammasome adaptor protein, ASC, has shown to bind amyloid-β (Aβ) and the internalization of ASC-Aβ complexes by microglia results in the amplification of pro-inflammatory responses. We sought to determine whether ASC binds αSyn and if ASC-αSyn complexes can activate the NLRP3 inflammasome.
Methods: We produced ASC-αSyn complexes via ASC and αSyn co-incubation for 16 hours at 37°C and evaluated their effects on NLRP3 inflammasome activation using a mouse SIM-A9 microglial cell culture model. Transmisison electron microscopy was performed to visualize the association of ASC and αSyn. NLRP3 inflammasome activation was assessed by performing immunocytochemistry, Western blotting and Simple Western immunoassays, measurement of cytokine and chemokine concentrations and cytotoxicity assays.
Results: Examination of electron microscopic images revealed that αSyn was found in close proximity and clustered around ASC fibrils. ASC-αSyn complexes activated the NLRP3 inflammasome in microglia to a greater extent than ASC or αSyn alone. This was determined by an increased expression of the NLRP3 sensor at the protein level, augmentation of ASC speck formation and activation of caspase-1. In addition, ASC-αSyn complexes triggered caspase-1-dependent interleukin (IL)-1β/IL-18 processing by SIM-A9 cells and cleavage of gasdermin D to mediate pore formation on the plasma membrane.
Conclusions: This study links ASC and αSyn to mechanisms that amplify pro-inflammatory responses, thereby promoting a state of chronic inflammation, which have relevance to PD and related α-synucleinopathies. Overall, these results reveal a role for ASC specks in perpetuating inflammation and point at the possible importance of ASC-αSyn complexes, as triggers, in the propagation and exacerbation of αSyn-linked pathology.

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SHIFT 02-036

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

INVESTIGATING INNATE IMMUNE BIOMARKERS OF PARKINSON'S DISEASE IN BLOOD, NASAL AND SALIVA SAMPLES

Clotilde Tournerie, Marta Camacho, Bina Patel, Aaditya Prabhu, Caroline Williams-Gray
University of Cambridge, Department Of Clinical Neuroscience, Cambridge, United Kingdom

Aims: Neuroinflammation provides novel avenues for development of new therapeutic strategies for Parkinson's Disease (PD). Evidence implicates peripheral as well as brain inflammation in PD pathogenesis, with numerous studies reporting adaptive immune cell changes. However, the role of innate immunity has been less well studied. Furthermore, there is an unmet need for easily accessible immune-based biomarkers to stratify patients for clinical trials and monitor response to therapies. This project aims to comprehensively characterise peripheral innate immune involvement in PD and to determine the feasibility of measuring innate immune changes in nasal swabs and saliva samples from PD patients across different disease stages and dementia risk groups.
Methods: In an ongoing study, we are collecting matched nasal swabs, saliva and blood samples from people with PD stratified by disease stage, REM Sleep Behaviour Disorder/prodromal PD, and healthy age and sex-matched controls. Immune cells are isolated by density gradient centrifugation from peripheral blood and by washing with isolation medium and centrifugation for nasal and saliva samples. Immunophenotyping is performed on fresh samples using spectral flow cytometry with a panel of twenty markers to characterise changes in the proportion and activation state of neutrophils, monocytes and NK cells.
Results: Pilot data has shown that immunophenotyping of saliva and nasal samples is feasible, with cell numbers sufficient to identify neutrophil, monocyte and NK cell subsets. Data on changes in nasal and saliva immune cell profiles according to disease status and stage will be presented at the conference.
Conclusions: Nasal swabs and saliva represent easily accessible biosamples from areas highly relevant to PD pathology. Characterisation of innate immune changes within these samples is feasible and warrants further exploration as a biomarker in PD.

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SHIFT 02-037

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

NOVEL LRRK2-ACTIVITY BIOMARKERS LINK PARKINSON'S DISEASE SEVERITY TO PERIPHERAL INFLAMMATION

Andrew West, Yuan Yuan, Kashyap Sreeram, Huizhong Li
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Aims: LRRK2-targeting therapeutics that inhibit LRRK2 kinase activity have advanced to clinical trials. Genetic studies suggest Rab10 is linked to reslience to Alzheimer's disease. LRRK2 phosphorylates Rab10 on endolysosomes to promote some types of immunological responses in myeloid cells. The identification of factors that regulate LRRK2-mediated Rab10 phosphorylation in neurodegenerative diseases, and whether phosphorylated-Rab10 levels change with disease progression, may provide insights into the role of Rab10 phosphorylation in disease and related therapeutic approaches.
Methods: We developed and validated a high-throughput single-molecule array assay to measure extracellular pT73-Rab10. Ratios of pT73-Rab10 to total Rab10 measured in biobanked serum samples were compared between informative groups of transgenic mice, rats, and a deeply phenotyped cohort of Parkinson's disease cases and controls. Multivariable and weighted correlation network analyses were used to identify genetic, transcriptomic, clinical, and demographic variables that predict the extracellular pT73-Rab10 to total Rab10 ratio.
Results: pT73-Rab10 is absent in serum from *Lrrk2* knockout mice but elevated by *LRRK2* and *VPS35* mutations, as well as *SNCA* expression. The extracellular ratio of pT73-Rab10 to total Rab10 is dynamic, increasing with inflammation and rapidly decreasing with LRRK2 kinase inhibition. The ratio of pT73-Rab10 to total Rab10 is elevated in iPD patients with greater motor dysfunction, irrespective of disease duration, age, sex, or the usage of PD-related or anti-inflammatory medications. pT73-Rab10 to total Rab10 ratios are associated with neutrophil degranulation, antigenic responses, and suppressed platelet activation.
Conclusions: The extracellular serum ratio of pT73-Rab10 to total Rab10 is a novel pharmacodynamic biomarker for LRRK2-linked innate immune activation associated with disease severity. We propose that those patients with higher serum pT73-Rab10 levels may benefit from LRRK2-targeting therapeutics that mitigate associated deleterious immunological responses.

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SHIFT 02-038

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

DISSECTING THE EARLY MECHANISMS OF DISEASE ONSET IN AN IMMUNE-INDUCED MOUSE MODEL OF PARKINSON'S

Zizheng Xian[1], Rebekah Parkinson[1,2], Ilvana Ziko[1], Tristan Wallis[1], Adekunle Bademosi[1], Eduardo Balmaceda[3], Frederic Meunier[1], Trent Woodruff[3], Nathalie Dehorter[1,2]
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Aims: Parkinson's disease (PD) is characterized by hallmark features such as α-synuclein aggregation, neuroinflammation and immune cell infiltration in the substantia nigra (SN). Yet, the mechanisms by which α-synuclein interacts with immune activation and triggers PD remain unclear. This study uses a novel immune-induced mouse model to investigate the early immunological and physiological events contributing to PD onset, specifically targeting immune activation pathways in the central neuron system as potential early intervention points.
Methods: This model involves peripherally injecting an immune-activating adjuvant with a fluorescently tagged α-synuclein peptide which triggers PD-like symptoms at 8 weeks post-immunization (wpi). We monitored early inflammatory responses with CD4+ T cells and microglia distribution in ileum and brain tissues for the 8 weeks' course. We also performed single molecule tracking to analyse peptide distribution, providing insights into its uptake and localization during pre-disease progression.
Results: Our analysis revealed CD4+ T cell infiltration in the brain of peptide-immunized mice at 1 wpi, compared to sham mice. This was followed by microglial activation within the SN at 2 wpi, endogenous α-synuclein aggregation and dopaminergic cell loss at 8 wpi. To further probe the role of the inflammatory pathway in the sequence triggering dopaminergic cell death, we blocked the microglia mediated NLRP3-dependent pathway with MCC950 from immunization day. We found that treatment prevented motor symptoms at 8 wpi, suggesting that MCC950 enacts a novel preventative role in this mouse model of PD.
Conclusions: This work reveals a specific sequence of immunological events that precede idiopathic PD onset in mice. It enhances our understanding of the pathophysiological mechanisms driving dopaminergic cell death in the early stages of the disease, establishing a foundation for new detection and preventative treatment strategies.

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SHIFT 02-039

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

SINGLE CELL CHARACTERIZATION OF NEUROINFLAMMATION AND NEUROIMMUNE INTERACTIONS IN PRODROMAL PARKINSON'S DISEASE

Le Zhang
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Aims: Rapid eye movement (REM) sleep behavior disorder (RBD) is a pre-clinical state to Parkinson's disease (PD) and other synucleinopathies. We hypothesize that RBD and PD progression is initiated by immune activation and neuroimmune interactions that establish PD pathology in the brain. To test this, we integrated neuroimmunology, single cell genomics, and computational analysis approaches in patients with RBD, new onset PD, and established PD.
Methods: Paired blood and CSF samples were collected from the same donors. Isolated PBMC cells from blood and CSF immune cells were processed using the 10x Genomics for single cell RNA sequencing (scRNA-seq). Colonoscopy and gut tissue biopsy were performed on patients and controls, with immune cells from these tissues were subjected for scRNA-seq.
Results: We identified pleocytosis in the CSF of RBD patients, suggesting CNS inflammation in prodromal PD. Through single cell analysis of paired blood and CSF samples from 13 healthy controls, 36 RBD, 15 PD and 18 PDRBD, we profiled nearly 1 million immune cells, creating the first human single cell CSF atlas of RBD and PD. We revealed significant increases in CSF macrophages in RBD, PD and PDRBD compared to controls. TNFR2 was significantly upregulated in CSF macrophages in RBD, PD and PDRBD and TNF signaling pathways were enriched in disease, pointing to the potential of anti-TNF therapy in preventing PD, supported by epidemiological data showing anti-TNF lowered PD risk in inflammatory bowel disease.
Conclusions: Our findings suggest that significant immune changes occur in the CNS in prodromal PD. The results will help define the role of the body-brain immune axis in regulating neuroimmune responses in PD progression. Comparing blood, CSF, and gut immune populations may allow the development of biomarkers predicting response to therapy in PD.

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SHIFT 02-041

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LRKK2, PARKIN, PINK1, DJ-1
4-5 April 2025

LONGITUDINAL ASSESSMENT OF COGNITIVE FUNCTIONS AMONG LRRK2 AND GBA1 PATIENTS WITH PARKINSON'S DISEASE

Avner Thaler[1], Vered Livne[2], Nir Giladi[1], Jesse Cedarbaum[3], Shelly Majar[1], Liat Yahimovich[1], Roy Alcalay[1], Anat Mirelman[1]
[1]Tel-Aviv Medical Center, Neurology, Tel-Aviv, Israel, [2]Tel-Aviv Medical Center, Tel-Aviv, Israel, [3]Coeruleus Clinical Sciences, Woodbridge, United States of America

Aims: To assess the progression of cognitive impairments among *LRRK2*-PD and *GBA1*-PD based on the movement disorder society (MDS) criteria for the diagnosis of mild cognitive impairment (MCI).
Methods: The following measures were assessed during 2 visits, 3 years apart: Montreal Cognitive Assessment (MoCA), Symbol-Digit Modality Test (SDMT), Verbal Fluency (VF), Stroop interference, Hopkins Verbal Learning Test (HVLT), Hooper Visual Organization Test (HVOT) and Trail Making Test (TMT B-A). The MDS criteria for Mild Cognitive Impairment (MCI) was applied. Repeated measures analysis of variance was used to explore time, group and interaction effects. Frequency of MCI in each group was assessed based on 1 and 2 SD from the mean of healthy age matched controls.
Results: Ninety-one healthy controls (mean age 61.35, 67.77% male), 63 idiopathic PD patients (iPD) (mean age 63.85, 70% male), 51 G2019S-*LRRK2*-PD patients (mean age 63.69, 57% male) and 61 *GBA1*-PD patients (mean age 63.62, 68% male) participated in this study. Age, sex, age at diagnosis, follow-up period, levodopa equivalent daily dose and years of education were similar between the groups. MDS-UPDRS part III and total scores were lower in *LRRK2*-PD at follow-up than the two other groups ($p<0.001$ and $p=0.008$). VF, TMT B-A, HVOT and SDMT scores deteriorated in all three groups of patients. A time and interaction effect in the MoCA ($p=0.04$, $p=0.004$) and Stroop ($p=0.014$) were detected, with *LRRK2*-PD performing better than the two other groups. On a group level, *GBA1*-PD fulfilled criteria for MCI already at baseline, iPD fulfilled criteria for MCI at the follow-up visit while the majority of *LRRK2*-PD remained cognitively intact.
Conclusions: *GBA1*-PD experience cognitive decline at an early stage of PD while *LRRK2*-PD maintain relatively intact cognitive capabilities.

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SHIFT 02-043

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

IL-17A EXACERBATES NEUROINFLAMMATION AND NEURODEGENERATION BY ACTIVATING MICROGLIA IN RODENT MODELS OF PARKINSON'S DISEASE

Yihua Qiu
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Aims: Neuroinflammation has been involved in pathogenesis of Parkinson's disease (PD), a chronic neurodegenerative disease characterized neuropathologically by progressive dopaminergic neuronal loss in the substantia nigra (SN). We recently have shown that helper T (Th)17 cells facilitate dopaminergic neuronal loss in vitro. Herein, we demonstrated that interleukin (IL)-17A, a proinflammatory cytokine produced mainly by Th17 cells, contributed to PD pathogenesis depending on microglia.
Methods: Mouse and rat models for PD were prepared by intraperitoneal injection of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or striatal injection of 1-methyl-4-phenylpyridinium (MPP+), respectively.
Results: Both in MPTP-treated mice and MPP+-treated rats, blood–brain barrier (BBB) was disrupted and IL-17A level increased in the SN but not in cortex. Effector T (Teff) cells that were adoptively transferred via tail veins infiltrated into the brain of PD mice but not into that of normal mice. The Teff cell transfer aggravated nigrostriatal dopaminergic neurodegeneration, microglial activation and motor impairment. Contrarily, IL-17A deficiency alleviated BBB disruption, dopaminergic neurodegeneration, microglial activation and motor impairment. Anti-IL-17A-neutralizing antibody that was injected into lateral cerebral ventricle in PD rats ameliorated the manifestations mentioned above. IL-17A activated microglia but did not directly affect dopaminergic neuronal survival in vitro. IL-17A exacerbated dopaminergic neuronal loss only in the presence of microglia, and silencing IL-17A receptor gene in microglia abolished the IL-17A effect. IL-17A-treated microglial medium that contained higher concentration of tumor necrosis factor (TNF)-α facilitated dopaminergic neuronal death. Further, TNF-α-neutralizing antibody attenuated MPP+-induced neurotoxicity.
Conclusions: The findings suggest that IL-17A accelerates neurodegeneration in PD depending on microglial activation and at least partly TNF-α release.

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SHIFT 02-045

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

COMPLEX I DEFICIENCY IN POLG AND PARKINSON'S DISEASE: DIFFERENTIAL INVOLVEMENT OF MTDNA DEFECTS

Anna Rubiolo[1,2], Sepideh Mostafavi[2], Irene Flønes[1,2], Charalampos Tzoulis[1,2]
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Aims: Mitochondrial dysfunction, particularly Complex I (CI) deficiency, is closely linked with idiopathic Parkinson's Disease (iPD), yet its role beyond the substantia nigra pars compacta (SNc) remains debatable due to conflicting reports. Our groundbreaking research addresses this ambiguity, highlighting that mitochondrial dysfunction is a crucial factor in only a subset of iPD cases. Here, we want to dissect the specific molecular landscape of the CI-deficient neurons.
Methods: This study delves into the molecular characteristics of CI-deficient neurons, requiring single-cell resolution due to the random, mosaic-like distribution of CI deficiency. The process involves double immunofluorescence staining on postmortem PD and POLG disease brain tissue (prefrontal cortex and substantia nigra), targeting TOM20 (mitochondrial marker) and NDUFS4 (CI subunit), followed by qPCR on laser-microdissected CI-deficient and intact neurons to analyze mtDNA deletions and copy number.
Results: Preliminary analysis of POLG tissue shows significant differences in mtDNA deletions and copy numbers between CI-positive and CI-negative neurons, with CI-negative neurons exhibiting significantly lower copy numbers and a higher percentage of deletions. In PD CI deficient neurons, however, mtDNA seems not to be affected, both in terms of deletions and copy number
Conclusions: Our innovative method offers a groundbreaking approach to assessing mitochondrial genetic integrity at the single-cell level. Initial insights from POLG and PD tissue have revealed that CI deficiency is associated with distinct mtDNA alterations. This differential involvement underscores the complexity of mitochondrial dysfunction in PD, suggesting that CI deficiency in PD may arise from mechanisms independent of mtDNA defects

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SHIFT 02-046

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

DISRUPTION OF THE MITOCHONDRIA-LYSOSOME AXIS BY CHCHD2 DYSFUNCTION DRIVES PROTEINOPATHY ASSOCIATED WITH AGING AND LEWY BODY DISEASE

Teresa Kee[1,2], Brianna Masters[2], Khoi Tran[2], Hanna Jeon[2], Sophia Khan[2], Edwin Vázquez-Rosa[3,4], Preethy Sridharan[4,5], Hisashi Fujioka[6], Dale Chaput[7], Xinming Wang[2], Xingyu Zhao[2], Andrew Pieper[8], David Kang[2,9], Alexa Woo[2]
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Aims: Coiled-coil-helix-coiled-coil-helix domain containing 2 (CHCHD2) is a multifunctional mitochondrial protein localized to the mitochondrial intermembrane space (IMS). Mutations in CHCHD2 have been associated with Lewy body disorders (LBDs), including familial autosomal dominant Parkinson's disease (PD). Previous animal models of CHCHD2-driven PD were limited to non-mammalian models. To address this, we characterized the first transgenic mouse models that neuronally express CHCHD2-WT or the PD-linked CHCHD2-T61I to recapitulate the phenotypes and pathology observed in human patients.
Methods: We employed cellular and molecular techniques, such as immunofluorescence, electrophysiology, western blotting, and TEM imaging—on novel transgenic animals and human LBD patient brains. Additionally, we conducted novel object recognition tests and mass spectrometry to compare CHCHD2-WT and CHCHD2-T61I.
Results: CHCHD2-WT mice are grossly normal, fertile, and express the total CHCHD2 transcripts at approximately 2.3-fold higher levels than endogenous CHCHD2. CHCHD2-WT protein primarily localizes to the IMS, with indistinguishable gliosis and synaptic integrity compared to WT. CHCHD2-WT mice exhibit

reduced age-related insoluble proteinopathy and neuroinflammation. In contrast, CHCHD2-T61I mice exhibit mitochondrial fragmentation, gliosis, synaptic dysfunction, and proteinopathy in vivo. Interestingly, CHCHD2-T61I mice show impaired cathepsin activity associated with lysosomal accumulation of insoluble CHCHD2-T61I in the brain. Furthermore, unlike CHCHD2-WT, CHCHD2-T61I promotes lysosomal membrane permeability and vacuolization and displays ultrastructural abnormalities in mitochondria and lysosomes observed via TEM. Additionally, CHCHD2-T61I mice exhibit deficits in novel object recognition memory at 12-18 months of age, whereas CHCHD2-WT mice do not show memory impairments compared to WT.

Conclusions: Pathological signatures include mitochondrial and lysosomal ultrastructural abnormalities, lysosomal membrane permeability and vacuolization, reduced capthpsin activity, and lysosomal accumulation of insoluble CHCHD2-T61I. CHCHD2-WT and CHCHD2-T61I mouse models will serve as invaluable tools to bettter understand the underlying mechanisms by which CHCHD2 dysfunction contributes to LBDs.

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SHIFT 02-048

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
4-5 April 2025

HOW EXERCISE AFFECTS TERMINALS OF NIGROSTRIATAL DOPAMINERGIC SYSTEM DEGENERATION AND ITS FUNCTIONAL COMPENSATION IN EARLY PD ANIMAL MODEL

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[1]Maj Institute of Pharmacology PAS, Neurodegeneration And Experimental Therapy Laboratory, Krakow, Poland, [2]Maj Institute of Pharmacology PAS, Krakow, Poland, [3]AGH University of Krakow, Department Of Analytical Chemistry And Biochemistry, Krakow, Poland

Aims: Ongoing large clinical studies search for question if regular physical activity can prevent or slow down neurodegeneration of dopaminergic system in PD. Animal models showed such possibility but exact mechanisms of protection or functional compensation are unknown. The aim was to precisely describe mechanisms of potential neuroprotection, regeneration and compensation of the nigrostriatal dopaminergic system similar to PD.
Methods: Regular training was performed for 4 weeks before and 4 weeks after unilateral 6-OHDA injection into the medial forebrain bundle of rats. Dopaminergic nigrostriatal system was selectively and progressively lesioned in medium or large size. Forepaw Adjusted Step test at different time-points, tyrosine hydroxylase (TH) expression densitometry in striatum, dopaminergic neuron density in substantia nigra and mass spectrometry proteomic analysis of synaptosomes were used to validate the effect of running.
Results: Asymmetric use of forelimbs showed smaller dysfunction in training animals than in sedentary 3 days after lesioning, especially in medium size lesion group rather than in large lesion. Training increased expression of TH in striatum in medium size lesion better than in larger lesion. Proteomic analysis confirmed more pronounced deficits in dopaminergic markers in large lesion. This was pronounced in sedentary animals. Stereological analysis of neuron density in substantia nigra did not prove neuroprotection.
Conclusions: Regular and intense treadmill training ameliorates some behavioral deficits in early degeneration stage. In this running rat early PD model training rather improves compensatory mechanisms within dopaminergic terminals rather than acts neuroprotective. The studies on natural compensation processes induced by exercise will bring us closer to therapies prolonging independent functioning of patients in multiple neurodegenerative diseases. **Funding:** supported by NCN 2019/35/B/NZ7/02862 and statutory funds of Maj Institute of Pharmacology, PAS, Poland.

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SHIFT 02-049

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
4-5 April 2025

ALPHA-SYNUCLEIN PREFORMED FIBRIL MOUSE MODEL ASSOCIATED WITH BRAIN ATROPHY, DOPAMINERGIC DEFICITS, NEURODEGENERATION, NEUROINFLAMMATION, MOTOR DYSFUNCTION, AND SLEEP DISTURBANCES

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Aims: This work aimed at developing a reliable translational mouse model of seeding/spreading α-synucleinopathy and dopaminergic dysfunction to accelerate the development of novel disease-modifying treatments for Parkinson's Disease (PD).
Methods: M83+/- transgenic (Tg) mice underwent unilateral stereotaxic injection of human preformed α-synuclein fibrils (PFFs) into the medial forebrain bundle (MFB) at approximately 12 weeks-of-age. Mice were longitudinally tested for locomotor deficits and sleep dysfunction. Dopaminergic dysfunction was assessed by a challenge test at 9 WPI. Regional neuroanatomical volumes and cortical thickness measures were assessed via automated analysis of anatomical MRI scans acquired at 10 weeks post-induction (WPI). Neurodegeneration was evaluated by qIHC and Simoa analyses of neurofilament light chain (NfL) at 10 WPI.
Results: PFF-injected mice showed spontaneous progressive motor dysfunction, including locomotor asymmetry (assessed by the cylinder test and tail suspension swing test) and nest building deficits, locomotor impairment in the Open Field Test, hindlimb clasping, and wire hang deficits. We also identified alterations of the sleep-wake architecture in the PFF-injected mice. Highly elevated plasma and CSF NfL levels and decreased dopamine metabolite levels in the CSF were accompanied by decreased cortical thickness and regional neuroanatomical volumes assessed by *in vivo* MRI, as well as extensive spread of α-synuclein pathology to distant brain regions. Significant neuroinflammation, especially increased total and activated microglia densities, was observed in PFFs-inoculated Tg mice compared to control animals, and in the ipsilateral hemisphere when compared to the contralateral side in PFFs animals.
Conclusions: This α-synuclein seeding and spreading mouse model recapitulates PD-related features at the structural, functional, and biochemical levels, and represents a robust model for preclinical efficacy studies aimed at advancing the development of therapeutics.

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SHIFT 02-050

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
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LEVERAGING MULTIPLE ALPHA-SYNUCLEIN INOCULATION SITES AND MACHINE-LEARNING TO REFINE NEURODEGENERATION-BASED DISEASE STAGING IN A MOUSE MODEL

Janice Park[1,2,3], Stephanie Tullo[1,3], Daniel Gallino[1,3], Olivier Parent[1,2,3], Yohan Yee[1,3], M. Mallar Chakravarty[1,2,3,4,5]
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Aims: Alpha-synuclein (αSyn) spreading as a mechanism for disease progression was initially proposed in the Braak hypothesis. Mouse models of synucleinopathies receiving αSyn inoculation into different brain regions support this hypothesis. However there are different known disease epicentres (brainstem; olfactory bulb) across the brain that yield the same phenotypic abnormality. Here, we use Subtype and Stage Inference Algorithm (SuStaIn), a machine-learning tool developed to define clinical subtypes based on similarity in spatiotemporal disease progressions, to test if distinct brain atrophy patterns originating from different experimentally-induced "disease epicenters" share overlapping spatiotemporal atrophy progression.
Methods: 11 week-old M83 hemizygous mice overexpressing mutant human A53T αSyn were injected with 2.5 µL saline (PBS) or pre-formed αSyn fibrils (PFF) into the right dorsal striatum, a region highly implicated in Parkinson's Disease (PD), or hippocampus, a non-traditional disease epicenter (n~8 inoculum/injection site/sex/timepoint). Mice underwent *in vivo* T1-weighted MRI at -7, 30, 90, and 120 days post-injection. Using deformation-based morphometry, we observed vastly different brain atrophy patterns stemming from each disease epicenter (Fig.A-B), yet evidence of motor deficits were observed in both groups. Using SuStaIn, we jointly analysed MRI data from both disease epicenters and calculated volumetric brain changes for 9 regions of interest relative to pre-injection data (n~192 images) normalized by timepoint-specific controls as inputs for SuStaIn.
Results: SuStaIn revealed three subtypes with distinct trajectories of regional volume decline: olfactory-first, hippocampus-first, and brainstem-first disease progressions (Fig.C-E). Surprisingly, despite the clear experimentally induced epicenters, the generated subtypes were consistent with Braak's hypothesis of PD

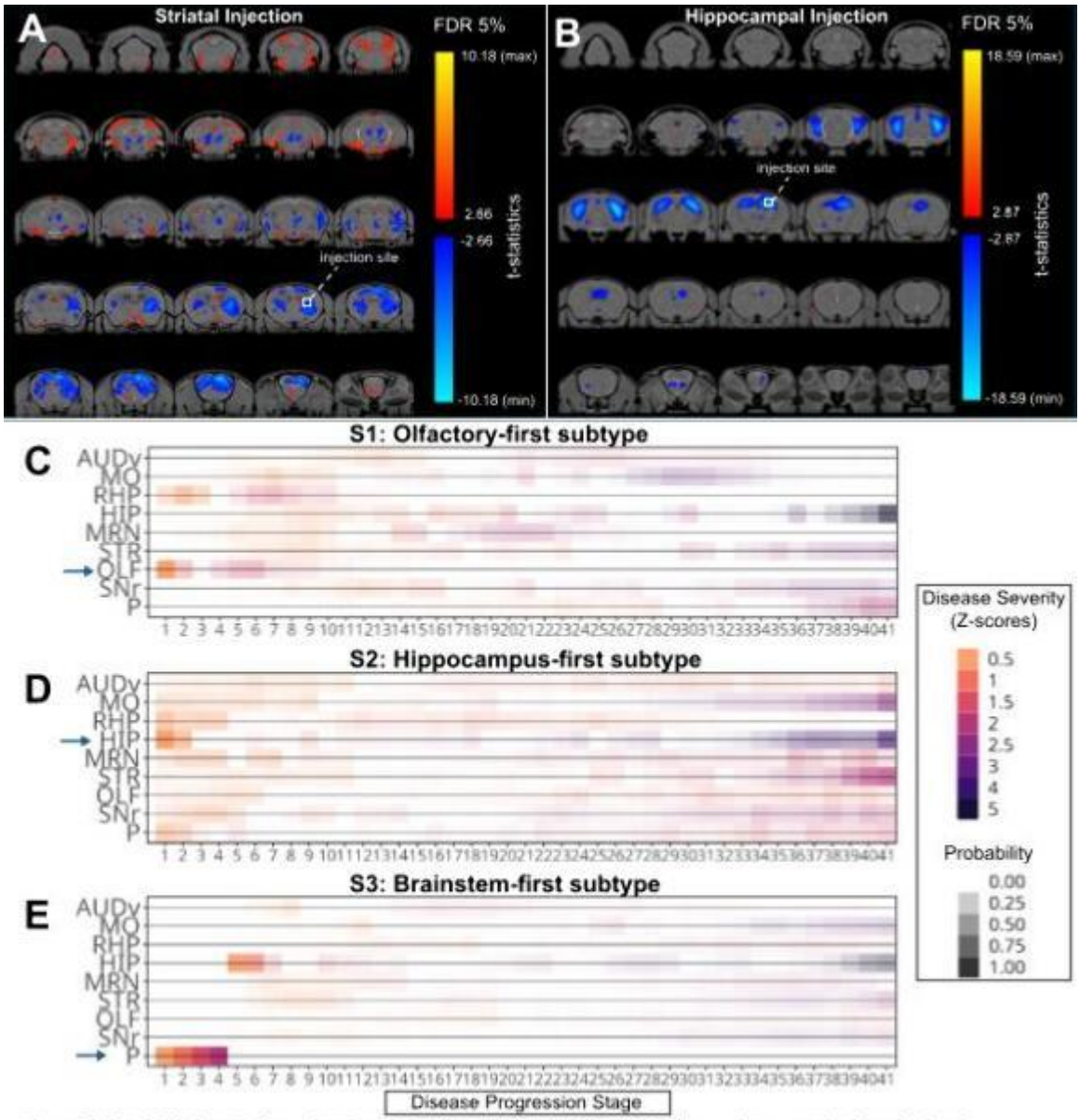

Figure: [A] and [B] show Deformation-Based Morphometry (DMB)-derived brain atrophy pattern in the striatal and hippocampal PFF-incoluated mice, respectively. Magnitude of deformation (expansion or contraction) in each voxel infer growth or reduction in brain volume. Heatmaps display regions of declining (in blue) and increasing (in red) brain volume over time for mice receiving PFF injection into the striatum **[A]** (from Tullo et al., in preparation) and hippocampus **[B]** compared to PBS-injected controls (white box highlighting the injection site). T-statistics maps show the effects of PFF injection over time (Linear mixed effects model: Lmer(Relative_Jacobian ~ **dpi * Treatment** + Sex + (1|ID)) separately for each injection site experiment. Based on these DBM-derived atrophy patterns, 9 atrophied regions were selected as biomarkers for SuStaIn (AUDv = ventral auditory area, MO = motor cortex, RHP = retrohippocampal region, HIP = hippocampal region, MRN = midbrain reticular nuclei, STR = striatum, OLF = olfactory region, SNr = substantia nigra, P = pons). **[C]**, **[D]** and **[E]** show positional variance diagrams from SuStaIn, indicating the olfactory-first, hippocampus-first, and brainstem-first subtypes. Blue arrows highlights the region where disease initiates in each SuStaIn subtype. Each box in the diagram represents the certainty that a brain region reached the z-score in that SuStaIn stage, with the colors representing z-score severity, and opacity indicating probability of subjects belonging to that stage.

staging.

Conclusions: Using a data-driven approach in a mouse model, our results demonstrate that there may be a consistent disease progression mechanism that targets regions most vulnerable to αSyn, regardless of the location of αSyn injection.

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SHIFT 02-051

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
4-5 April 2025

RE-WEIGHTING MDS-UPDRS PARTS II AND III ITEMS TO IMPROVE ASSESSMENT OF MOTOR DECLINE IN UNTREATED PARKINSON'S DISEASE

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Aims: There is considerable interest in improving the sensitivity of Parkinson's disease (PD) measures to adequately capture the effect of disease modifying therapies. PARCOMS-Motor was developed using two different datasets (natural history and clinical trial placebo arms) to optimize motor decline assessment in patients with untreated PD.
Methods: Subjects with confirmed PD naïve to dopaminergic treatment from the Parkinson's Progression Markers Initiative (PPMI) and the Critical Path for Parkinson's (CPP) datasets were included in the analysis. Items from MDS-UPDRS Parts II and III were selected and weighted based on responsiveness to clinical decline using partial least square regression. The responsiveness of PARCOMS-Motor was measured using a 1-year mean-to-standard-deviation ratio (MSDR), a ratio of signal-to-noise with higher values indicating better sensitivity.
Results: In PARCOMS-Motor, 34 of the 46 items from the MDS-UPDRS Parts II and III were retained in either the CPP or PPMI derived composite scales: 17 (50%) were retained in both the PPMI and the CPP derived composite scales; six (18%) were included only in the CPP composite scale; and 11 (32%) were retained only in the PPMI scale. Items retained in both PPMI and CPP derived scales predominantly measured irregular/involuntary movement (including items capturing bradykinesia, tremor and rigidity) concepts. In both scales, activities of daily living and oral dysfunction items had similar weights. In PARCOMS-Motor there was a 13.1% and 27.5% increase in the MSDR compared to the original scales, for PPMI and CPP respectively.
Conclusions: More responsive scales were derived from the MDS-UPDRS motor items using two distinct data sources. The two PARCOMS-Motor scales were not entirely consistent, which may be explained by differences in disease characteristics of patients enrolled in clinical trials versus natural history datasets.

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SHIFT 02-052

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
4-5 April 2025

RE-WEIGHTING MDS-UPDRS PART II AND PDQ-39 ITEMS TO DETECT MAXIMAL DECLINE IN ACTIVITIES OF DAILY LIVING IN UNTREATED PARKINSON'S DISEASE

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Aims: Traditional measures used in clinical trials of disease-modifying treatments (DMTs) in early Parkinson's disease (PD) may fail to detect treatment effects on patients' daily functioning over feasible study timeframes for otherwise effective treatments. This work used established methods to generate a composite scale from MDS-UPDRS-Part II and PDQ-39 items optimized for sensitivity to detect functional decline over 1-year.
Methods: Data from 140 subjects with confirmed early PD who were naïve to dopaminergic therapies were selected from the placebo groups of five DMT trials within the Critical Path for Parkinson's dataset. Patients were censored at PD treatment initiation. Partial least squares regression was used to select and weight items from MDS-UPDRS-Part II and PDQ-39 that maximize the observable signal of disease progression in early unmedicated PD (PARCOMS-Function). PARCOMS-Function's ability to detect change was measured using a 1-year mean-to-standard-deviation ratio (MSDR), a ratio of signal-to-noise with higher values indicating better sensitivity.
Results: This method selected 15 of the 52 possible items to form PARCOMS-Function – seven from MDS-UPDRS-Part II and eight from PDQ-39. The items with the highest contribution (indicating responsiveness to change in this population) were hygiene (17.2%), speech (12.6%), and handwriting (11.2%) from Part II and walking half a mile (8.7%), muscle cramps (8.3%), and buttons and shoelaces (6.3%) from PDQ-39. The 1-year MSDR of PARCOMS-Function was 0.6534, reflecting increases in the ability to detect change of 12.3% compared to Part II alone, and 339.1% compared to PDQ-39 alone.
Conclusions: PARCOMS-Function is a re-weighted optimized version of existing measures, with greater sensitivity to detect functional decline in early unmedicated patients with PD. Use of PARCOMS-Function could increase trial efficiency and power to detect meaningful delay in disease progression with DMTs.

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SHIFT 02-053

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MODELING OF DISEASE PROGRESSION
4-5 April 2025

IMPACT OF GLUCOCEREBROSIDASE DEFICIENCY ON MICROGLIAL FUNCTION AND A-SYNUCLEIN PATHOLOGY IN PARKINSON'S DISEASE

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Aims: This study aimed to investigate the role of microglia in the interplay between glucocerebrosidase (*GBA1*) deficiency and α-synuclein (α-syn) aggregation in Parkinson's disease. Specifically, it explored how altered α-syn levels influence microglial function under reduced GCase activity, focusing on microglial contributions to the pathological processes linked to *GBA1* deficiency and α-syn aggregation.
Methods: Human pluripotent stem cells (hPSCs) were differentiated into hematopoietic progenitor cells (HPCs) and subsequently into microglia. Successful differentiation was confirmed through FACS analysis using surface markers: CD34, CD41, and CD43 for HPCs, and CD45 and CD11b for microglia. A glucocerebrosidase knockout (*GBA1* KO) cell line was used to investigate microglial responses to *GBA1* deficiency and α-syn pathology. Functional assays were conducted by treating wild-type and *GBA1* KO microglia with α-syn preformed fibrils (α-syn PFFs). Phagocytic activity was measured using a pHrodo conjugation phagocytosis assay, and immunocytochemistry (ICC) with IBA-1, SNCA and p-SNCA antibodies was performed to analyze microglial responses. Bulk RNA sequencing was conducted on wild-type (WT) and *GBA1* KO microglia, with or without α-syn PFFs treatment.
Results: In WT microglia treated with α-syn PFFs, most cells displayed amoeboid morphology, while *GBA1* KO microglia exhibited both amoeboid and ramified morphologies. Bulk RNA sequencing revealed no significant differences in hPSCs or HPCs due to GCase deficiency, but substantial gene expression changes were observed in *GBA1* KO microglia following α-syn PFFs treatment, highlighting their transcriptional response to α-syn pathology.
Conclusions: *GBA1* deficiency modulates microglial function, particularly under α-syn aggregation

conditions, as evidenced by morphological and transcriptional changes. Microglia play a pivotal role in the interaction between *GBA1* deficiency and α-syn pathology, contributing to PD progression.

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SHIFT 02-054

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHERS
4-5 April 2025

ADVANCEMENTS IN MICROBIOME RESEARCH: QUANTIFYING MICROBIAL LOAD AND DIFFERENTIAL ABSOLUTE ABUNDANCE IN PARKINSON'S DISEASE

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Aims: One fundamental aim of microbiome research is identifying specific bacterial taxa that influence host physiology. Previous studies on the Parkinson's Disease (PD) gut microbiome have identified differences in the **relative** abundance of bacterial taxa between PD patients and controls. However, these relative measurements inherently reflect proportional changes, where an increase in one taxon leads to a perceived decrease in others, even if their absolute concentrations remain unchanged. This limitation impedes our ability to discern the true magnitude of differences between groups. This study addresses this gap by measuring **total microbial load** and differences in **absolute** abundance of bacterial taxa in PD versus matched housemate controls.
Methods: Participants (*n*=111 PD, *n*=82 household controls (HC)) were recruited from the Stanford Movement Disorder Clinic and local PD support groups. Participants provided blood and stool samples and completed a questionnaire. DNA was extracted using the Qiagen QIAamp PowerFecal Pro DNA kits. We measured moisture content of each sample to correct for the water content of the stool and any dilution introduced by a preservative solution. ddPCR Quantification of 16S rRNA gene was performed.
Results: The total microbial load is decreased in PD compared to HC, as measured by total 16s rRNA bacterial copies per dry gram of stool (p=0.019). In addition, the comparison of differential absolute abundance with published differential relative abundance yielded both complementary and contradictory insights, underscoring the limitations of relying solely on relative abundance data.
Conclusions: By quantifying both the total microbial load and the absolute abundance of bacterial taxa, we provide a more accurate depiction of microbiome alterations in PD. These results can later be combined with data from the blood samples collected to develop mechanistic hypotheses about the gut-brain connection in PD.

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SHIFT 02-055

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHERS
4-5 April 2025

CLINICAL PRESENTATION AND PROGRESSION IN AUTOPSY CONFIRMED MULTIPLE SYSTEM ATROPHY

Ida Wilkens[1], Johanne Heine[2], Viktoria Ruf[3], Yaroslau Compta Hirnyj[4], Laura Molina-Porcel[5], Claire Troakes[6], Albert Vamanu[6], Sophia Downes[6], David Irwin[7], Jesse Cohen[7], Edward B. Lee[8], Christer Nilsson[9], Elisabet Englund[10], Mojtaba Nemati[1], Sabrina Katzdobler[1], Johannes Levin[1,11,12], Alex Pantelyat[13], Joseph Seemiller[13], Stephen Berger[13], John Van Swieten[14], Elise Dopper[14], Annemieke Rozenmuller[15], Gabor Kovacs[16,17], Nathaniel Bendahan[18], Anthony Lang[18], Jochen Herms[3,11,12], Günter Höglinger[1,11,12], Franziska Hopfner[1]
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Aims: Multiple system atrophy (MSA) is a neurodegenerative disorder, characterized by a range of clinical symptoms including parkinsonism, cerebellar ataxia and dysautonomia. The 2022 International Parkinson and Movement Disorder Society (MDS) MSA diagnostic criteria allow for a clinical diagnosis based solely on motor symptoms. This study aimed to characterize the onset and progression of clinical symptoms across different MSA subgroups.
Methods: Demographics, disease onset and progression were analyzed retrospectively in a cohort of autopsy-confirmed MSA patients. The study focused on the timing of symptom manifestation, the predominant feature (parkinsonism, cerebellar ataxia, autonomic dysfunction) and the development of additional features over time.
Results: A total of 141 patients were identified. At disease onset, 57 patients presented with parkinsonism, 27 with autonomic symptoms, and 17 with cerebellar features. Nineteen patients exhibited both

parkinsonism and autonomic symptoms simultaneously at onset, 17 % (n=3) of those did develop cerebellar features during disease progression. In contrast, three of four patients who initially presented with both cerebellar ataxia and autonomic symptoms went on to develop parkinsonism. Disease duration and onset of symptoms varied widely across subtypes. Notably, 8% (n=11) of patients presented exclusively with motor symptoms and did not develop autonomic dysfunction.

Conclusions: Our analysis confirmed that the 2022 MDS MSA diagnosis criteria capture the clinical symptoms in MSA. The clinical disease progression varied widely across subtypes. Further, the 2022 MDS MSA diagnosis criteria detect an underrecognized subgroup of MSA patients solely presenting with motor symptoms. Our results underscore the diverse clinical spectrum of MSA and emphasize the importance of early recognition of motor symptoms for an accurate diagnosis.

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SHIFT 02-056

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHERS
4-5 April 2025

ASSOCIATION OF OBSTRUCTIVE SLEEP APNEA WITH COGNITION, PUTAMEN VOLUME, AND DOPAMINE TRANSPORTER AVAILABILITY IN PARKINSON'S DISEASE

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Aims: Obstructive sleep apnea (OSA) is a common nonmotor symptom in Parkinson's disease (PD) and is known to be associated with poorer cognitive outcomes in PD. The effect of OSA on structural changes and dopamine transporter (DAT) availability and whether those changes mediate the association between OSA and cognition in PD have not been elucidated well. This study aimed to investigate the association of OSA with cognitive function, brain regional atrophy, and DAT availability in PD.
Methods: In this retrospective cohort study, we included 44 patients with drug naïve PD patients who underwent DAT scan, 3D brain MRI, polysomnography, and cognitive assessments. The participants were divided into PD with OSA group and PD without OSA group according to the apnea-hypopnea index (AHI) with a cut-off value of 15. Baseline clinical, cognitive, and imaging characteristics were compared between the groups. The association of AHI with cognitive functions, brain regional volumes, and DAT scan standardized uptake value ratio were investigated by multivariable regression analysis.
Results: Demographic features were comparable between the two groups. General cognition assessed by MMSE, CDR, and CDR-SOB was significantly poorer in PD with OSA group after controlling for age at onset, sex, disease duration, and education. The PD with OSA group also exhibited decreased N2 sleep, anterior putamen DAT availabilities, and putamen volume. Multivariable regression analysis revealed that AHI was negatively associated with MMSE score, putamen volume, and anterior putamen DAT availability. N2 sleep mediated the effect of AHI on MMSE.
Conclusions: The results of this study suggest that OSA is associated with poorer general cognition, decreased stage N2 sleep, and decreased anterior putamen SUVR in PD patients. Especially, decreased stage N2 sleep mediate the effect of OSA on cognition in PD.

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SHIFT 02-059

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
4-5 April 2025

IMPACT OF SNCA A53T AND GBA GENE MUTATIONS ON NEURITE OUTGROWTH AND RESPONSE TO PARKINSON'S DISEASE STRESSORS IN IPSC-DERIVED NEURONS

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Aims: Specific mutations in the *SNCA* gene, which encodes alpha-synuclein, increase the risk of familial Parkinson's disease (PD). Additionally, *GBA* gene mutations, which affect glucocerebrosidase enzyme activity, are associated with sporadic and familial forms of PD, impacting lysosomal function and causing neurodegeneration. This study aims to characterize iPSC-derived glutamatergic neurons with *SNCA* A53T mutations and various *GBA* gene defects, comparing them to healthy control neurons. The focus is on assessing differences in neurite outgrowth and responses to PD-inducing agents.
Methods: iPSC-derived glutamatergic neurons with *SNCA* A53T mutations and *GBA* gene defects (null/null, null/N409S, and null/R159W) were compared to healthy control neurons. Neurite outgrowth was monitored over time using imaging and morphometric analysis. The cells' responses to PD-inducing agents such as 1-Methyl-4-phenylpyridinium (MPP+), rotenone, and alpha-synuclein oligomers, were evaluated: cell viability was assessed via MTT and caspase assay, and mitochondrial activity through TMRM assay over time.
Results: Preliminary observations indicate differences in neurite outgrowth between genetically modified neurons and healthy controls. Full data collection is ongoing to further elucidate these effects and to provide a comprehensive understanding of the differences across the genotypes.
Conclusions: Initial findings suggest that iPSC-derived glutamatergic neurons with *SNCA* A53T or *GBA* defects exhibit distinct characteristics compared to healthy controls. Once all experiments are completed, these cells will be thoroughly characterized and deemed suitable models for evaluating developmental compounds and investigating PD mechanisms.

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SHIFT 02-060

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
4-5 April 2025

ANALYSIS OF SYNAPTIC PATHWAYS IN AGGREGATE SYNUCLEIN-BEARING CORTICAL NEURONS TO IDENTIFY MOLECULAR TARGETS INVOLVED IN SYNAPTIC VULNERABILITY

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Aims: To gain molecular insights into the dysregulated synaptic pathways associated with phospho-α-synuclein pathology progression.
Methods: Whole-transcriptome molecular signatures from PFF- mouse model were characterized using spatial transcriptomics (GeoMx) to reveal gene signatures associated with α-synuclein pathology (Goraslki et al). Analysis of the GeoMX-derived synaptic transmission pathways enriched in differentially expressed genes from phospho-α-synuclein pathology-bearing neurons available from Goralski et al. studies was performed using the curated SynGO gene ontology database.The list of DEGs from mouse layer 5 cortical neurons bearing α-synuclein pathology was loaded against the 1602 genes annotated on SynGO.
Results: Enrichment analysis of these signature expression patterns revealed conserved gene expression changes impacted pathways involved in the synaptic vesicle cycle, postsynaptic density, and synapse organization. We identified upregulated genes that may provide resilience, as noted for genes associated with postsynaptic density, synapse organization, and signaling. Among these genes, we found increased expression of genes involved in synaptogenesis and neuronal maturation.
Conclusions: The downregulation of pathways involved in synapse organization identifies candidate targets that may be involved in the initial loss of synapses or an inability to maintain them. Identifying molecular vulnerabilities and how the integrity of maintenance is impaired would contribute to a better understanding of early pathological alterations and guide the development of therapeutic interventions.

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SHIFT 02-061

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY, NEURAL NETWORKS, PLASTICITY, NEUROGENESIS
4-5 April 2025

EARLY ALPHA-SYNUCLEIN OLIGOMERIZATION AND SYNAPTIC DYSFUNCTION IN A HUMAN MODEL OF PARKINSON'S DISEASE

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Aims: Lewy bodies, inclusions that contain insoluble alpha synuclein (α-syn) aggregates, are traditionally associated with Parkinsons disease (PD) pathology. It is hypothesized that pathogenic α-syn aggregates spreading from degenerating to healthy neurons underlies the disease progression of PD. Recent evidence suggests that soluble α-syn oligomers, not organized in Lewy bodies, are similarly involved in α-syn pathogenesis. Moreover, while α-syn is highly expressed at the presynapse, it is currently unknown where and when early oligomerization starts. We therefore aim to investigate early α-syn oligomers and their localization within neuronal subdomains, and the subsequent neuronal and synaptic dysfunctions.
Methods: We generated human induced pluripotent (hiPSC) -derived cortical neurons obtained from patients with triplications in the *SNCA* gene, encoding α-syn. In addition to *SNCA* patients and healthy controls we investigated isogenic *SNCA*-null lines, generated using CRISPR/Cas9 gene editing, without detectable α-syn expression. Using immunocytochemistry and proximity ligation assays we investigated the oligomerization status of α-syn and its interaction with other proteins, and their localization within the neuronal subdomain.
Results: Overexpression of wild type α-syn led to increased phosphorylated α-syn at position S129, indicative of α-syn aggregation. Moreover, we show that human cortical excitatory neurons express α-syn at the presynapse. We validated proximity ligation assays using α-syn aggregate specific antibodies to detect early oligomers. These results allow us to further investigate the precise spatiotemporal location of early α-syn oligomerization in human neurons.
Conclusions: Here, we propose a human disease model to investigate early α-syn oligomerization status and resulting neuronal and synaptic dysfunction.

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SHIFT 02-062

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / AGGREGATION INHIBITORS
4-5 April 2025

TARGETING TRPML1 TO ENHANCE AUTOPHAGY AND INHIBIT A-SYNUCLEIN AGGREGATES: A NOVEL THERAPEUTIC APPROACH FOR PARKINSON'S DISEASE

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Aims: Parkinson's disease (PD) involves the loss of dopamine-producing neurons and the accumulation of α-synuclein aggregates, leading to neurodegeneration. Current treatments focus on symptom management, but there is increasing interest in disease-modifying therapies targeting underlying mechanisms, such as enhancing autophagy to clear toxic proteins. Small-molecule therapies targeting proteins like TRPML1 aim to boost autophagy and lysosomal function, offering a potential solution to slow disease progression and improve patients' lives.
Methods: TRPML1's activity was evaluated using calcium assay and lysosomal patch clamp technique. We tested autophagic activity using TFEB and LC-3. PD efficacy was evaluated cell model and PFF/SNCA A53T stereotaxic injection mouse model.
Results: We have identified a novel TRPML1 agonist that has been verified to activate TRPML1 effectively. Our compound successfully triggers cell autophagic processes, enhancing the cellular cleanup mechanism. Moreover, it has shown promising results in animal models, demonstrating its potential therapeutic efficacy.
Conclusions: In conclusion, our therapies can slow Parkinson's progression and improve quality of life by restoring cellular balance and reducing neurotoxicity. Grounded in advanced lysosomal biology and neurodegenerative research, these treatments aim to offer transformative solutions in the clinic, bringing new hope to patients. We are committed to advancing these therapies and anticipate a positive impact on the scientific and medical communities.

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SHIFT 02-065

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
4-5 April 2025

ADVANCING ACCESS TO DISEASE-MODIFYING THERAPY RESEARCH TREATMENT-NAIVE PARKINSON'S DISEASE THROUGH PHYSICIAN AWARENESS AND DATA-DRIVEN PATIENT IDENTIFICATION

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Aims: Parkinson's disease (PD) research is increasingly focused on disease-modifying therapies (DMTs), particularly in early-stage or treatment-naïve patients where neuronal preservation or restoration is most feasible. However, many patients with early-stage PD are well-managed on current SoC. Moreover, community neurologists are unaware of ongoing clinical trials and may initiate dopaminergic therapy, inadvertently restricting patient eligibility for research. This study evaluates the impact of provider education and real-time electronic health record (EHR)-driven pre-qualification in improving recruitment for a Phase LRRK2+ 2 treatment-naive PD trial.
Methods: SiteRx implemented a dual-approach, combining targeted provider education—via webinars and direct outreach—with health record-based patient identification. Structured and unstructured EHR data were analyzed to identify treatment-naïve patients meeting trial eligibility criteria. Tracked metrics included referral volume, referral-to-consent conversion, and screen-fail rates. Qualitative provider feedback was also assessed.
Results: During the recruitment period, the integrated strategy identified and referred 55+ treatment-naive PD patients in 12 months. Nearly 57% of referrals proceeded to on-site screening, a conversion rate significantly surpassing the study-wide benchmark. Additionally, screen-fail rates among SiteRx referred patients were 40% lower than the trial average (33% vs. 55%), reflecting improved patient selection due to provider education and pre-qualification of patients based on health history.
Conclusions: Leveraging provider education and real-time health record-driven patient identification demonstrates a scalable model for improving recruitment of treatment-naïve PD patients into DMT trials. By increasing physician awareness of evolving therapeutic options and optimizing patient selection before standard treatment initiation, recruitment strategies can be refined to facilitate earlier enrollment into disease-modifying research. These findings underscore the importance of bridging clinical practice with emerging trial opportunities, ensuring that eligible patients have access to investigational therapies before disease progression limits treatment potential.

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SHIFT 02-066

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α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
4-5 April 2025

DEFINING OPTIMAL THRESHOLDS FOR TIME-TO-EVENT ENDPOINTS FOR PARKINSON'S DISEASE CLINICAL TRIALS.

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Aims: Time-to-event (TTE) endpoints are used in Parkinson's disease (PD) trials. Event(s) are defined as minimum clinically meaningful threshold changes from baseline on MDS-UPDRS scores (Total, Part II or III). This work explores whether minimum threshold score change TTE endpoints are optimal for detecting treatment effects.
Methods: The Parkinson's Progressive Markers Initiative (PPMI, https://www.ppmi-info.org) dataset was downloaded (Version 2023-06-12). Two PPMI populations were selected: (i) the full population, i.e., treatment naïve at baseline (n=2347); (ii) on a stable levodopa equivalent daily dose (LEDD) for >= 20 months (n=351). The power to detect treatment effects in these populations on TTE endpoints over 18 months was estimated by quantitative simulation. Clinical trial power was estimated across TTE thresholds for different MDS-UPDRS scores (Total, Part II or III), sample and treatment effect sizes.
Results: In general, simulated clinical trial power initially increased with increasing TTE threshold, reached an optimal range of values before subsequently decreasing. The exact shape of these threshold-to-power curves was sensitive to the population, treatment effect size and sample size. Of note, thresholds based on minimal clinically meaningful changes were not always optimal. For example, the power to detect a 30% effect size with 250 subjects (complete PPMI population) was 39% for a 3-point MDS-UPDRS III score TTE (minimum clinically meaningful change) and 63% for a 5-point change but surprisingly much higher for larger score changes.
Conclusions: TTE endpoints based on minimal clinically meaningful thresholds may not be optimal, as larger thresholds were associated with higher power to detect treatment effects particularly in treatment naïve populations. Adapting thresholds to a target clinical trial population (e.g., treatment naïve) could serve to reduce sample sizes and/or trial durations.

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SHIFT 02-067

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
4-5 April 2025

REGULATORY LETTER OF SUPPORT FOR THE APPLICATION OF CSF A-SYNUCLEIN SEED AMPLIFICATION ASSAY FOR USE IN CLINICAL TRIALS FOCUSED ON EARLY INTERVENTION

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Aims: Novel methodologies for sensitive detection of pathologic α-synuclein (α-syn) in biofluids have the potential to accelerate development of transformative therapies. A precompetitive initiative sought regulatory review of the evidence regarding α-syn seed amplification assay (SAA) suitability as a drug development tool for clinical trials in conditions associated with abnormal α-syn.
Methods: The Critical Path for Parkinson's (CPP) Consortium at the Critical Path Institute initiated a global, precompetitive working group focused on evaluating biofluids biomarkers and comprised of top experts from CPP, academia, nonprofits, and industry. They conducted a comprehensive review of data on α-syn SAA in CSF and the association of pathologic α-syn with Parkinson's and related conditions.
Results: The review was submitted to FDA's Office of Drug Evaluation Sciences under the Letter of Support pathway. The regulatory package highlighted performance of α-syn SAA in CSF as a predictive and trait biomarker of PD across multiple independent observational cohorts in geographically diverse populations. Additionally, data from two randomized controlled trials of α-syn targeted therapeutic demonstrated predictive accuracy of SAA, offering evidence to support a context of use for the biomarker in clinical trials. Upon review of the evidence, the FDA issued a letter of support (LOS) to recommend the application of the α-syn SAA as a susceptibility / risk biomarker for enrichment of clinical trials of PD and related clinical

syndromes with participants who are biologically defined as positive for pathologic α-syn.

Conclusions: The FDA Letter of Support encourages sharing patient-level data from clinical trials and natural history studies to enable confidence in the use of α-syn SAA along with other relevant biomarkers as drug development tools for clinical trials.

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SHIFT 02-068

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / COMBINATION THERAPY, SEX/RACE, PERSONALIZED MEDICINES, AI, OTHER
4-5 April 2025

ELIGIBILITY CRITERIA OF PREVIOUS RANDOMIZED CLINICAL TRIALS IN PATIENTS WITH DEMENTIA WITH LEWY BODIES

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Aims: There are no disease modifying therapies for Dementia with Lewy Bodies (DLB), though several agents have been investigated in randomized clinical trials (RCTs). It is unknown how their selection criteria relate to each other and to what extent they are clinically applicable. We therefore aimed to establish an overview of selection criteria of existing DLB-RCTs and illustrate the effect of these criteria on eligibility for enrollment.
Methods: ClinicalTrials.gov was searched for previous phase 2/3 DLB-RCTs. Selection criteria were clustered into themes. A combination of common themes was applied to the extensively phenotyped DLB cohort-study 'DEvELOP' (*n*=186) to illustrate the eligible proportion after application. Additionally, three scenarios for one common theme (least/most restrictive, most common) were applied to elucidate varying eligibility that arises with the diversity of parameters among DLB-RCTs.
Results: Thirty RCTs were identified. There was notable heterogeneity in definitions, measurement tools and associated parameters among and within the criteria in the themes. Five prevalent themes (present in 30-100% of the studies) were: age, medical comorbidities, medication use, cognitive scores and caregiver involvement. The combination of common selection criteria: cardiovascular comorbidities, cholinesterase-inhibitor use and an MMSE-score of 14-26 (most common) resulted in 18% eligibility from DEvELOP-patients. For the MoCA, respectively the least restrictive (≥14), the most restrictive (18-24) and the most common range (≥18) resulted in 92%, 57% and 77% eligibility.
Conclusions: Our results suggest that a combination of common selection criteria substantially reduces eligibility. Moreover, diversity in the operationalization of criteria results in varying eligibility. This could negatively affect generalizability to the clinic and the comparison between RCT results. Ultimately, hampering drug development. Future trial designs should consider the impact of selection criteria on eligibility and inclusion characteristics to ensure external validity.

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SHIFT 02-069

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / DRUG DELIVERY SYSTEMS
4-5 April 2025

EFFICACY OF ND0612 FOR PEOPLE WITH PARKINSON'S DISEASE EXPERIENCING MOTOR FLUCTUATIONS: SUBGROUP-ANALYSES FROM A RANDOMIZED, ACTIVE-CONTROLLED PHASE 3 STUDY

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Aims: Primary results in the intent-to-treat population demonstrated that treatment with an optimized ND0612 regimen (ND0612 + immediate-release levodopa/carbidopa [IR-LD/CD]) provided an additional 1.72h [95% CI: 1.08h, 2.36h] of 'Good' ON-time (ON without troublesome dyskinesia) vs an optimized IR-LD/CD regimen ($p<0.0001$). We evaluated the efficacy and safety of an individually optimized ND0612 regimen vs IR-LD/CD for different subgroups of people with Parkinson's disease experiencing motor fluctuations.
Methods: Phase 3, double-blind, active-controlled trial (NCT04006210) comparing optimized ND0612 + IR-LC/CD vs optimized IR-LD/CD regimens. Subgroups were analyzed separately for the primary endpoint ('Good' ON-time) using ANCOVA with additional fixed factors for the subgroup variable and interaction term between the treatment group, and subgroup variable.
Results: The adjusted mean [95% CI] treatment effect of ND0612 was overall homogeneous across the different analyzed subgroups, including age (1.75h vs 1.63h for <65y [n=143] vs ≥65y [n=116]), sex (2.05h vs 1.59h for female [n=94] vs male [n=165]), BMI (2.07h vs 1.36h for BMI median ≤25.7 [n=129] vs >25.7 [n=130]), geographic region (1.49h vs 2.21h for Europe/Israel [n=177] vs USA [n=82]), Baseline Good ON-time (1.27h vs 2.20h for baseline median of ≤12.1h [n=129] vs >12.1h [n=129] Good ON), and Baseline OFF-time (1.16h for <5h [n=109], 1.68h for 5–7h [n=92], and 2.84h for >7h [n=58]). Treatment effects for subgroups categorized by oral optimized levodopa dose (<700mg [n=36], 700–1500mg [n=188], 1500–2000mg [n=29], >2000mg [n=6]) were 2.01h, 1.73h, 1.13h, and 2.54h, respectively, with no significant difference between groups. No relevant differences in safety or tolerability were observed between any of the subgroups assessed.
Conclusions: Treatment effects were homogenous across different analyzed subgroups. Findings from these analyses support improved Good ON-time, consistent with the overall effect of 1.72h.

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SHIFT 02-070

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / DRUG DELIVERY SYSTEMS
4-5 April 2025

ONE YEAR EFFICACY AND SAFETY OF ND0612 FOR MOTOR FLUCTUATIONS IN PARKINSON'S DISEASE: OPEN-LABEL EXTENSION PHASE OF THE BOUNDLESS STUDY

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Aims: The double-blind phase of the BouNDless study demonstrated that treatment with investigational ND0612 provided patients with Parkinson's disease (PD) experiencing motor fluctuations an additional 1.72h of ON-time without troublesome dyskinesia (Good ON-time) compared with immediate-release levodopa/carbidopa (IR-LD/CD) (P<0.0001), with a favorable safety and tolerability profile. Here we describe 1-year efficacy outcomes from the ongoing open-label extension (OLE) phase of the study.
Methods: Patients who completed the double-blind phase of the BouNDless study were eligible to enter into the ND0612 OLE (up to 54 months). All anti-PD medications could be adjusted according to individual response. This analysis was performed until the last patient completed 1-year post OLE-enrollment. Changes in diary states, measured from ND0612 initiation in the run-in phase of the pivotal study, were normalized to 16h and analyzed using mixed model repeated measures (MMRM) without imputation.
Results: Of 232 participants who entered the OLE phase (n=113 previously randomized to the ND0612 regimen, n=119 to IR-LD/CD), 167 (72%) completed 1 year of ND0612 treatment in the OLE phase. By Month 6, patients had a LS mean±SE change of –2.21±0.16h in OFF-time (P<0.0001) and +2.38±0.18h (P<0.0001) in Good ON-time (including +2.66±0.25h in ON-time without any dyskinesia). Efficacy benefits were sustained at Month 12 with a change of –1.86±0.18h in OFF-time (P<0.0001) and +1.96±0.18h in Good ON-time (including +2.19±0.26h in ON-time without any dyskinesia). The ND0612 regimen was generally safe and well-tolerated, with an adverse event profile consistent with the prior double-blind phase.
Conclusions: Results from this open-label extension phase confirm the 12-month efficacy and safety of treatment with the ND0612 regimen in increasing Good ON-time and reducing OFF-time in patients with PD and motor fluctuations.

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SHIFT 02-071

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / DRUG DELIVERY SYSTEMS
4-5 April 2025

QUALITY OF LIFE WITH 24-HOUR SUBCUTANEOUS LEVODOPA/CARBIDOPA INFUSION (ND0612): QOL RESULTS FROM A PHASE 3 RANDOMIZED, ACTIVE-CONTROLLED STUDY

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Aims: Pivotal data from the BouNDless study (NCT04006210) showed that treatment with investigational ND0612 provided patients with Parkinson's disease (PD) and motor fluctuations an additional 1.72h [95% CI: 1.08h, 2.36h] of ON-time without troublesome dyskinesia compared with immediate-release levodopa/carbidopa (IR-LD/CD; *P*<0.0001). Here, we evaluate quality of life (QoL) data from the phase 3, randomized, active-controlled BouNDless study.
Methods: Patients with PD on ≥4 oral LD/CD doses/day (≥400 mg/day LD) and experiencing ≥2.5h of daily OFF-time underwent 4-6 weeks of open-label IR-LD/CD dose adjustment followed by 4-6 weeks of open-label ND0612 conversion (+ IR-LD/CD). Patients were then randomized to 12-weeks double-blind treatment with either their optimized regimen of ND0612 or IR-LD/CD. Change from randomization to end of double-blind treatment in QoL was assessed using the PD Questionaire-39 (PDQ-39) and 5-level EuroQoL (EQ-5D-5L) and analyzed using ANCOVA following multiple imputation and MMRM respectively
Results: At the end of the double-blind phase, improvements in PDQ-39 summary index scores achieved with the ND0612 regimen in the open-label run-in phase were maintained with ND0612 treatment compared to a return to enrollment values in the IR-LD/CD group. A mean [95% CI] treatment difference of –2.69 [–4.83, –0.55] was observed at the end of the double-blind phase favoring the ND0612 regimen (nominal *P*=0.014). PDQ-39 domain analyses consistently favored ND0612 treatment, mainly in mobility, bodily discomfort, cognition, and stigma. EQ-5D-5L scores showed consistent changes from randomization to end of double-blind phase; at Week 12, the mean [95% CI] treatment difference was 0.06 [0.00, 0.12] (nominal *P*=0.0331) favoring the ND0612 regimen.
Conclusions: ND0612 improved QoL compared to IR-LD/CD, further supporting the clinical meaningfulness of the observed reduction in motor fluctuations from the perspective of a patient with PD.

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SHIFT 02-073

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / ENZYME MODULATORS
4-5 April 2025

ASSESSMENT OF LYSOSOMAL B-GLUCOCEREBROSIDASE ACTIVITY AND PATHWAY BIOMARKERS IN HEALTHY VOLUNTEERS AND PATIENTS WITH PARKINSON'S DISEASE WITH A GBA1 MUTATION

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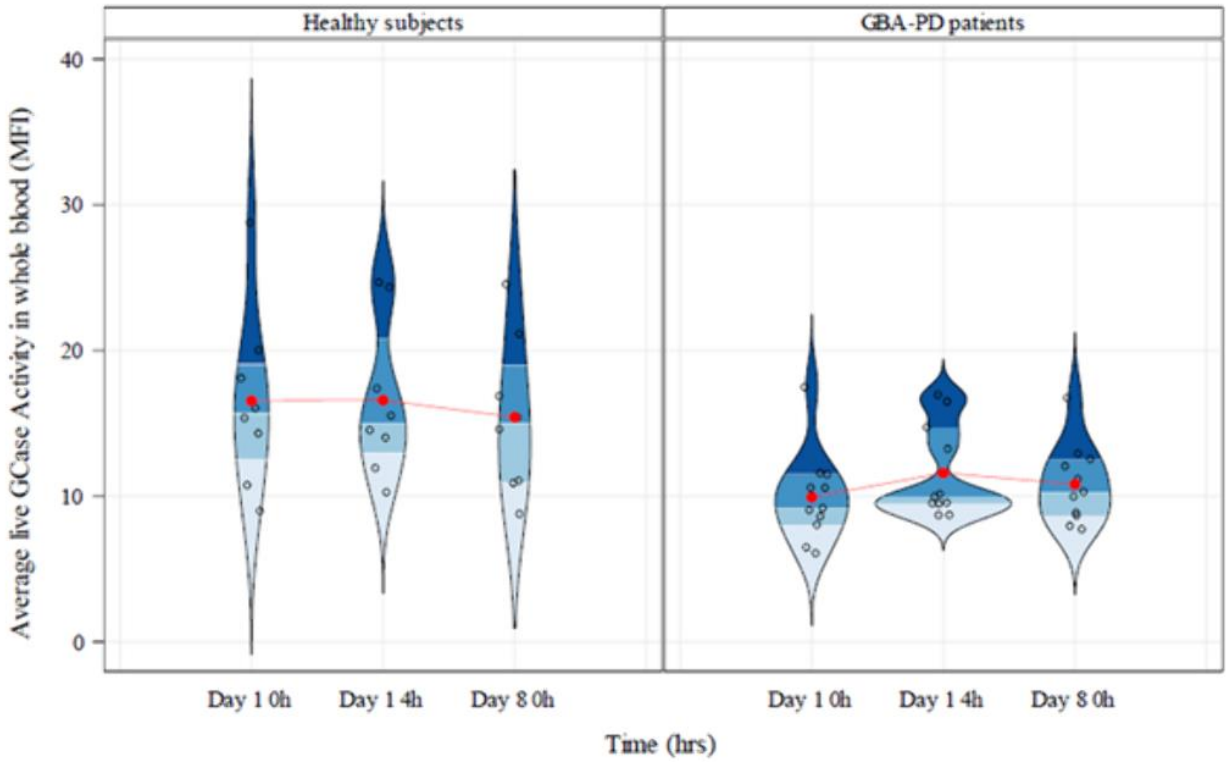
Aims: Heterozygous loss-of-function mutations in *GBA1*, which encodes glucocerebrosidase (GCase), are a significant risk factor for developing Parkinson's disease (PD). As a result, a major priority for the field is the development of therapeutics to increase GCase activity. A roadblock for therapies targeting GCase is the measurement of target and pathway engagement. Current approaches to assess GCase activity in blood lack specificity for lysosomal GCase and sensitivity. Here we evaluated a novel approach to measure lysosomal GCase activity in fresh blood samples to determine the suitability of this approach for target engagement with GCase therapeutics in future clinical trials.
Methods: Whole blood samples were obtained from 8 healthy volunteers (HVs) and 12 PD patients with a *GBA1* mutation (GBA-PD) at 3 time points (Day 1, 0 and 4h, and Day 8, time matched to 0h). Using a novel approach, lysosomal GCase activity was evaluated by two independent labs in matched samples. Additional analysis of plasma glucosyl-β sphingosine (GluSphing) was also performed.



Results: Figure 1: Violin graph depicting average live GCase activity in whole blood Lysosomal GCase activity was significantly lower in GBA-PD patients compared to HVs with an average reduction of 33% (p=0.004) [figure 1]. This decrease was consistent across both analysis sites with modest intra- and inter-day fluctuations observed. Plasma GluSphing concentrations were higher in GBA-PD patients than in HVs, although not significant (p=0.06). Inter- and intra-day variation in plasma GluSphing was low.

Conclusions: We developed a robust assay to measure lysosomal GCase activity in whole blood samples. Using this assay, we observed biochemically relevant reductions in GCase activity in GBA-PD patients compared to HVs. These results support the use of this assay to assess target engagement of GCase therapeutics in clinical trials.

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SHIFT 02-075

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROTRANSMITTER-BASED AGONISTS AND MODULATORS, GLP-1 RECEPTOR AGONISTS
4-5 April 2025

CROSS-SECTIONAL ANALYSIS OF INTERRELATIONS BETWEEN FALL-RATE, COGNITIVE MEASURES, UPDRS-SUBSCALES, AND NPI-APATHY IN THE REACT-PD STUDY COHORT

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Aims: React-PD is a Phase 2b trial, investigating the effect of the cortical enhancer pirepemat on fall-rate in subjects with PD experiencing recurrent falls. Falls, as well as apathy, cognitive decline, and some other motor- and non-motor manifestations of PD are hypothesized to be linked to impaired cortical function. Here we aimed to explore the pattern of variable interrelations in a well-characterized cohort of PD-subjects with frequent falls and cognitive impairment.
Methods: Baseline data from the REACT-PD study cohort, including MDS-UPDRS, MoCA, NPI-apathy, fall-rate, and demographics were analyzed using principal component analysis methodology (PCA), to uncover the overall correlational structure. All variables were subject to zero-mean/unit variance scaling, log-transformed as needed (auto-transform) and block-scaled by variable domain. Statistical significance was determined by cross-validation.
Results: PCA yielded three significant components. Variable loadings showed a correlation structure with several distinct clusters: MoCA-subscores; UPDRS-part 4 (motor complications); UPDRS-parts 2 and 3 tremor subitems; apathy frequency/severity/caregiver distress. There was also a cluster with axial UPDRS part 2 and 3 items (speech, walking/balance). Baseline fall rate was correlated to motor complications of therapy, especially complex motor fluctuations, and some axial motor symptoms, and inversely correlated to tremor, but essentially uncorrelated to general parkinsonian motor features. Baseline fall rates were also correlated to the frequency/severity of apathy. Further, apathy scores were inversely correlated to cognitive scores. A positive correlation between cognitive scores and tremor was also observed.
Conclusions: These findings are in line with the notion of tremor-dominant being a more benign PD phenotype and support the concept of cortical decompensation being associated with poorly treatment responsive symptoms such as falls, apathy, and axial motor symptoms.

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SHIFT 02-077

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS, NEUROSURGERY
4-5 April 2025

FEASIBILITY OF USING THE NUSHU SNEAKER TECHNOLOGY TO ANALYZE GAIT AND VIBROTACTILE FEEDBACK IN EARLY, MODERATE AND ADVANCED PARKINSON'S DISEASE

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Aims: To determine the feasibility of real-time recording of gait metrics and response to vibrotactile stimuli provided by the NUSHU sneaker in Parkinson's disease (PD). Gait changes in PD are complex and variable, which is difficult to detect during short clinic assessments. Gait disturbances, especially freezing of gait (FOG), are challenging to treat as they are often medication resistant yet frequently lead to falls, contributing to morbidity and mortality. A novel device, the NUSHU sneaker (Magnes AG), allows wearers to gather continuous gait analysis while providing vibrotactile stimuli, serving as potential treatment for gait without additional devices.
Methods: Ten participants with PD will be recruited in each of the following categories: early -within 4 years of diagnosis, moderate -within 4 to 7 years, and advanced -over 10 years. Ten adult controls will be recruited. At baseline visit, participants will be fitted for the NUSHU sneaker to wear home. The MDS-UPDRS III, Timed Up and Go (TUG), Montreal Cognitive Assessment (MoCA), and FOG questionnaire will be conducted. Gait analysis performed via the NUSHU sneaker will assess stride time and length, swing and stance (duration of time between heel strike and toe off), velocity, cadence, swing phase, and stance phase. Subsequent assessments at 4, 8, and 12 weeks will repeat gait exams and assessments.
Results: This pilot protocol will be conducted at the Weill Cornell Parkinson's Disease & Movement Disorders Institute.
Conclusions: The goal of this pilot study is to assess feasibility of using wearable technology in an accessible platform to collect real-time gait analysis. We also aim to report preliminary data on treatment effect provided by the vibrotactile feedback of the NUSHU. Long term we hypothesize that this can lead to improved gait and reduction of falls.

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SHIFT 02-078

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / VITAMINS, ANTIOXIDANTS, NEUROPROTECTIVE COMPOUNDS
4-5 April 2025

NEUROPEPTIDES WITH NEUROTROPHIC EFFECTS AND PHOSPHOLIPIDS IN THE TREATMENT OF PARKINSON'S DISEASE

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Aims: Parkinson's disease remains one of the most disabling and pressing problems that significantly reduces the quality of life of patients. In recent years, the neurostimulating effects of pulsed magnetic fields, neuropeptides with neurotrophic effects, and hypothalamic phospholipids have attracted increasing attention from researchers.
Methods: 60 patients (38 men and 22 women) aged 46 to 69 years were deployed, the duration of the disease was 7.1±2.2 years, the severity of the disease on the Hon and Yar scale was 2.4± 0.4. points. To assess the degree of effectiveness of various M. Tinetti scales used, cognitive measures - MMSE, MoCA, Matisse, SCOPA-Cog assessment scales, assessment of the quality of life according to the McDowell index. Under observation were 2 groups: 1st- 32 patients received injections of neuropeptides with neurotrophic effects, who received an extra ion-reflex impulsive magnetic electrophoresis sessions using hypothalamus phospholipids by applying head's frontooccipital longitudinal galvanization techniques were conducted; 2rd- 28 patients treated with protocol formed a control group.
Results: against the background of combined intake, there is an increase in motor activity, a decrease in rigidity, tremor, hypokinesia. Indicators of stability and gait on the M. Tinetti scale are riskily risky by 22.7%. The McDowell index of life disorders decreased by 43 points (from the original 90). Statistically dangerous neurodynamic and operational functions. Increased cognitive function on the MMSE scale showed positive dynamics from 22.9 ± 1.5 to 24.9± 1.5; on the SCOPA-Cog scale – by 12 points, on the Matisse scale – by 9.7% ($p<0.01$). Significantly dangerous tests for the logical memory of the results, as well as tests for counting and thinking.
Conclusions: Neuropeptides with neurotrophic effects and magnetoelectrophoresis with hypothalamic phospholipids can improve the treatment of Parkinson's disease.

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SHIFT 02-081

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4-5 April 2025

IDENTIFICATION OF SEX-SPECIFIC CAUSAL GENES FOR PARKINSON'S DISEASE VIA PROTEOME-WIDE ASSOCIATION STUDIES

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Aims: Integrate brain protein quantitative trait locus (pQTL) data with sex-stratified genome-wide association studies (GWAS) of Parkinson's disease (PD) for increased power to discover sex-specific PD associated genes.
Methods: Sex-stratified GWAS of PD from Blauwendraat et al. 2021 included non-Hispanic White individuals of European ancestry (N_{Women}=104,082; N_{Men}=110,616). Human brain proteome data with matching genome-wide data were obtained from Wingo et al. 2022 and 2023 ($N_{Non\text{-}stratified}$=722; N_{Women}=507; N_{Men}=301). In brief, the FUSION package estimated genetic effects on protein abundance and produced non-sex-stratified ($N_{Proteins}$=2,934) and sex-stratified protein-specific variant weights ($N_{Proteins}$=1,800 for males; $N_{Proteins}$=2,463 for females). This method only returns variants weights for proteins that present significant genetic associations (i.e., protein levels exhibiting significant heritability). Proteome-wide association studies (PWAS) were performed via FUSION to integrate sex-stratified PD GWAS with non-sex-stratified and sex-stratified protein weights (**Figure-1**).

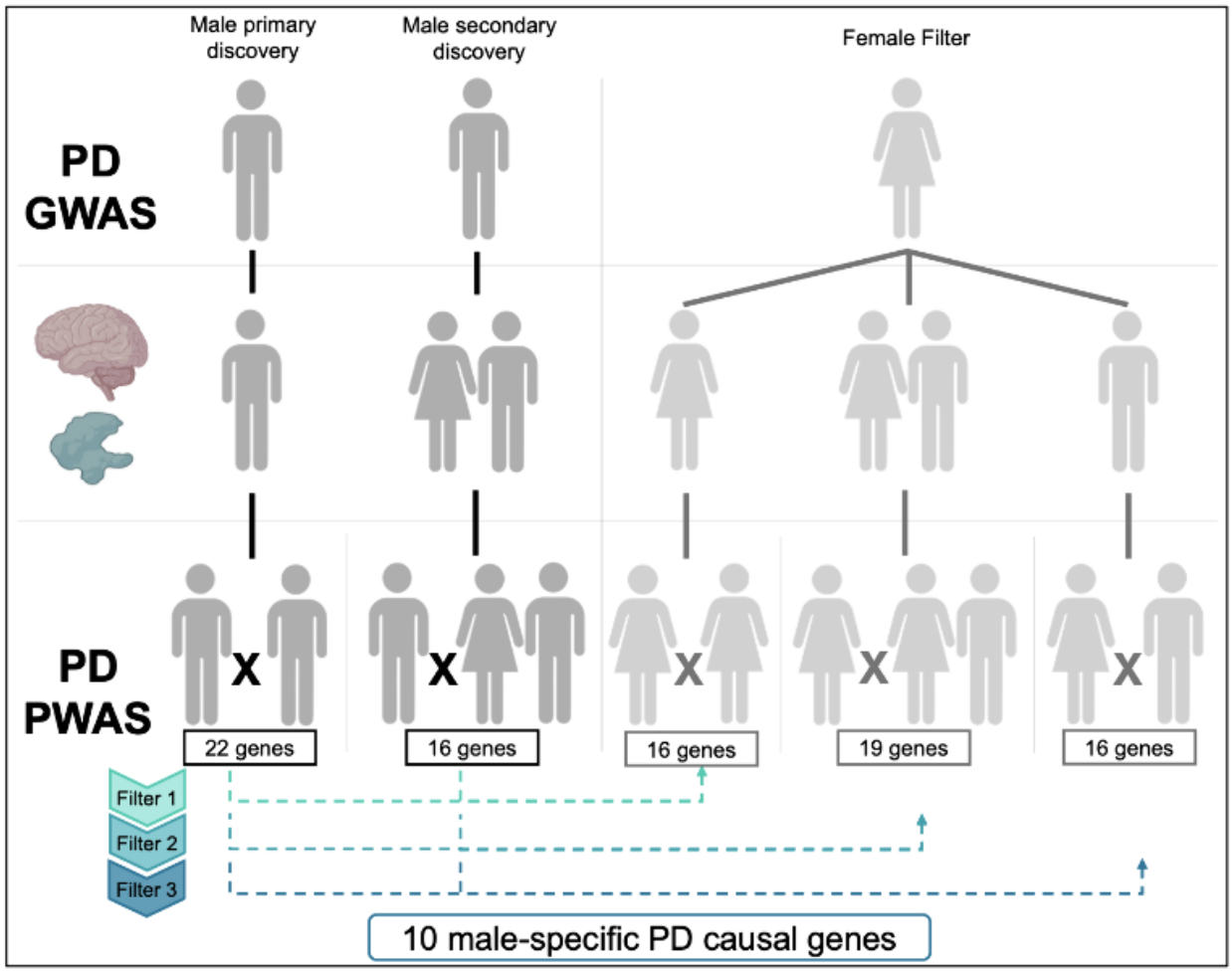

Figure 1. PWAS design for identifying male-specific PD causal genes. The primary discovery (left column) integrates the male-specific PD GWAS with male-stratified pQTL data to perform a fully sex-matched PWAS. The secondary discovery (middle column) sought to assess whether sex-matched pQTL data are relevant to identify sex-specific risk genes or whether non-stratified pQTL data could be leveraged to identify subthreshold signals from the sex-stratified PD GWAS. To reinforce sex-specificity, findings from male discoveries were then filtered for any nominally significant outcomes in female-specific analyses (3 columns on the right). The study design is consistent (but inverted) for female-specific discoveries.

Results: Sex-matched PD PWAS identified 16 female and 22 male PD causal genes. Sex-stratified PD GWAS combined with non-stratified protein weights identified 19 female and 16 male PD causal genes. Sex-specific filtering of results from both discoveries prioritized 1 female and 10 male PD causal genes (**Figure-2**). Notably, 9 out of 10 male-specific PD causal genes and the female-specific gene were novel compared to prior non-stratified PD GWAS (Nalls et al. 2019 and Chang et al. 2017).

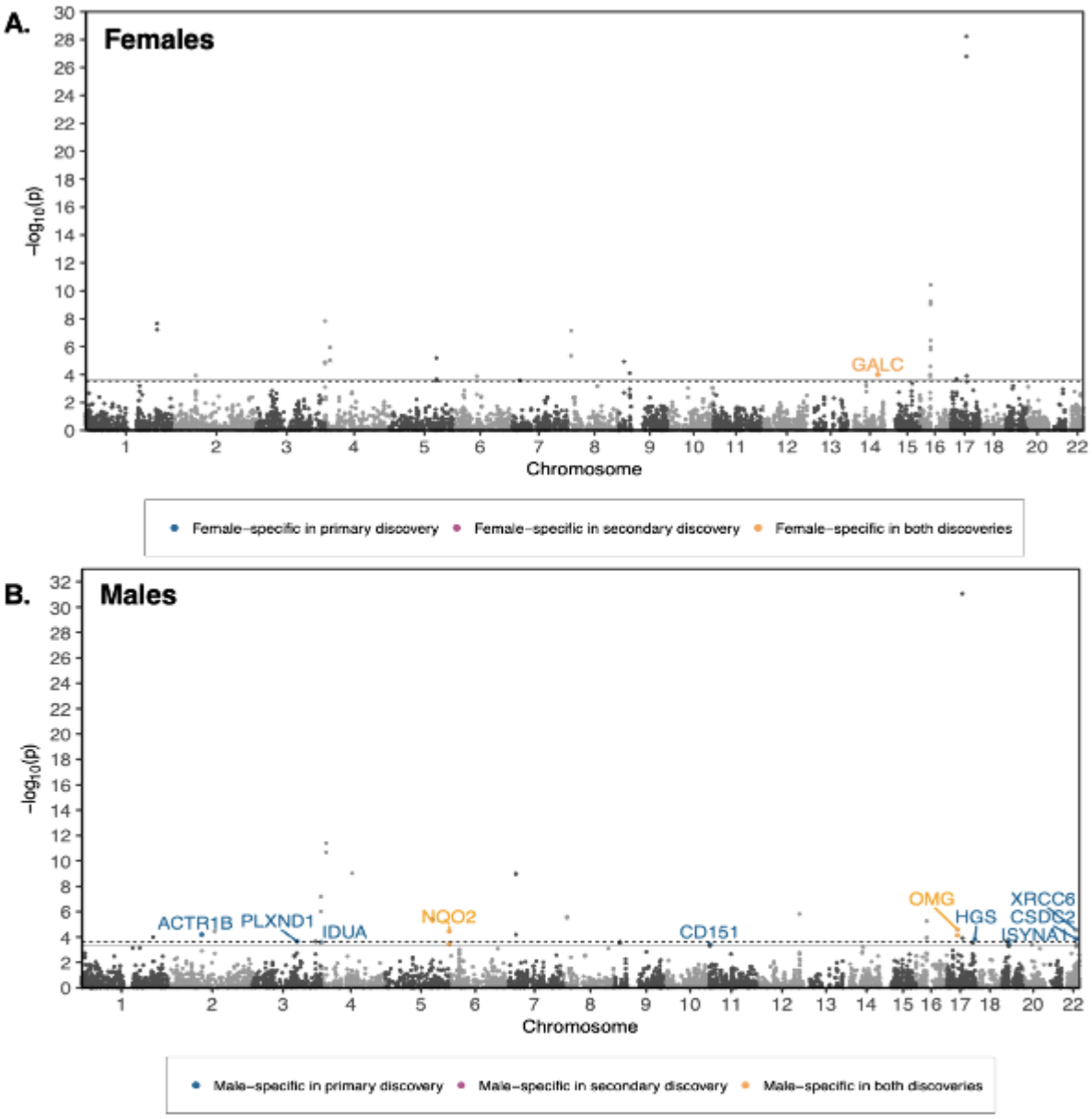

Figure 2. Sex-specific PD PWAS results in both female and male discoveries. Datapoints represent association tests between a protein and PD, and the significance of each test is indicated on the y-axis as the -log10 p-value. Associations are ordered on the x-axis by gene-start genomic location across autosomes. The black horizontal lines (solid for primary discovery and dashed for secondary discovery) denote the proteome-wide significance thresholds at FDR p<0.05. Sex-specific genes with insignificant association signal in the opposite sex are annotated according to discovery design. **A.** Genes identified as female-specific **B.** Genes identified as male-specific. These findings demonstrate that both discoveries contributed important sex-specific PD risk genes, indicating that both sex-stratified and non-stratified pQTL data are valuable. Non-stratified pQTL data may have contributed to sex-specific PD risk genes due to increased power.

Conclusions: We conducted sex-stratified PWAS of PD and identified a set of 10 genes whose genetically regulated protein levels appear causal to PD risk in men specifically, pinpointing potential sex-specific drug targets. Supporting analyses in additional proteogenomic resources are ongoing and are anticipated to further elucidate sex-specific mechanisms related to PD pathogenesis and will help corroborate these initial discoveries.

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SHIFT 02-082

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
4-5 April 2025

PRESCRIPTION PATTERNS AND TRENDS OF ANTIPARKINSONIAN DRUGS IN KOREAN PATIENTS WITH PARKINSON'S DISEASE: A REAL-WORLD DATA ANALYSIS

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Aims: This study aimed to analyze prescription patterns of antiparkinsonian drugs in Korean patients with PD using real-world data (RWD).
Methods: Using the Korean National Health Insurance Service (KNHIS) database, we identified 160,476 patients with PD from 2002 to 2019. We analyzed initial drug prescriptions, including monotherapy and polytherapy, dosage patterns, combination therapies, and dosage adjustments over time. Group-based trajectory modeling was employed to identify distinct levodopa prescription trajectories.
Results: Most patients initiated monotherapy (66.3%), with levodopa being the predominant across all age groups, with a decline in the dopamine agonist (DA)/levodopa ratio with advancing age. Initial levodopa doses in the monotherapy group averaged approximately 300 mg, irrespective of age group. In the polytherapy group (33.7%), combinations of levodopa or DA predominated (>90% across ages); 73.4% started with two drugs, 21.8% with three, and 4.8% with four or more. In the initial levodopa monotherapy group, the trends in levodopa dosage increases and add-on therapy consistently increased, especially in the first year, regardless of age group or initial levodopa dosage. Trajectory analysis revealed four distinct levodopa prescription patterns: (A) a high starting dose with continuous increase and a slight late decrease (21%); (B) a high starting dose with an early peak followed by continuous decrease (11%); a moderate starting dose with delayed increase and reaching a late maximum (28%); and (D) a moderate starting dose with an early decrease (40%).
Conclusions: This analysis of RWD provides clinicians with valuable insights into age-dependent prescription variations and specific timing of medication changes or dosage increases, with levodopa playing a central role, observed in real-world PD management. This information empowers clinicians to make personalized, informed treatment decisions when managing PD.

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SHIFT 02-089

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
4-5 April 2025

FREQUENCY OF PRODROMAL DEMENTIA WITH LEWY BODIES IN A COHORT OF PATIENTS UNDERGOING CARDIAC SURGERY: FINDINGS FROM THE FINDERI STUDY

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Aims: Prodromal dementia with Lewy bodies (PDLB) is an under-researched disorder as an early diagnosis is a major challenge. PDLB subtypes can be divided into three subtypes based on the symptoms occurring at presentation: onset with delirium (PDLB-delirium), onset with psychiatric symptoms (PDLB-psychiatric) and onset involving mild cognitive impairment (PDLB-MCI). Our aim was to investigate the frequency of PDLB subtypes in a cohort of patients undergoing cardiac surgery, as postoperative delirium (POD) and postoperative cognitive dysfunction (POCD) are a common complication in this context that can unmask patients with PDLB-delirium and PDLB-MCI.
Methods: In our prospective observational cohort FINd DElirium RIsk factors (FINDERI) study, we investigated the incidence of PDLB in patients aged ≥ 50 years undergoing elective cardiac surgery. Patient records, questionnaires and chart reviews were analyzed for the frequency of probable PDLB types after applying consensus criteria.
Results: In the FINDERI cohort, 31 of 504 patients (6.2%) met the criteria for probable PDLB. Furthermore, we observed PDLB-MCI in 2 of 504 patients (0.4%), while probable PDLB-delirium was noted in 16 of 504 patients (3.3%). Probable PDLB-psychiatric was also observed in 16 of 504 patients (3.2%).
Conclusions: Our results show that we detected PDLB postoperatively in a cardiac surgery cohort with no prior diagnosis of neurodegenerative disease. There is overlap between the PDLB subtypes, accordingly the total number of PDLB patients is lower than the sum of the individual prodromal DLB types. Postoperative cognitive and neuropsychiatric testing in cardiac surgery patients will likely prove useful in identifying patients with PDLB who present with prolonged delirium or POCD.

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
4-5 April 2025

COGNITION IN AN AT RISK COHORT FOR PARKINSON'S DISEASE FROM THE PROSPECTIVE POPULATION-BASED HEBA PROJECT

Noelia Peña Arauzo[1], Katharina Tietgen[1], Corinne Horlings[1], Atbin Djamshidian[1], Katharìna Schwarzovà[1], Iris Egner[1], Heike Stockner[1], Sonja R. Jónsdóttir[2], Tainá Marques[2], Claire Pauly[2,3], Rejko Krüger[2,3,4], Kathrin Marini[1], Christoph Theyer[1], Werner Poewe[1], Philipp Mahlknecht[1], Laura Zamarian[1]
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Aims: To perform in-depth cognitive testing in the longitudinal and multicenter *Healthy Brain Ageing (HeBA)* project and to investigate potential cognitive changes in a Parkinson´s disease (PD) risk cohort.
Methods: Here we present a preliminary monocentric analysis in the HeBA sample with in-person assessments performed between March 2023 and February 2024. Based on information from the initial remote part of the HeBA study (online survey regarding risk factors for PD and University of Pennsylvania Smell Identification Test), we classified participants as high- and low-risk for PD. A subset of participants without neurodegenerative disorder underwent detailed in-person visits including neuropsychological assessment (Montreal Cognitive Assessment [MoCA], Consortium to Establish a Registry for Alzheimer's Disease [CERAD-plus], symbol digit modalities test [SDMT]). They also completed questionnaires on non-motor symptoms (NMS).
Results: Of the 116 subjects included in this preliminary analysis (mean age 63±5 years, 67% female), 65 participants (56%) were classified as high-risk, 51 (44%) as low-risk. The high-risk group reported a higher NMS burden (Mann-Whitney, $P<.05$). Subjective memory complaints were more frequent in the high-risk group (22% versus 4%; Chi-square, $P<.006$). High-risk participants showed lower objective performance than low-risk participants in verbal learning only (Mann-Whitney, $P=.029$). In a regression analysis subjective memory complaints and verbal learning were significant predictors of group classification in high- and low-risk (Nagelskerke $R^2=.14$, $P=.001$). By adding ratings of depressive symptoms to the model, verbal learning remained the only significant predictor (Nagelskerke Δ-$R^2=.03$, $P=.109$).
Conclusions: Compared with low-risk participants, high-risk individuals showed significant changes in subjective and objective cognitive measures. Longitudinal evaluations in the larger multicenter HeBA study will help further understanding of cognitive changes in prodromal PD.

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC, BEHAVIORAL AND MOTOR TESTS
4-5 April 2025

AUTOMATICALLY SCREENING FOR PRODROMAL PARKINSONISM IN ISOLATED REM SLEEP BEHAVIOR DISORDER USING SPEECH BIOMARKERS FOR ARTICULATORY PERFORMANCE

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Aims: Isolated REM sleep behavior disorder (iRBD) is an early alpha-synucleinopathy and can precede overt motor Parkinson's Disease (PD) for decades. Speech changes have proven to be a robust and sensitive indicator of early motor-function impairment in PD and also iRBD (Hlavnička et al., 2017). The goal of this research is to evaluate the feasibility of using speech biomarkers to screen iRBD patients.
Methods: This research is based 60 Czech iRBD (11F, mean age=67.08±7.42, mean UPDRS III=6.93±4.88) and 60 Czech HC (11F, mean age=65.18±7.35, mean UPDRS III=4.8±3.96) (Rusz et al., 2021) with recordings from fast syllable repetitions of the sequence /pataka/. From the recordings, acoustic features on diadochokinetic rate and irregularity were extracted using ki:elements' proprietary speech analysis pipeline SIGMA. Then, we calculated a composite score for articulatory performance, computed group difference between HC and iRBD and subsequently defined an optimal cut-off to separate both groups and report the area under the curve for this screening use case. Each participant was also assessed with the Unified Parkinson's Disease Rating Scale (UPDRS).
Results: The articulation score significantly differs between both groups ($H = 22.663$, $p < 0.001$, $\eta 2 = 0.184$, Cohen's $d = 0.472$) with the iRBD group showing significantly less articulatory performance in the /pataka/ task. Using the overall articulation score and a cut-off, iRBD patients could be screened out with an AUC of .75 (sensitivity = 0.80, specificity = .65).
Conclusions: The results show that an automatic articulation measure based on acoustic speech biomarkers could be utilized to screen for iRBD. Future research has to show whether this result persists in a study with different languages. Results might impact future applications both in clinical trials as well as healthcare.

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SHIFT 02-096

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

PARKINSON'S PROGRESSION MARKERS INITIATIVE (PPMI): INVESTIGATING BIOMARKER DRIVEN PD PROGRESSION

Bridget Mcmahon[1], Andrew Siderowf[2], Tanya Simuni[3], Caroline Tanner[4], Britt Mollenhauer[5], Christopher Coffey[6], Douglas Galasko[7], Kathleen Poston[8], Lana Chahine[9], Roseanne Dobkin[10], Tatiana Foroud[11], Karl Kieburtz[12], Daniel Weintraub[13], Kalpana Merchant[3], Mark Frasier[14], Todd Sherer[14], Sohini Chowdury[14], Ethan Brown[4], Roy Alcalay[15], Aleksandar Videnovic[16], Kimberly Fabrizio[1], Emily Flagg[1], Craig Stanley[1], Ken Marek[1], Dixie Eckland[17]
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Aims: PPMI, a longitudinal, observational study, enrolls PD participants, individuals at risk for PD, and healthy controls (HCs). The study investigates clinical, imaging, genetic and biofluid biomarkers to elucidate the course of PD from start of neurodegeneration through clinical PD to accelerate therapeutic development. Since 2010 PPMI has evolved into a broad international study demonstrating the natural history of PD clinical and imaging progression. Recent data has utilized the unique PPMI resource to validate the α-synuclein seed amplification assay (asyn SAA) in CSF. PPMI data is open source, available at www.ppmi-info.org
Methods: The PPMI Program enrolls and follows densely phenotyped populations (n=3200) at 51 clinical sites worldwide. Participants include an early untreated PD cohort, a prodromal hyposmic and RBD cohort and HCs. Participants are assessed annually for at least 5 years using clinical (motor and non-motor) scales (e.g. MDS-UPDRS, MoCA), Patient Reported Outcomes (PROs), quantitative imaging (DAT, SBR, MRI midbrain melanin), and biologic measures of synuclein, lysosomal function, and analytes related to neurodegeneration. The myPPMI, a web portal, provides opportunities for acquisition of data and return of personalized data to study participants remotely.
Results: Recent data demonstrate that >90% of PD participants and approx. 50-70% of RBD and hyposmic

participants are asyn SAA+. These data coupled with DAT imaging and olfactory function results have led to a biomarker driven definition for PD and the introduction of the concept of Neuronal Synuclein Disease (NSD) encompassing PD, dementia with Lewy Bodies and RBD.

Conclusions: PPMI has successfully enrolled and follows study participants throughout the course of disease, continuing to maintain open-source clinical data and a biomarker repository that informs our NSD definition and understanding of PD progression.

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SHIFT 02-097

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

CONTENT VALIDITY OF DIGITAL MOTOR ASSESSMENTS AND ACCOMPANYING ELECTRONIC PATIENT-REPORTED OUTCOMES IN A PARKINSON'S DISEASE HUMAN FACTORS STUDY

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Aims: Meaningfulness, relevance, and applicability were evaluated to understand the content validity of at-home, smartphone-administered electronic performance outcomes (ePerfO) of motor function and related electronic patient-reported outcomes (ePROs) in participants with Parkinson's disease (PD).
Methods: Participants with mild-to-moderate PD (self-reported Hoehn and Yahr scale 1-2 or symptomatic equivalent) completed weekly digital motor function assessments and an MDS-UPDRS Part II ePRO over a 1-month period at home. Motor assessments included a timed walk test, finger tapping, pronation-supination of the hand, and three tremor assessments (resting, postural, and kinetic). Participants then completed an in-house content validity questionnaire to report their perceptions across three domains, which were used to calculate net promoter scores (NPS; -100 to 100).
Results: Average age was 67 years (range 43-77) and 68% of the participants were male sex. Most participants had at least a bachelor's degree (92%) and reported high familiarity with using smartphones (83%). All participants agreed the walk test related to their daily experiences of living with PD and they felt safe performing the assessment at home (NPS 100). Participants generally preferred completing assessments at home to in-clinic (NPS>0 for all assessments). The MDS-UPDRS ePRO had favorable ratings (NPS 67-92); however, at least one digital motor assessment outperformed the ePRO in each domain. The finger-tapping and pronation-supination tasks had the highest NPS for being a good way of measuring participants' abilities, the tremor assessment was considered the most relevant to clinical care for PD, and the walk test was most meaningful to daily experiences.
Conclusions: This human factors study suggests a high degree of meaningfulness, relevance, and applicability of the smartphone-administered motor function assessments and questionnaires for individuals with early-stage PD.

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SHIFT 02-098

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

PERSPECTIVES OF INDIVIDUALS WITH ISOLATED REM SLEEP BEHAVIOR DISORDER ON RISK DISCLOSURE AND COHORT RECRUITMENT IN ALPHA-SYNUCLEINOPATHY RESEARCH

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Aims: Background: Isolated REM sleep behavior disorder (iRBD) is an early α-synucleinopathy associated with a high risk of phenoconversion to Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy. Previous questionnaire studies in people with iRBD showed a preference for risk disclosure. However, recruitment from the general population poses a challenge, as those affected are actively made aware of a possible impending neurodegenerative disease without yet experiencing symptoms. **Objective:** To capture the views of individuals with iRBD on the ethical justifiability and experiences with being actively recruited within a research project from the general population.
Methods: Methods: This mixed-methods study utilized an interdisciplinary-developed questionnaire to assess views of individuals with iRBD regarding risk disclosure. For the cohort study, individuals were recruited via newspaper advertisements, followed by a structured telephone screening and video-polysomnography. Individuals diagnosed with iRBD were invited to annual clinical consultations.
Results: Results: 70 individuals with iRBD (age: 69.67±6.10) participated (N=98 invited). Most individuals (64.29%) supported being informed on their high risk of developing PD but only if it was ensured beforehand that they actually wanted to know their risk. The majority (95.7%) regarded our active recruitment method as adequate, even though 60.6% of the participants experienced the information on the increased risk of phenoconversion as (somewhat) burdensome. Also, 85.6% indicated they would participate again in the recruitment and valued the access to information and care, the possibility of taking part in lifestyle interventions as well as facilitating research progress.
Conclusions: Conclusion: Almost all respondents viewed our active recruitment method as appropriate and the majority supports proactive risk disclosure. Participants also gave important hints on how communication and further support should be provided in order to minimize their personal burden.

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SHIFT 02-099

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

DISEASE-RELATED VIDEO-BASED GAIT PATTERN SCORE AS A BIOMARKER IN PARKINSON'S DISEASE

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Aims: We propose a novel video-based gait pattern score as a biomarker for PD, which could provide comprehensive and objective monitoring of motor symptoms in PD.
Methods: We recruited advanced PD patients (aPD), de-novo PD patients (ePD), idiopathic rapid eye movement behavior disorder patients (iRBD), and healthy controls (HC). For all participants, basic demographic information was collected. The MDS-UPDRS scores were evaluated for iRBD, ePD and aPD patients (medication OFF and ON states). The FP CIT PET was performed in the ePD group. All participants were video-recorded while performing timed-up and go test. Subsequently, a scaled subprofile model-principal component analysis (SSM-PCA) was performed to identify a PD-related gait pattern.
Results: A total of 193 gait videos from 33 aPD patients, 37 ePD patients, 60 iRBD patients and 30 HC were collected for this study. The aPD-related gait pattern significantly differentiated between HC and aPD (AUC=1.00). Among the 16 gait parameters analyzed, the number of turning steps was a significant positive predictor (Z-score=2.22), while step length and velocity were significant negative predictors (Z-score=-1.62 and -1.72, respectively). aPD gait scores showed increasing patterns from HC, iRBD, ePD, to aPD groups with significant differences between groups (p=2.92 x 10^-39). aPD-related gait pattern correlated with UPDRS part 1 and part 3 scores (p=0.047 and p=8.0 x 10^-4, respectively). The aPD-related gait pattern reflected significant medication effect of the aPD group (p=1.9 x 10^-4; Cohen's d=1.24). Furthermore, aPD-related gait pattern significantly correlated with the anterior-posterior gradient of putaminal dopamine binding in the ePD group(p=0.026).
Conclusions: Given its accessibility and the objectivity of the video-based analysis, we consider PD-related gait pattern score a highly promising biomarker for early diagnosis and ongoing monitoring of motor symptoms in PD patients.

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SHIFT 02-100

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

COMPARISON OF NATURALLY PRODUCED EVS AND ARTIFICIAL CDVS

Antri Stefani[1], Pauline Ley[1], Martin Wolf[1], Rodolphe Poupardin[1], Thomas Heuser[2], Samir El Andaloussi[3], Dirk Strunk[1,4]
[1]Cell Therapy Institute, PMU, Salzburg, Austria, [2]Vienna Biocenter core facilities, Vienna, Austria, [3]Karolinska Institutet, Laboratory Medicine, Stocolmkh, Sweden, [4]Austrian Red Cross (ÖRK), Vienna, Austria

Aims: Extracellular vesicle (EV)-based biomarker discovery can be more sensitive than from conventional liquid biopsies. Here we studied nano-vesicle reference material for theranostic EV-biomarker discovery for Parkinson's disease (PD). EV isolation methods, like tangential flow filtration (TFF) and size exclusion chromatography (SEC), showed limitations concerning time and resource consumptions. We therefore explored cell extrusion as efficient method to create artificial cell derived vesicles (CDVs) as reference material. We investigated whether CDVs are comparable to naturally produced EVs derived from the same cell lines.
Methods: We used fluorescent neuroblastoma cells SH-SY5Y expressing GFP-coupled alpha-synuclein (a-Syn), a key protein for PD development and progression. Two control cell lines HEK-CD63-mNEON and HEK-WT were included for comparison. Vesicles were enriched by TFF and cell extrusion. We determined EV quantity and size by tunable resistive pulse sensing (TRPS), and EV quality by tetraspanin and a-Syn expression in dot blots and, fluorescence nano-tracking analysis (fNTA). CDVs and EVs were imaged by cryo-transmission electron microscopy (cryoTEM).
Results: We found that CDVs were comparable to EVs in size with a mode diameter of 88±11nm and 93±16nm, respectively. We obtained mean 10^{11} CDVs and 10^{10} EVs per two million starting cells. Both expressed a-Syn and tetraspanins CD9/63/81 but CDVs were mean 10-fold less fluorescent than corresponding EVs. Bilayer membrane-coated EVs and CDVs of appropriate size were readily detected by cryoTEM in a frequency corresponding to input concentration.
Conclusions: Testing additional extrusion parameters will be necessary to improve reference nano-particle production.

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SHIFT 02-101

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

DISTINCT PATHWAYS LINKING HYPOSMIA AND DYSAUTONOMIA TO COGNITIVE IMPAIRMENT IN PARKINSON'S DISEASE

Yeeun Sun[1], Han Kyu Na[1], Chan Wook Park[1], Jung Hyun Lee[1], Young H. Sohn[1], Chul Hyoung Lyoo[2], Phil Hyu Lee[1]
[1]Yonsei University College of Medicine/Severance Hospital, Neurology, Seoul, Korea, Republic of, [2]Gangnam Severance Hospital, Yonsei University College of Medicine, Department Of Neurology, Seoul, Korea, Republic of

Aims: Olfactory and autonomic dysfunction are common non-motor symptoms in Parkinson's disease (PD). Although both hyposmia and dysautonomia are known to exert effect on cognition, the underlying pathophysiology remains controversial. We evaluated the potential contribution of hyposmia/dysautonomia to cognition, and further investigated whether their associations are mediated by differential gray matter atrophy
Methods: This retrospective study included 207 newly diagnosed PD patients who underwent autonomic function test, cross-cultural smell identification test (CC-SIT), neuropsychological battery, 3-dimensional T1-weighted magnetic resonance imaging, and dopamine transporter imaging at the point of diagnosis. Neural correlates of olfactory and autonomic dysfunction were investigated based on correlation analyses (CC-SIT score and regional gray matter volume [GMV] for hyposmia; composite autonomic scoring scale [CASS] score and regional GMV for dysautonomia), and we further investigated their association with composite score of each cognitive domain.
Results: Lower CC-SIT score revealed significant association with reduced GMV in the prefrontal cortex and limbic regions (amygdala, hippocampus, and anterior cingulate cortex), and worse cognitive performance in the memory and frontal/executive domain. Meanwhile, higher CASS score showed significant correlation more prominent and broader gray matter atrophy, including the frontotemporoparietal cortices, caudate nucleus, putamen, and throughout the limbic regions, and worse cognitive dysfunction in attention, visuospatial, and frontal/executive domains. Mediation analysis revealed that the association between olfactory and cognitive dysfunction were partially mediated by amygdala atrophy. Meanwhile, the association between CASS score and cognitive deficit (attention and frontal/executive domain) were fully mediated by cortical GMV.
Conclusions: Our findings suggest that olfactory and autonomic dysfunction may contribute to cognitive impairment through distinct pathways: the olfactory pathway may lead to subcortical atrophy and subsequent cognitive deficits, whereas autonomic dysfunction may influence cognition via cortical atrophy.

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SHIFT 02-102

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

DEVELOPMENT AND IN VITRO CHARACTERIZATION OF [3H]GMC-058 AS RADIOLIGAND FOR IMAGING PARKINSONIAN-RELATED PROTEINOPATHIES

Andrea Varrone[1], Vasco Sousa[1], Manolo Mugnaini[2], Sandra Biesinger[2], Gunnar Nordvall[3], Dan Sunnemark[4], Charles Elmore[5], Lee Kingston[5], Ileana Guzzetti[6], Sjoerd Finnema[7], Magnus Schou[8]
[1]Karolinska Institutet, Department Of Clinical Neuroscience, Solna, Sweden, [2]AbbVie, Molecular & Imaging Biomarkers, Abbvie Deutschland Gmbh & Co. Kg, Ludwigshafen, Germany, [3]AlzeCure Pharma, Huddinge, Sweden, [4]Offspring Biosciences AB, Södertälje, Sweden, [5]AstraZeneca, Pharmaceutical Science, Mölndal, Sweden, [6]AstraZeneca, Medicinal Chemistry, Ria, Biosciences R&d, Gothenburg, Sweden, [7]AbbVie, Neuroscience, Translational Imaging, North Chicago, United States of America, [8]AstraZeneca, Precision Medicine Diagnostic Development And Hbs Science, Solna, Sweden

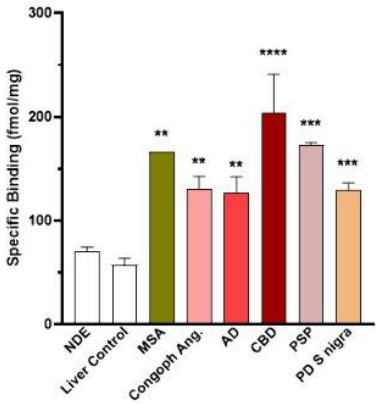
Aims: Molecular imaging of α-synuclein (α-syn) pathology in Parkinson's disease (PD) and related movement disorders is a clinical unmet need. The aim of this study was to develop and characterize in vitro a radioligand for imaging α-syn pathology.
Methods: A library of 78 small molecules was developed and screened using recombinant α-syn fibrils and brain homogenates from Alzheimer´s disease (AD) donors. Selection criteria were: $K_{i\,\alpha\text{-syn}}$ <30 nM, $K_{i\,tau}$ and $K_{i\,A\beta}$ >200 nM. Three compounds, GMC-073 ($K_{i\,\alpha\text{-syn}}$: 8 nM), GMC-098 ($K_{i\,\alpha\text{-syn}}$: 9.7 nM), and GMC-058 ($K_{i\,\alpha\text{-syn}}$: 22.5 nM) fulfilled the criteria and were radiolabelled with ^{3}H for autoradiography (Table 1).

Table 1

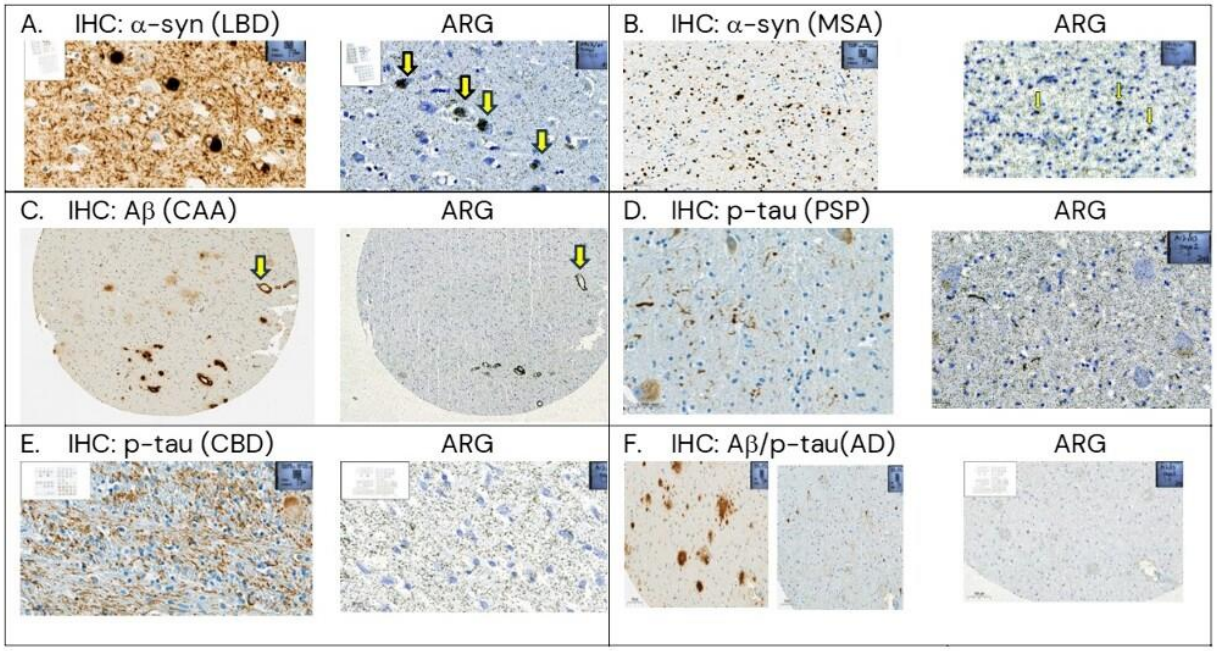
Name	Molecular weight	XLogP	α-syn (K_i, nM)	Aβ (K_i, nM)	Tau-NFT (K_i, nM)
GMC-058	367,5	3,49	22,5	1490	1320
GMC-073	445,5	3,37	8,0	2630	248
GMC-098	442,5	4,13	9,7	226	805

Results: [^{3}H]GMC-058 was the only compound with negligible displaceable binding in controls and was

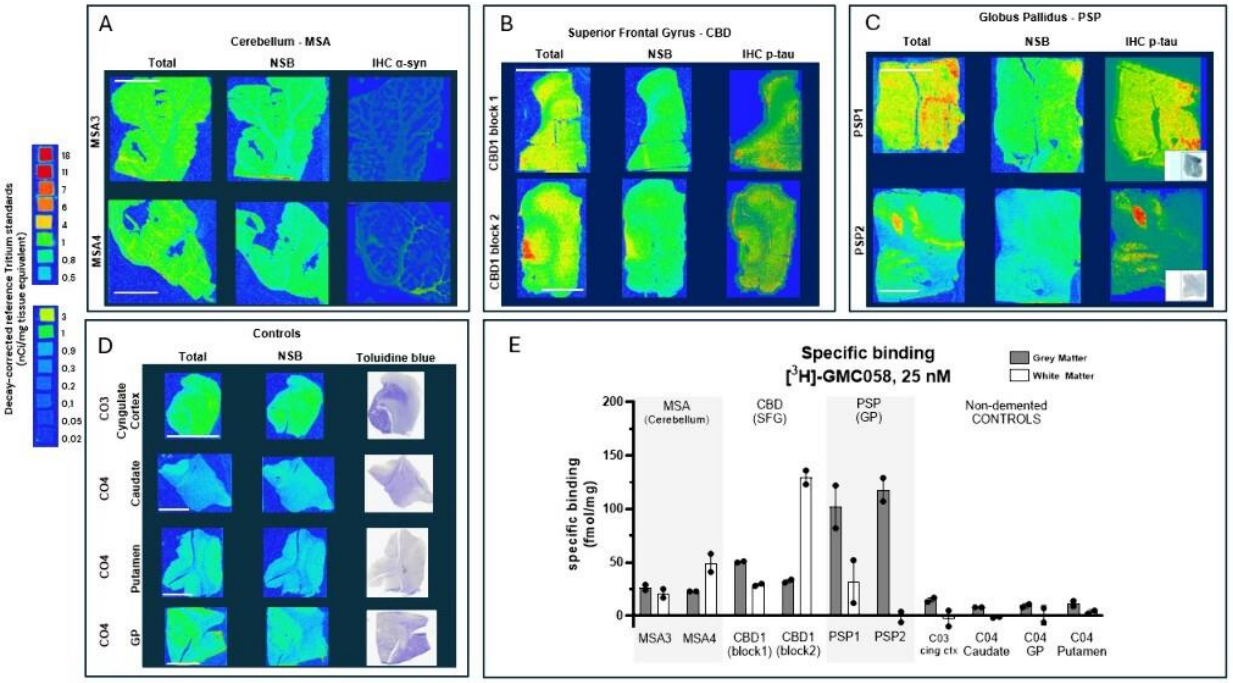
further evaluated using tissue microarrays. Specific binding of [^{3}H]GMC-058 in PD and multiple system atrophy (MSA) was higher than in controls, but was also detected in cerebral amyloid angiopathy (CAA), AD, progressive supranuclear palsy (PSP) and cortico-basal degeneration (CBD) (Figure



1). [^{3}H]GMC-058 binding co-localised with α-syn inclusions in PD and MSA, with dense Aβ plaques in CAA and AD, and with p-tau inclusions in PSP and CBD (Figure



2). Autoradiography studies using fresh-frozen tissue showed specific binding in MSA cases, as well as cases with CBD and



PSP (Figure 3).

Conclusions: [^{3}H]GMC-058 is a novel radioligand displaying moderate affinity for aggregated α-syn, with an in vitro profile also suitable for detecting tau pathology in 4R tauopathies.

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SHIFT 02-103

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

CHARACTERISATION OF PROTEIN AGGREGATES WITH SURFACE-BASED SINGLE-MOLECULE FLUORESCENT IMAGING

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[1]University of Cambridge, Yusuf Hamied Department Of Chemistry, Cambridge, United Kingdom, [2]University of Cambridge, Department Of Chemistry, Cambridge, United Kingdom

Aims: The biophysical properties of protein aggregates are strongly linked to neurodegenerative diseases. Characterising these aggregates with advanced analytical techniques can shed light on their pathological roles, and help the further development of more effective diagnostics and therapeutics.
Methods: We designed a chemically modified surface to selectively capture and image protein aggregates from complex human samples. This modification, utilising household chemicals (Rain-X), provides a simple yet robust approach to integrating single-molecule microscopy, allowing for precise mapping and analysis of protein aggregates. It achieves up to 100-fold less nonspecific binding from protein aggregates compared to commonly used polyethylene glycol (PEG) surfaces.
Results: Our platform was applied to multiple biofluids (human serum, saliva, cerebrospinal fluid) to identify and characterise different biomarkers related to neurodegenerative diseases, including alpha-synuclein, abeta and ASC speck. Super-resolution imaging of the aggregates revealed detailed morphological features, offering an additional metric for quantifying and assessing protein aggregates.
Conclusions: This versatile platform enables the characterisation of protein aggregates across various sample types, providing a powerful tool for the precise mapping of their biophysical properties, and contributing to our understanding of their role in neurodegenerative disease pathology.

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SHIFT 02-107

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
4-5 April 2025

CORRELATIONS BETWEEN CSF BIOMARKERS OF NEUROINFLAMMATION AND SYNAPTIC DYSFUNCTION, NEUROMELANIN AND [18F] DOPA-PET IN PARKINSON'S DISEASE.

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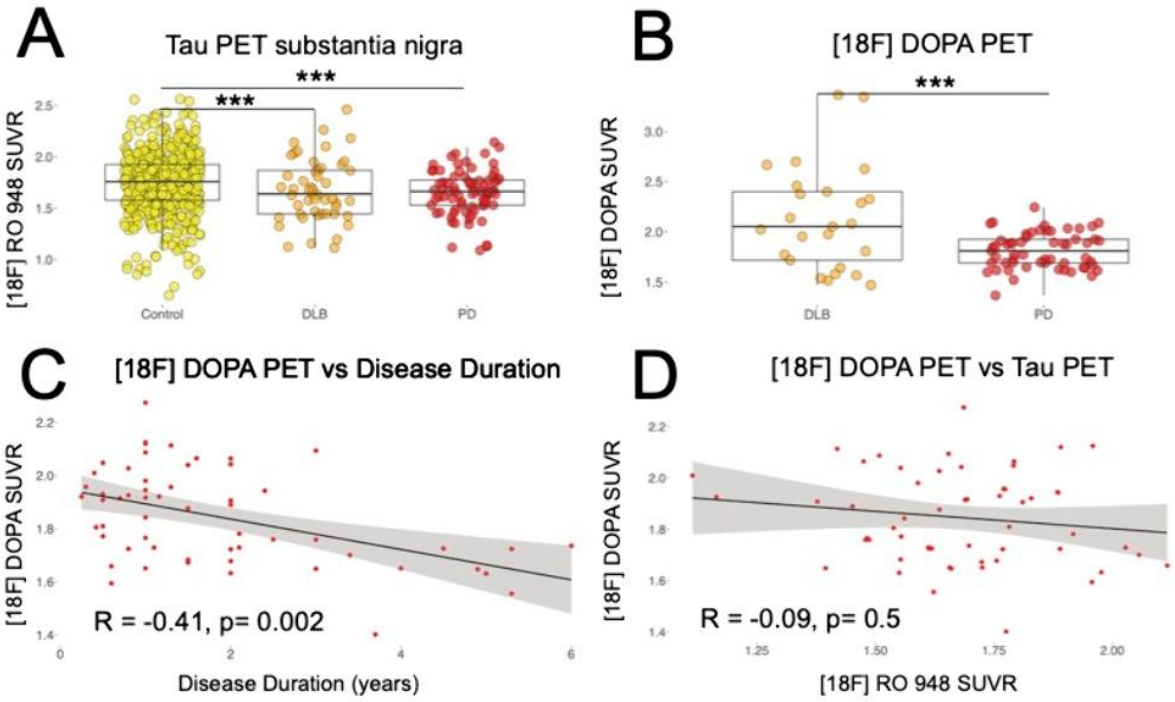
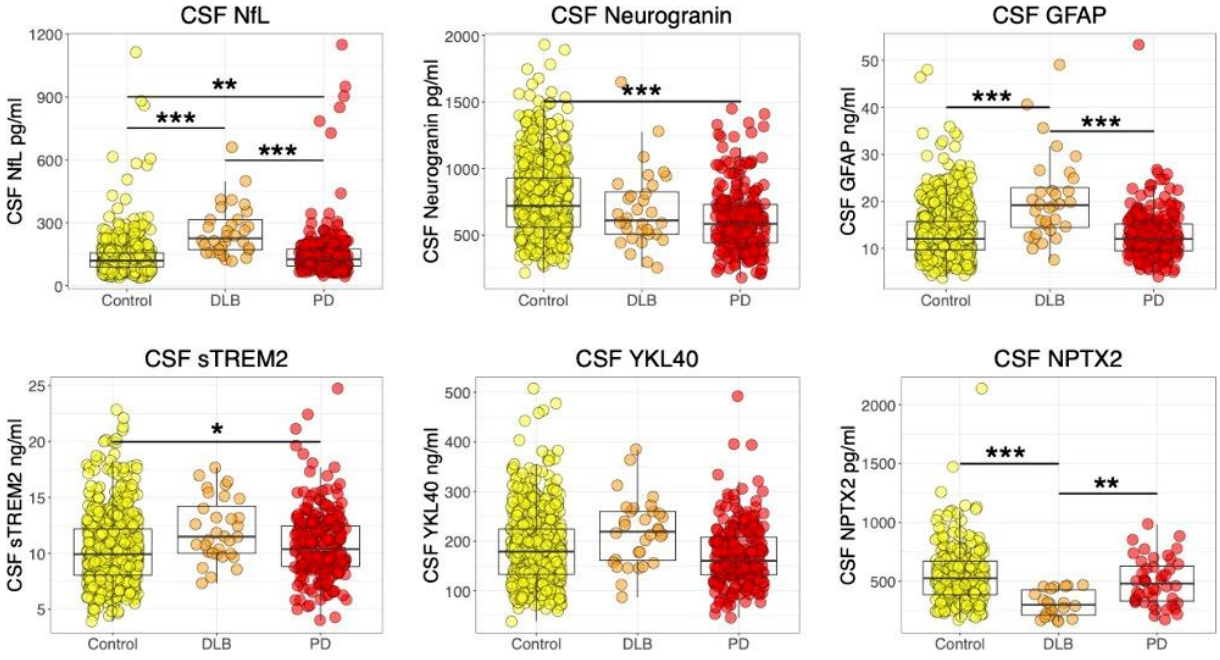
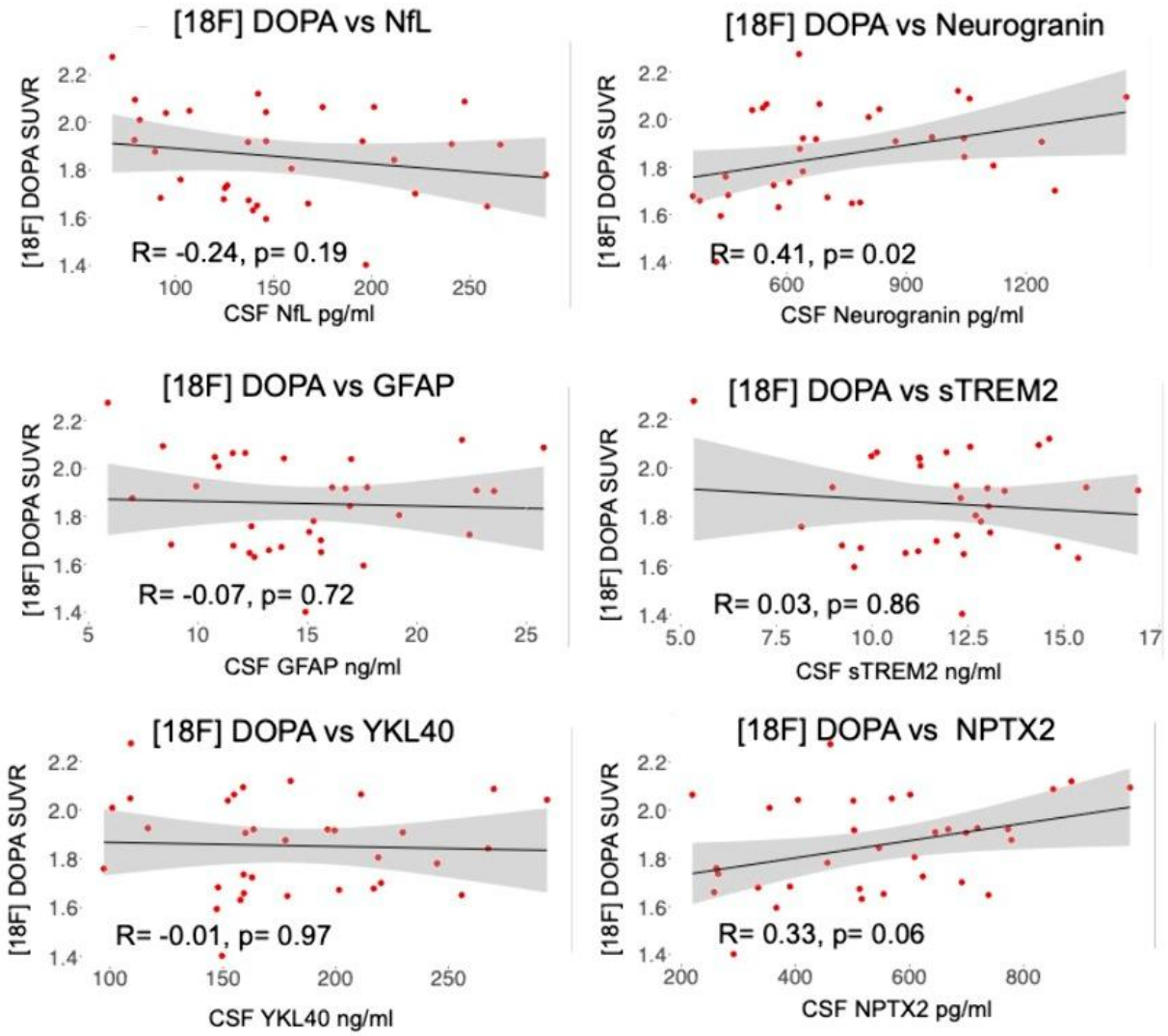
[1]Lund University, Department Of Clinical Sciences Malmö, Clinical Memory Research Unit, Lund, Sweden, [2]Skåne University Hospital, Memory Clinic, Malmö, Malmö, Sweden

Aims: To investigate the association of disease duration, CSF markers of synaptic dysfunction and neuroinflammation with dopamine cell loss as measured by [^{18}F]DOPA PET in patients with PD. We further explore whether the dopamine cell loss in the putamen was reflected in a reduction in off-target retention of [^{18}F]RO948.
Methods: Participants were part of the BioFINDER studies, including BioFINDER-1 and BioFINDER-2 cohorts. From BioFINDER-2 cohort 514 healthy controls, 77 PD and 50 Dementia with Lewy bodies (DLB) were included. All underwent [^{18}F]RO948 PET and 57 PD and 25 DLB underwent [^{18}F]DOPA PET. CSF biomarkers were available for 619 healthy participants, 224 PD and 32 DLB patients from BioFINDER-1 and 2.
Results: CSF neurofilament light (NfL) levels were higher in PD (pg/mL 158±139) compared to controls (137±90, p=0.002), whileCSF neurogranin was lower in PD (pg/mL 622±252) compared to controls (773±285, p<0.001). [^{18}F]DOPA uptake correlated negatively with disease duration (-0.41, p=0.002) and positively with neurogranin levels (R= 0.41, p=0.02). We found no correlations between markers of neuroinflammation, NfL and [^{18}F]DOPA PET. [^{18}F]RO948 PET SUVRs in the substantia nigra were lower in PD ([mean±SD] 1.68±0.22) compared to controls (1.76±0.3, p<0.001). However, no correlation was found between [^{18}F]DOPA-PET in the caudal putamen and [^{18}F]RO948 PET in substantia nigra.


A
Tau PET substantia nigra
[18F] RO 948 SUVR
Control
DLB
PD
B
[18F] DOPA PET
[18F] DOPA SUVR
C
[18F] DOPA PET vs Disease Duration
R = -0.41, p= 0.002
Disease Duration (years)
D
[18F] DOPA PET vs Tau PET
R = -0.09, p= 0.5
[18F] RO 948 SUVR


CSF NfL
CSF NfL pg/ml
CSF Neurogranin
CSF Neurogranin pg/ml
CSF GFAP
CSF GFAP ng/ml
CSF sTREM2
CSF sTREM2 ng/ml
CSF YKL40
CSF YKL40 ng/ml
CSF NPTX2
CSF NPTX2 pg/ml
Control
DLB
PD



Conclusions: [^{18}F]DOPA-PET retention is associated with disease duration as well as to decreased CSF synaptic markers in PD but not with inflammatory markers. Although midbrain tau PET off-target retention is lower in PD patients compared to controls it does not correlate to [^{18}F]DOPA-PET signal.

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SHIFT 02-108

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
4-5 April 2025

SUBCORTICAL NEUROINFLAMMATION IS ASSOCIATED WITH INCREASED DEMENTIA RISK IN PARKINSON'S DISEASE: LONGITUDINAL FINDINGS FROM THE NET-PDD STUDY.

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Aims: Aims: 50% of patients with Parkinson's disease (PD) develop PD-related dementia (PDD) within 10 years post-diagnosis but the underlying neurobiological determinants of dementia risk are not well understood. This study aims to assess the contribution of neuroinflammation and tau aggregation to dementia development using PET neuroimaging.
Methods: Methods: Our ongoing longitudinal study, 'NEuroinflammation and Tau accumulation in Parkinson's Disease Dementia' (NET-PDD) has assessed newly-diagnosed PD patients in subgroups of high- (n=11) and low-risk (n=13) of dementia (stratified via pentagon copying, semantic fluency, MAPT genotype) versus age-/sex-matched controls (n=14). We measured neuroinflammation and tau accumulation using PET-MR neuroimaging with [^{11}C]-PK11195 and [^{18}F]-AV1451 ligands at baseline and 3-year follow-up. Longitudinal changes in non-displaceable binding potential (BP_{ND}) across 43 bilateral regions of interest (Hammers' parcellation) were compared between groups.
Results: Results: High-risk patients demonstrated significantly higher [^{11}C]-PK11195 BP_{ND} in brainstem regions at baseline and follow-up, and a greater increase in binding over time versus low-risk patients and controls. Additionally at follow-up, high-risk patients demonstrated significantly higher [^{11}C]-PK11195 BP_{ND} in the thalamus, striatum, and amygdala versus low-risk patients. In contrast, there were no differences in [^{18}F]-AV1451 BP_{ND} between high-risk patients and low risk patients or controls at either timepoint, and no difference in change in [^{18}F]-AV1451 binding over time between high-risk and low-risk patients. Whole brain [^{11}C]-PK11195 binding significantly correlated with whole brain [^{18}F]-AV1451 binding in low-risk and high-risk patients at baseline and follow-up but not with longitudinal changes.
Conclusions: Conclusions: Our findings suggest increased regional subcortical and brainstem neuroinflammation in early PD relates to higher PDD risk but tau accumulation is less clearly related to PDD risk. This neuroinflammatory process may be an early modifiable target to prevent or slow developing dementia.

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SHIFT 02-109

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET
4-5 April 2025

ASSOCIATION BETWEEN CEREBRAL GLUCOSE METABOLISM AND AMYLOID DEPOSITION IN PARKINSON'S DISEASE

Yeeun Sun[1], Han Kyu Na[1], Jung Hyun Lee[1], Chan Wook Park[1], Young H. Sohn[1], Chul Hyoung Lyoo[2], Phil Hyu Lee[1]
[1]Yonsei University College of Medicine/Severance Hospital, Neurology, Seoul, Korea, Republic of, [2]Gangnam Severance Hospital, Yonsei University College of Medicine, Department Of Neurology, Seoul, Korea, Republic of

Aims: Although Parkinson's disease (PD) is primarily characterized by intraneuronal α-synucleinopathy, emerging evidence suggests that it often coexists with other pathological features, particularly amyloid pathology. The presence of concomitant amyloid pathology in Parkinson's disease has been associated with a poorer prognosis, characterized by accelerated cognitive decline and reduced survival. Nevertheless, there is scant evidence elucidating the influence of amyloid pathology on cerebral glucose metabolism in patients with PD.
Methods: In this retrospective cross-sectional observational study, we included 39 patients with PD (dementia, n = 24; non-demented, n = 15) and 25 healthy controls who underwent both 18F-Fluorodeoxyglucose (18F-FDG) and 18F-Florbetaben (18F-FBB) positron emission topography (PET). Regional 18F-FDG uptake were compared across amyloid-positive (Aβ+) PD, amyloid-negative (Aβ-) PD, and Aβ- CU subjects. Furthermore, partial correlation analyses were employed to investigate the association between regional 18F-FDG uptake and global and regional 18F-FBB uptake within PD patients using age, sex, education years, and disease duration as covariates.
Results: Compared to healthy controls, PD patients revealed hypometabolism in the prefrontal, temporal, parieto-occipital regions regardless of amyloid status. Within patients with PD, Aβ+ group exhibited more severe glucose hypometabolism in anterior cingulate cortex, caudate, amygdala, and nucleus accumbens compared to Aβ- PD group. While global 18F-FBB uptake showed significant negative correlation with 18F-FDG uptake amygdala (rho = -0.492, P = 0.003), caudate (rho = -0.350, 0.043), insular (rho = -0.357, P = 0.038) and anterior cingulate cortex (rho = -0.360, P = 0.037) in a dose-dependent manner, significant intra-regional relationships between 18F-FBB and 18F-FDG was observed in the anterior cingulate cortex only (rho = -0.330, P = 0.049).
Conclusions: Our findings suggest that cerebral amyloidosis may contribute to altered patterns of the regional cerebral glucose metabolism in patients with PD.

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SHIFT 02-110

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

NOVEL ULTRA-SENSITIVE SIMOA DIGITAL IMMUNOASSAY FOR DETECTION OF PSD-95 IN HUMAN PLASMA, SERUM AND CSF

Kishore Malyavantham, Shubhankar Nath, Hana Na, Nikita Kulkarni, Raymond Fernalld, Briana Cooper
Quanterix, Billerica, United States of America

Aims: The postsynaptic density (PSD) is a massive protein complex, critical for synaptic strength and plasticity in excitatory neurons. PSD-95 (postsynaptic density protein 95) is a membrane-associated guanylate kinase (MAGUK) scaffolding protein encoded by the DLG4 gene and is associated with excitatory synapses. Recent studies present PSD-95 as an emerging biomarker in Alzheimer's disease (AD), levels of which correlate with neuronal loss, cognitive decline, and other measures of synaptic plasticity.
Methods: The assay is a two-step digital sandwich immunoassay employing paramagnetic beads with capture antibodies and biotinylated detector antibodies. Digital detection is mediated by Streptavidin-ß-galactosidase (SβG) and Resorufin-β-D-Galactopyranoside (RGP), amplifying specific PSD-95 immune complexes immobilized on the bead surface of fluorescently coded beads.
Results: PSD-95 was quantifiable in all the tested blood samples and CSF. The limit of detection was 0.35 pg/mL. Normal CSF and plasma demonstrated a range of 50 – 1850 pg/mL (mean 190 pg/mL) and 10-100 pg/ml (mean 25 pg/ml), respectively. Mean dilution linearity of plasma, serum and CSF was within 80-120%. Spike recovery using recombinant antigen averaged 60-80%, suggesting a matrix-effect.
Conclusions: The Simoa PSD-95 Advantage PLUS assay enables highly sensitive detection across plasma, serum, CSF offering a less invasive alternative to CSF sampling for longitudinal studies. Measuring PSD-95 in blood supports early diagnosis and monitoring of neurodegenerative diseases like Alzheimer's and Parkinson's by reflecting synaptic dysfunction. This assay aids drug development, pre/clinical research by enabling the evaluation of therapies targeting synaptic health, and further understanding of disease progression.

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SHIFT 02-111

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

AN ULTRA-SENSITIVE DIGITAL IMMUNOASSAY (SIMOA) FOR PARKINSON'S DISEASE BIOMARKERS: TOTAL AND PHOSPHO (SER-129) ALPHA-SYNUCLEIN

Kishore Malyavantham, Shubhankar Nath, Raymond Fernalld, Mingwei Zhao
Quanterix, Billerica, United States of America

Aims: Alpha-synuclein is a key protein involved in synaptic function and is heavily implicated in Parkinson's Disease (PD), characterized by motor dysfunctions like tremor and rigidity. In PD, alpha-synuclein misfolds and aggregates into Lewy bodies (LBs). Notably, ~90% of alpha-synuclein in LBs is phosphorylated at serine 129 (pS129), whereas in healthy brains, pS129 is minimal. Measuring both total and pS129 forms provides insights into disease mechanisms further aiding in understanding pathology and assessment of therapeutic targets.
Methods: A two-step Simoa digital sandwich immunoassays were developed to quantify total and pSer129 alpha-synuclein in EDTA-plasma and CSF. The assay uses paramagnetic beads with capture antibodies and biotinylated detectors, followed by Streptavidin-ß-galactosidase-mediated digital detection for signal amplification.
Results: Both assays demonstrated high sensitivity with LoDs of 1.18 pg/mL (total) and 0.03 pg/mL (pS129) and LLoQs of 3.29 pg/mL (total) and 0.77 pg/mL (pS129). In healthy subjects, plasma levels averaged 4236 pg/mL (total) and 126 pg/mL (pS129), while CSF levels were 786 pg/mL (total) and 60 pg/mL (pS129). Intra- and inter-assay %CVs were <10% and <20%, respectively.
Conclusions: The ultrasensitive Simoa assays enable precise detection of total and pS129-alpha-synuclein in blood, reducing the reliance on invasive CSF sampling and offering a potential complement to seeding assays. With minimally invasive plasma samples, these assays support patient stratification, monitoring of disease progression, and tracking of therapeutic responses in clinical trials, providing a powerful tool for advancing understanding of PD pathology.

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SHIFT 02-112

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

THE MICHAEL J. FOX FOUNDATION'S EFFORTS TO DEVELOP SPECIALIZED ALPHA-SYNUCLEIN MONOMERIC PROTEIN FOR THE ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY

Nicole Polinski[1], Richard Mott[2], Anna Valentine[2], Graham Fairfoul[3], Marcelo Barria Matus[3], Alison Green[3], Christina D Orru[4], Byron Caughey[4], Jonathan Jones[5], Panos Kopsiaftis[5], Matthew Biggs[5], Robert Cleverley[5], Zoe Arnott[5], Elisia Clark[1], Gloria Thakuria[1], Jaime Eberling[1]
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Aims: The emergence of assays to detect aggregated alpha-synuclein (aSyn) using the aSyn seed amplification assay (aSyn SAA) is leading to breakthroughs in the ability to biologically diagnose Parkinson's disease (PD) and stratify patients for clinical trials testing aSyn-targeted therapeutics. In this assay, large volumes of recombinant monomeric aSyn protein are spiked with biosamples from patients with suspected synucleinopathies. Through rounds of elongation and fragmentation, aggregated aSyn seed in the biosample templates the monomeric aSyn substrate to amplify the presence of aggregates for detection using beta-sheet dyes. Sourcing the required quantities of the aSyn substrate protein that aggregates in the presence of the seed without spontaneous aggregation is challenging. To address this issue, we sought to produce and distribute large quantities of aSyn monomeric protein validated for use in the aSyn SAA method.
Methods: Working with protein manufacturers and experts in aSyn SAA, we systematically optimized methods for multi-gram production of recombinant monomeric wildtype human aSyn that has confirmed compatibility in different aSyn SAA setups.
Results: We have developed a robust method for generating aSyn SAA-compatible monomeric aSyn protein. The material does not exhibit spontaneous aggregation when seeded with brain homogenate or CSF from healthy individuals yet aggregates to generate a positive signal in the presence of brain homogenate or CSF from patients with synucleinopathies.
Conclusions: SAA-compatible aSyn monomeric protein has historically been difficult to source and produce given the large volumes required and specific performance properties needed. We have successfully developed a reliable method for generating large quantities of SAA-compatible wildtype human aSyn protein. We will make this material available to the research community to improve standardization of the SAA assay and further democratize the method.

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SHIFT 02-113

Poster on Board - Shift 02
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4-5 April 2025

CONCORDANCE OF NEUROPATHOLOGIC DIAGNOSIS OF LEWY BODY DISEASE WITH BASELINE ALPHA-SYNUCLEIN SEED AMPLIFICATION ASSAY IN PPMI

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Aims: To determine whether the alpha-synuclein seed amplification assay (aSyn-SAA) performed on cerebral spinal fluid (CSF) collected at the baseline (BL) PPMI visit is concordant with the detection of Lewy body disease (LBD) pathology at autopsy.
Methods: Since 2017, the Parkinson's Progression Markers Initiative (PPMI) study has coordinated brain collections for enrolled participants, with 24 brain autopsy results available as of February 2024. Neuropathologic evaluation followed current consensus guidelines for LBD, glial cytoplasmic inclusions (GCI), Alzheimer's disease neuropathologic change, hippocampal sclerosis, vascular brain injury, primary age-related tauopathy, limbic-predominant age-related TDP-43 encephalopathy, age-related tau astrogliopathy, and chronic traumatic encephalopathy.
Results: aSyn-SAA results were available for 20 participants with brain autopsy, including 19 enrolled in the PD cohort and one enrolled in the prodromal cohort with REM Sleep Behavior Disorder (RBD). Of the 12 with a BL sporadic PD diagnosis, 11 had aSyn-SAA detected on BL CSF; all of whom had LBD at autopsy. Of the PD GBA carriers, all 4 had aSyn-SAA detected on BL CSF; all of whom had LBD at autopsy. Of the 3 PD LRRK2 carriers, 2 had aSyn-SAA detected on BL CSF, both of whom had LBD at autopsy. One LRRK2 PD was aSyn-SAA not detected on BL CSF and at autopsy showed no LBD. One participant enrolled as sporadic PD had aSyn-SAA not detected at BL, who showed GCI at autopsy with no LBD. Finally, the one participant

enrolled as RBD had aSyn-SAA detected at BL, 6-, 12-, 24-, 36-, and 48- months and was diagnosed with dementia with Lewy bodies 36 months after BL; autopsy showed LBD.

Conclusions: In the PPMI cohort, aSyn-SAA detected/not-detected at enrollment was 100% concordant with the presence/absence of LBD at autopsy.

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Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

AUTOANTIBODIES AS POTENTIAL NOVEL BIOMARKERS TO PREDICT PARKINSON'S DISEASE PROGRESSION

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Aims: Parkinson's Disease (PD) is a heterogenous disorder with an incompletely understood etiology and pathogenesis. Improved understanding of molecular heterogeneity underlying clinical features and disease course would allow earlier and more individualized intervention. Given recent evidence supporting the unique utility of antibodies as early predictive markers in PD; we utilized longitudinal plasma samples obtained from Parkinson's Progression Markers Initiative (PPMI) through the Accelerating Medicine Partnership® (AMP®) Parkinson's Disease (AMP PD), to identify potential autoantibody signatures predictive of disease progression.
Methods: Rate of disease progression was calculated by measuring the slope of change of the MDS-UPDRS scores (I-III) between baseline and last visit (12-36 months), and subjects were arbitrarily separated between Fast progressors (n=20; slope >0.25) vs Slow progressors (n=14, slope <0.25). Autoantibody profiles (IgA and IgG) were generated using KREX® technology (Sengenics) on 3 longitudinal plasma samples from PD subjects, and 2 longitudinal samples (baseline and 36 months) from healthy controls (n=14).
Results: At a false discovery rate (FDR) of 10%, baseline levels of Upstream Transcription Factor 1 (USF1) IgA and IgG were significantly associated with rate of progression (log2FC=0.25/0.29 (IgA/IgG)), and trajectories of USF1 IgA and IgG levels over 36 months also differed between groups. Finally, levels of IgG and IgA were evaluated in relation to MDS-UPDRS scores part I (non-motor activities of daily living) and II (motor activities of daily living), and only one IgG, TIE 1 (tyrosine kinase with immunoglobulin like and EGF like domains 1), was significantly associated with MDS-UPDRS part I (log2FC=0.03).
Conclusions: These preliminary findings revealed potentially promising novel biomarkers to predict clinical progression in PD but need to be replicated in a larger independent cohort.

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SHIFT 02-115

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

A-SYNUCLEIN SAA IN PD AND ATYPICAL PARKINSONISM: COMPARISON OF TWO ASSAYS DIFFERING FOR THE CAPACITY TO AMPLIFY A-SYNUCLEIN IN MSA.

Marcello Rossi[1], Carly Farris[2], Franco Magliocchetti[1], Giulia Giannini[1,3], Simone Baiardi[1,3], Yihua Ma[2], Claudia M. Vargiu[1], Pietro Cortelli[1,3], Giovanna Calandra-Buonaura[1,3], Luis Concha[2], Piero Parchi[1,3]
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Aims: To compare the performance between a novel seed amplification assay (SAA) for misfolded α-synuclein (syn) developed by Amprion and an in-house SAA (ISNB syn SAA), using a single-centre cohort of well-characterized patients.
Methods: We applied the two CSF SAAs to 119 MSA, 39 PSP and 49 PD patients, and 50 controls (CTRLs) aged < 50. The Amprion SAA produces two outcomes for SAA+ cases based on the type of detected syn seeds; Type 1 seeds are predominantly found in Lewy body disease (LBD), and Type 2 seeds are predominantly found in MSA. ISNB-SAA detects LBD seeds only.
Results: With the Amprion SAA, 106 (89.1%) MSA cases were synSAA+ [100 (92.6%) Type 2; 5 (4.6%) Type 1; 1 (0.9%) undetermined] and 13 (10.9%) were synSAA-. 44 (897.7%) PD cases were synSAA+ [39 (87%) Type 1; 3 (7%) Type 2]; 2 (4.1%) undetermined], 4 (8%) were synSAA- and 1 inconclusive. 2 (5.3%) PSP cases and 7 (14%) CTRLs were synSAA+ [1 (9%) Type 1 and 8 (89%) Type 2]. The calculated sensitivity for the Type 2 profile in MSA was 84.0%, with a 97.5% specificity against PSP and 86% against CTRLs. The sensitivity for the Type 1 profile in PD was 79.6%, with 95.8% specificity against MSA, 97.5% against PSP and 100% against CTRLs. The ISNB-SAA showed LBD-specific syn seeding activity in 39 (79.6%) PD, 3 (2.5%) MSA, and none of the PSP or CTRL samples. The sensitivity for LBD was 79.6%, with 97.5% specificity against MSA and 100% specificity against both PSP and CTRLs.
Conclusions: Amprion-SAA, performed at ISNB, showed a lower specificity than ISNB-SAA, but it uniquely discriminated MSA from both PD and PSP with good accuracy.

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

NON-INVASIVE ANALYSIS OF PERIPHERAL BIOMARKERS FOR EARLY DIAGNOSIS OF ALPHA-SYNUCLEINOPATHIES

Alice Russotto[1], Arianna Ciullini[2], Antonio Longobardi[1], Merve Bacinoglu[3], Rachele Domina[3], Federico Cazzaniga[3], Fabio Moda[2,4], Roberta Ghidoni[1], Claudia Saraceno[1]
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Aims: Clinical diagnosis of Parkinson's disease (PD), multiple system atrophy (MSA) and dementia with Lewy bodies (DLB) is challenging, particularly in the early stages, due to the presence of overlapping symptoms. The goal of this study is to establish a panel of biomarkers for PD, MSA, and DLB using innovative and non-invasive methods. Specifically, we aim to explore the peripheral distribution of disease-associated alpha-synuclein and investigate novel molecules implicated in these neurodegenerative diseases.
Methods: Patients with PD, MSA, DLB, other neurodegenerative diseases (OND), and healthy subjects (HS) underwent olfactory mucosa (OM), urine and blood sampling. A combination of assays was performed: ultrasensitive Single Molecule Array (SIMOA) to detect neurofilament light chain (NfL), phosphorylated tau (p-Tau-181, p-Tau-231), ELISA to evaluate alpha-synuclein and synapsin-3 levels, and Nanoparticle Tracking Analysis (NTA) to characterize extracellular vesicles (EVs) in urine and blood.
Results: Our preliminary results revealed by SIMOA a significant increase in plasma levels of NfL in MSA patients compared to PD and HS, while no significant differences were found in p-Tau-181 and p-Tau-231 levels. Plasma alpha-synuclein levels were similar across all groups, instead in PD and MSA urine samples have shown a trend to increase than other groups. The characterization of b-EVs by NTA has revealed an increase of the concentration (particles/mL) and ratio (conc/size) in neurodegenerative groups compared with HS. The other analyses are still ongoing.
Conclusions: Our preliminary findings highlight the potential of OM, blood and urine as rich sources of biomarkers that can be easily and periodically collected. These biomarkers may significantly contribute to the clinical understanding and diagnosis of PD, MSA, and DLB, offering a promising direction for non-invasive diagnostic strategies in neurodegenerative diseases.

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α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

EXTRACELLULAR VESICLES AS BIOMARKERS FOR PARKINSON'S DISEASE

Antri Stefani[1], Martin Wolf[1], Nicole Maeding[1], Rodolphe Poupardin[1], Dieter Volc[2], Sabine Schmidhuber[3], Markus Mandler[3], Dirk Strunk[1,4]
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Aims: Extracellular vesicles (EVs) are key players in cell-to-cell communication in health and disease. Their presence in most tissues and body fluids makes them excellent targets for biomarker discovery. We aim to develop an EV-based biomarker assay that will serve as a tool for vaccine response monitoring in Parkinson's disease (PD) patients. We selected PD-driving alpha-synuclein (aSyn) and unsupervised omics as diagnostic targets.
Methods: Tangential flow filtration (TFF), size exclusion chromatography (SEC) and ultracentrifugation were applied to enrich EVs from PD patient's urine and blood. We determined EV quantity by tunable resistive pulse sensing (TRPS), and EV quality by tetraspanin + aSyn biomarker expression in enhanced chemiluminescence dot blots, super-resolution microscopy, and enzyme-linked immunosorbent assay (ELISA). Subtractive biomarker discovery by multi-omics will be performed in addition. The level of EV-aSyn in patient samples were compared with respective healthy controls (n = 20 each).
Results: Various isolation methods resulted in different EV enrichment levels and separation from protein and lipoprotein. We confirmed EV identity and enrichment by CD9/63/81 dot blots and super-resolution microscopy in all preparations. Highest aSyn signals were acquired in patient EV samples isolated by ultracentrifugation compared to SEC for blood samples and TFF for creatinine-normalized urine samples. Preliminary experiments confirmed the presence of aggregated aSyn in patient EVs by ELISA. Variable aSyn signals were acquired in bulk liquid biopsy material, different SEC fractions and EV enriched preparations. Preliminary proteomics data are currently subjected to detailed bioinformatics analysis.
Conclusions: New theranostic biomarkers from easily accessible non-invasive sources are important for patient acceptance and study performance. Once established the biomarker will be validated as diagnostic tool for monitoring vaccine response.

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Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / SKIN, CSF-, AND BLOOD-BASED BIOMARKERS
4-5 April 2025

PATHOLOGICAL AND CLINICAL VALIDATION OF PLASMA ALZHEIMER'S BIOMARKERS IN PARKINSON'S DISEASE

Thomas Tropea[1], Patricia Stevenson[2], Matthew Flitter[2], David Meehan[2], Amanda Morris[2], Ming Lu[2], Leonardo Iaccarino[2], Emily Collins[2], Michael Hodsdon[2], Leslie Shaw[1], Edward B. Lee[1], Daniel Weintraub[3], Andrew Siderowf[1], Mark Mintun[2], Alice Chen-Plotkin[1]
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Aims: Alzheimer's Disease (AD) pathology commonly co-occurs in the brains of people with Lewy body disorders, including Parkinson's disease (PD) and dementia with Lewy bodies (DLB) and associates with worse cognitive and motor dysfunction. Recently-developed blood-based biomarkers can accurately detect amyloid and tau pathology in AD populations, but further validation is necessary in PD/DLB cohorts.
Methods: Plasma phosphorylated tau-217 (P-tau217) concentrations were measured in i) antemortem plasma samples from cases with a neuropathological diagnosis of Lewy Body pathology (N=46 PD, N=10 DLB) from the UPenn Center for Neurodegenerative Disease Research cohort; and in ii) healthy participants (N=64 samples) and patients with a clinical diagnosis of PD (N=273 samples) with available longitudinal cognitive assessments. In the clinical cohort, plasma P-tau217 was measured at baseline and, if available, at times of change in cognitive diagnosis from normal, mild cognitive impairment, or dementia.
Results: Levels of P-tau217 are greater in pathology cases with (med 0.3 [IQR 0.2-0.4]) versus without (med 0.1 [IQR 0.1-0.2]) Alzheimer's copathology. In clinical cases, at study entry, P-tau217 levels do not differ between cases with (med 0.1 [IQR 0.1-0.1]) versus without (med 0.1 [IQR 0.1-0.1]) cognitive progression, however cases with cognitive progression had greater increases in serially measured P-tau217 compared to those without cognitive progression (β=0.008, p=0.03).
Conclusions: Plasma measures of P-tau217 detect Alzheimer's copathology in PD. Ongoing work will evaluate differences in P-tau217 levels between cases of dementia due to Alzheimer's disease versus Lewy body disorders with Alzheimer's copathology.

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4-5 April 2025

LONGITUDINAL MEASUREMENTS OF CEREBROSPINAL FLUID BIOMARKERS OF ALZHEIMER'S DISEASE AND NEURONAL DAMAGE IN DEMENTIA WITH LEWY BODIES

Juliette Van Alphen[1,2], Anouk Den Braber[1,2,3], Marleen Koel-Simmelink[4], Betty Tijms[1,2], Charlotte Teunissen[1,4], Wiesje Van Der Flier[1,2,5], Afina Lemstra[1,2]
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Aims: Pathology studies report up to 80% Alzheimer's disease(AD)-copathology in Dementia with Lewy Bodies (DLB). *In vivo* cerebrospinal fluid(CSF)-studies report a lower percentage: ±50%. Little is known about the development of CSF-biomarkers in DLB. We aimed to investigate longitudinal changes in biomarkers of AD and neuronal damage in DLB versus healthy controls (HC).
Methods: We included 38 DLB-individuals (68.0±5.6y, 89.5%male, MMSE 25.9±2.3) and 48 age-matched HC (68.0±6.2y, 47.9%male, MMSE 29.1±1.1) with 2 longitudinal measures of CSF (follow-up time 2.0±0.9y). In repeated CSF-samples(*n*=172), $A\beta_{1-42}$, t-tau and p-tau_{181} were measured with Lumipulse(*n*=162), Innotest(*n*=7) and Elecsys(*n*=3). Additionally, in repeated CSF-samples(*n*=56) of the DLB-group only, neurofilament-light chain (NfL) and glial fibrillary acidic protein (GFAP) were measured with SIMOA. Paired t-tests for SIMOA-results and repeated measures ANOVAs for Lumipulse-results were performed to investigate (group/)time-differences. For all AD-biomarker-results, the change in proportion with abnormal $A\beta_{1-42}$ and p-tau_{181}/$A\beta_{1-42}$-ratio was described.
Results: CSF-$A\beta_{1-42}$ and -t-tau were significantly lower in DLB(*n*=28) versus HC (*p*<.001 and *p*=.027). CSF-$A\beta_{1-42}$ significantly declined over time in both groups (*p*<.001). The p-tau_{181}/$A\beta_{1-42}$-ratio was significantly higher in DLB versus HC (p<.001). CSF-NfL was significantly higher in DLB at follow-up (*p*=.008). For p-tau_{181} and GFAP no significant group/time-differences were found. The proportion of DLB-individuals(*n*=38*)* with abnormal $A\beta_{1-42}$(<714pg/mL) slightly increased over time from 50% to 55%(*n*=19 to 21). The proportion with an abnormal p-tau_{181}/$A\beta_{1-42}$-ratio(>0.072pg/mL) remained stable: 37%(*n*=14). In healthy controls these changes were 15% to 17%(*n*=7 to 8) and 15% to 20%(n=*7* to 9).
Conclusions: Our data suggest that only CSF-$A\beta_{1-42}$, -p-tau_{181}/$A\beta_{1-42}$-ratio and -NfL significantly change over time in DLB-individuals. The proportion of patients with abnormal AD-biomarker levels is relatively stable.

Further investigation of the development of mixed pathology over long time-frames becomes increasingly important considering disease modifying treatments for AD-pathology.

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SHIFT 02-127

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-INFLAMMATORY, ANTI-OXIDANT
4-5 April 2025

NEUROPROTECTIVE EFFECT OF LOW INTENSITY PULSATILE MAGNETIC FIELDS IN RAT CNS

Nasra Yasin
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Aims: This study investigates the neuroprotective effects of low-intensity pulsatile magnetic fields (PMF) on rat CNS cells. PMFs are known to influence various biological processes, including gene expression, cell proliferation, differentiation, and apoptosis. This study aimed to determine how different combinations of magnetic field (MF) strength and frequency impact neuronal survival under conditions of apoptosis, oxidative stress, and inflammation.
Methods: Primary neuronal cultures from Day 1 Sprague-Dawley rats were maintained in neurobasal medium with supplements. PMF was applied using Helmholtz coils to generate fields at frequencies of 2.5, 5, or 10 Hz and strengths of 0.25 or 1.0 Gauss for 2 hours daily. On DIV5, neurons were exposed to apoptotic inducer etoposide (3, 6, 12, 24 μM), oxidative agent 6-hydroxydopamine (12.5, 25, 50, 100 μM), or inflammatory agent lipopolysaccharide (LPS, 2.5, 5, 10 or 20 μg/ml), with continuous PMF exposure for the following 24 hours. Cell viability was assessed using MTT, LDH, and Mitotracker red assays on DIV6. RNA sequencing was performed on rat microglial cells to determine which biological pathways were affected by PMF.
Results: PMF at frequencies of 2.5 or 5 Hz and a strength of 0.25 Gauss significantly protected against apoptosis, oxidative stress and LPS. Higher field strength (1.0 Gauss) at these frequencies did not confer protection. PMF exposure also increased levels of the magnetic field sensitive protein (CRY1), which may play a role in DNA repair and enhanced neuronal survival.
Conclusions: This study identified optimal PMF parameters for neuroprotection in rat cortical neurons. These findings suggest that PMF could be used to develop new treatments for neurodegenerative diseases, where apoptosis, oxidative stress and neuroinflammation cause neuronal damage.

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SHIFT 02-130

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / A-SYNUCLEIN
4-5 April 2025

EFFICACY OF ALPHA-SYN AGGREGATE DISASSEMBLING COMPOUNDS IN PRIMARY CORTICAL NEURONS

Linnea Strid Orrhult[1], Marc Sevenich[2], Albin Skilje[1], Johan Pihl[1], Antje Willuweit[2]
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Aims: Neurodegenerative diseases like Parkinson's disease (PD) are triggered by harmful aggregation of proteins such as the physiological monomer alpha-synuclein (αSyn). αSyn oligomers continue to grow into insoluble fibrils/aggregates that impair multiple cellular functions, eventually leading to neuronal death. In the current study, the aim was to test therapeutic all-D peptides and evaluate their modulation of αSyn aggregation using an in vitro model. The compounds tested here were designed to bind and stabilize the physiological αSyn monomer unit, which results in disassembly of aggregates like fibrils and oligomers.
Methods: An established αSyn aggregation assay for target discovery and validation was used, with adjustments to evaluate compound effects. In short, therapeutic compounds were added in a concentration-response format into the medium of primary mouse embryonic (E18) cortical neurons at 7 days in vitro (DIV). One day later, αSyn aggregation was induced by addition of pre-formed fibrils (PFFs) at 8 DIV upon medium exchange. Using an unbiased automated image analysis workflow, the effect of the compounds on αSyn aggregation (assessed by phosphorylation of Ser129) and cell health was evaluated two weeks after PFF addition.
Results: None of the compounds affected cell health, i.e. the total cell number and number of neuronal cells. A decrease in PFF induced αSyn aggregation was observed with effective concentrations in the nM range even after single administration to the cell medium. Indications of the specificity of the compound effect were determined by a multivariate analysis using principal component analysis.
Conclusions: The compounds developed for disassembly of αSyn aggregates are effective in nM concentration range in primary neurons, which is consistent with their high efficacy in disassembling synthetic αSyn aggregates.

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SHIFT 02-131

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / A-SYNUCLEIN
4-5 April 2025

40 HZ GAMMA ENTRAINMENT PRESERVES DOPAMINERGIC NEURONS AND MODULATES NEUROINFLAMMATION IN A PARKINSON'S DISEASE MOUSE MODEL

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Aims: Parkinson's disease (PD) is a neurodegenerative disorder characterized by α-synuclein aggregation, striatal denervation, and dopaminergic neuron loss in the substantia nigra (SN). Building on our previous work demonstrating Gamma ENtrainment Using Sensory stimuli (GENUS) as a potential therapeutic for neurodegeneration, we investigated the effects of GENUS on dopaminergic neurons, neuronal properties, and microglial activity in a PD mouse model.
Methods: Audiovisual 40 Hz stimulation was applied for 1 hour/day over 28 days to 10-month-old male and female mThy1-hSNCA-Line 15 PD-model mice. Gamma entrainment was assessed using local field potential (LFP) recordings in the nucleus accumbens (NAc), striatum (STR), and SN. Immunohistochemistry targeted PD markers: α-synuclein, tyrosine hydroxylase (TH), dopamine transporter (DAT), vesicular glutamate transporter 1 (VGLUT1), parvalbumin (PVALB), ionized calcium-binding adaptor molecule 1 (Iba1), and cluster of differentiation 68 (CD68). To evaluate intrinsic neuronal excitability with and without GENUS stimulation, whole-cell patch-clamp electrophysiology was conducted on striatal medium-spiny neurons from Line 15 mice and wild-type controls.
Results: GENUS-induced gamma entrainment was confirmed via LFP recordings in all three brain regions. Additionally, GENUS reduced α-synuclein burden, a hallmark of PD, while increasing TH and DAT expression, suggesting dopaminergic neuron preservation and enhanced dopamine signaling. GENUS also lowered microglial activation markers and VGLUT1 expression, indicating a potential reduction in neuroinflammatory processes and highlighting the benefit of further investigation into GENUS's role in mitigating glutamate-induced excitotoxicity. Moreover, elevated PVALB expression following GENUS aligned with electrophysiological findings of reduced intrinsic excitability in striatal neurons, supporting the stabilization of neuronal activity.
Conclusions: In PD, α-synuclein aggregation and microglial activation drive neurodegeneration and inflammation. In the Line 15 PD model, GENUS modulates these processes, reshaping neural network dynamics and proposing a novel therapeutic avenue to target PD's core mechanisms.

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SHIFT 02-133

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / DOPAMINE, ACETYLCHOLINE, NEUROTRANSMITTERS, GLP-1 RECEPTOR
4-5 April 2025

GOLEXANOLONE IMPROVES THE MECHANISMS IN SUBSTANTIA NIGRA LEADING TO STRIATAL DOPAMINE LOSS AND MOTOR AND NON-MOTOR ALTERATIONS IN 6-OHDA RATS

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Aims: Golexanolone, a new drug in clinical development, improves motor and non-motor deficits in 6-OHDA rats (1). We hypothesized that in substantia nigra (SN) of 6-OHDA rats, activated microglia would show increased glutaminase, increasing glutamate. Increased glutamate uptake would induce GABA release from activated astrocytes, leading to reduced intracellular and increased extracellular GABA, which enhances $GABA_A$ receptors activation in neurons, reducing tyrosine hydroxylase (TH) in SN and dopamine in striatum, leading to motor and non-motor deficits. Golexanolone would improve motor and non-motor symptoms by improving this pathway. The aim if this study was to assess this hypothesis.
Methods: We used the 6-OHDA rat model. Golexanolone treatment started one week after surgery. Rats were sacrificed at 3 weeks for mechanistic analysis. Another group performed behavioural tests at 6-8 weeks. Motor symptoms were assessed in the CatWalk, fatigue in the treadmill and short-term memory in Y maze. TH, glutamate and dopamine were analysed by immunofluorescence. Double immunofluorescence glutaminase-Iba1 (microglia) and GABA-GFAP (astrocytes) were performed.
Results: 6-OHDA rats show increased glutaminase in microglia and glutamate levels, reduced GABA into activated astrocytes and reduced TH in SN and reduced dopamine levels in striatum. Golexanolone completely reversed the increase in glutaminase and glutamate and reduction of GABA into astrocytes and partially the reduction of TH in SN. Golexanolone also reversed completely the dopamine loss in striatum and afforded sustained improvement of fatigue, short-term memory and of many parameters of locomotor gait as analysed in the Catwalk.
Conclusions: Golexanolone improves the mechanisms leading to dopamine loss and motor and non-motor deficits in 6-OHDA rats and may induce similar beneficial effects in patients with Parkinson's disease. (1) Izquierdo-Altarejos et al. Front Aging Neurosci. 2024;16:1417938.

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SHIFT 02-134

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
4-5 April 2025

DEVELOPMENT OF A MINIMALLY INVASIVE VECTORIZED ALPHA-SYNUCLEIN ANTIBODY GENE THERAPY FOR PARKINSON'S DISEASE

Kimberly Pietersz[1], Julian Rambow[1], Barbara Hobo[1], Bas Blits[2], Guus Scheefhals[3], Vanessa Donega[4,5], Fred De Winter[1], Joost Verhaagen[1,6]
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Aims: Adeno-Associated Viral (AAV) vectors show promise for gene therapy in Parkinson's Disease (PD)[1]. Post-mortem analysis of PD brain tissue shows loss of dopaminergic neurons in the substantia nigra (SN) but also in noradrenergic areas such as the locus coeruleus (LC)[2]. Thus, both types of catecholaminergic cells are affected in PD. We aim to develop a minimally invasive gene therapy approach targeting α-synuclein aggregates using a vectorized high-affinity monoclonal antibody 26F1[3].
Methods: We explored several short Tyrosine Hydroxylase (TH) promoters described in literature for their capability to drive transgene expression in catecholaminergic cells. TH is the rate-limiting enzyme in catecholamine synthesis. We first tested the constructs *in vitro* in SH-SY5Y cells. Subsequently, the TH promoter constructs with either luciferase or GFP as reporter genes were packaged into AAV.PhP.eB, a vector that crosses the blood-brain-barrier. The performance of these constructs was subsequently studied after systemic administration in mice.
Results: All promoters were functional *in vitro* in SH-SY5Y cells that express the enzyme TH. Interestingly, the smallest 300 bp promoter gave a similar expression profile as the 2500 bp promoter. *In vivo*, bioluminescence confirmed activity of all promoters in the cranial area. Analysis of the cellular expression profile using GFP revealed that the 300 bp promoter only showed expression in the olfactory bulb, whereas the 2500 bp promoter directed expression in several catecholaminergic areas, including the SN and LC.
Conclusions: Our results show that promoter activity in SH-SY5Y cells does not necessarily predict transgene expression in catecholaminergic neurons after AAV.PhP.eB delivery *in vivo*. We are currently testing a vectorized antibody that targets catecholaminergic areas in an animal model for Parkinson's disease that overexpresses α-synucleinA53T. We anticipate presenting results from these ongoing studies at this conference.

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SHIFT 02-135

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / KINASES, OTHER ENZYMES
4-5 April 2025

15-LIPOXYGENASE MEDIATED LIPID PEROXIDATION REGULATES LRRK2 KINASE HYPERACTIVITY IN IDIOPATHIC PARKINSON'S DISEASE

Sean Pintchovski[1], Matthew Keeney[2], Eric Hoffman[2], Julie Weir[2], Weston Wagner[2], Sandra Castro[2], Abigail Scheirer[2], Kyle Farmer[2], Marco Fazzari[2], Roberto Di Maio[2], Andrei Konradi[1], Teresa Hastings[2], Emily Rocha[2], William Shrader[1], J. Timothy Greenamyre[2]
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Aims: Mutations that increase leucine-rich repeat kinase 2 (LRRK2) kinase activity are the most prevalent genetic form of familial Parkinson's disease (fPD), directly linking LRRK2 hyperactivity to PD pathology. Recent work demonstrates that wild-type (WT) LRRK2 kinase activity is also unexpectedly elevated in idiopathic PD (iPD) patients where there is no clear genetic cause, although the mechanism underlying this phenomenon has remained poorly understood. This study aimed to elucidate the molecular mechanisms regulating LRRK2 kinase hyperactivity in iPD.
Methods: *In vitro* and *in vivo* disease-relevant systems were employed, including fPD- and iPD-derived lymphoblastoid cell lines (LCLs), genetically modified human cell lines, and the established rat rotenone model of iPD. Orthogonal histochemical and biochemical assays were used to assess the activity levels of LRRK2 kinase and its downstream target Rab10.
Results: 15-Lipoxygenase (15-LO) mediated production of 4-hydroxynonenal (4-HNE), a lipid hydroperoxidation end-product, forms post-translational adducts with Cys2024 and Cys2025 in the kinase activation loop of WT LRRK2, significantly increasing its kinase activity. Elevated basal 4-HNE levels and LRRK2 kinase activity levels were observed in both fPD and iPD patient-derived LCLs, as well as in dopaminergic neurons from the substantia nigra (SN) of the rat rotenone model. Pharmacological inhibition or genetic ablation of 15-LO prevents 4-HNE post-translational modification of LRRK2 kinase and its subsequent pathogenic hyperactivation *in vitro* and *in vivo*. Furthermore, in the rat rotenone model, 15-LO inhibition is sufficient to prevent rotenone-induced loss of dopaminergic neurons in the SN. Critically, it appears that 15-LO inhibition does not lower elevated LRRK2 kinase activity below physiological levels, whereas direct LRRK2 kinase inhibitors can completely inhibit LRRK2 kinase activity.
Conclusions: 15-LO inhibitors could provide a new therapeutic strategy to safely modulate LRRK2 kinase activity and treat PD.

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SHIFT 02-136

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / KINASES, OTHER ENZYMES
4-5 April 2025

GLP SAFETY AND PK/PD STUDIES FOR NOVEL ORAL HIGHLY SELECTIVE LRRK2 INHIBITOR (BT-0267)

Alexei Pushechnikov[1], Ruben Karapetian[1], Vasily Kazey[1], Nikolay Savchuk[1], Iain Dukes[1], Thomas Gasser[2,3], Tudor Oprea[4], Stepan Mochalov[5], Volodymyr Kysil[5], Aleksei Riakhovskii[5], Elena Bulanova[5]
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Aims: Development of a LRRK2 inhibitor drug candidate for both idiopathic and LRRK2(mutant)-associated PD.
Methods: Apply a balanced PK approach focusing on less potent but more brain-penetrant molecules to have reduced tox effects in lungs/kidneys due to a differential distribution.
Results: BT-0267 is a potentially best in class oral, highly selective LRRK2 inhibitor with outstanding pharmacokinetics and high brain permeability. BT-0267 has demonstrated a correlation between the in vivo unbound fraction exposure and the phospho-S935LRRK2/total LRRK2 ratio in multiple rodent and primate animal models. BT-0267 confirmed no adverse effects in lungs, no pneumocyte vacuolization increase in NHP vs control group, indicating an outstanding safety profile in non-GLP and GLP safety studies. BT-0267 shown a high brain permeability in non-human primates (NHP) by CSF/Fu plasma ratio - a strong sign for a broad therapeutic window. We demonstrated correlation between the urine biomarker di-22:6-BMP and the LRRK2 target engagement in NHP. GLP toxicology studies confirmed broad safety and tolerability of BT-0267 to advance the drug candidate to clinic.
Conclusions: Discovered LRRK2 inhibitor with superior kinome selectivity compared to the publicly known best references. BT-0267 demonstrates outstanding in vivo PK and a high Brain(unbound)/Plasma(unbound) ratio. GLP toxicology studies confirmed broad safety and tolerability of BT-0267 to advance the drug candidate to clinic.

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SHIFT 02-138

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
4-5 April 2025

SCREENING OF SMALL MOLECULE INHIBITORS TARGETING ALPHA-SYNUCLEIN AGGREGATION VIA SEED AMPLIFICATION ASSAY

Michelle Pinho, Claudio Soto, Sandra Pritzkow
UT Health Mc Govern medical School, Department Of Neurology, University Of Texas Mcgovern Medical School, Houston, United States of America

Aims: Alpha-synuclein (αSyn) aggregation is a hallmark event of neurodegenerative diseases, including Parkinson's disease (PD), and Dementia with Lewy Body (DLB). A key pathway responsible for the pathological progression of these diseases is the spreading of αSyn aggregates between cells and brain regions through a seeding mechanism, making it a critical target for therapeutic intervention. This study utilizes the αSyn seed amplification assay (αSyn-SAA) to screen for small molecule compounds capable of inhibiting the seeding and aggregation of αSyn. αSyn-SAA reproduces in vitro the seeding/nucleation process that features the formation and spreading of protein aggregates in the brain. Utilizing αSyn-SAA, we systematically evaluated an FDA-approved library of compounds for their ability to inhibit or disrupt the formation of αSyn aggregates.
Methods: We optimized the αSyn-SAA technology to rapidly and robustly amplify αSyn seeds derived from postmortem human brains affected by DLB. Using this biologically relevant assay, we screened FDA-approved drugs for their ability to inhibit the seeding of αSyn aggregates.
Results: Our results demonstrate that αSyn-SAA can be used as a powerful high-throughput screening assay capable to identify hit compounds able to inhibit αSyn seeding in vitro. Moreover, the assay enables to estimate the compounds IC50 and to perform structure-activity relationship studies necessary for hit optimization. Our screening results uncovered several small molecules able to inhibit or reduce αSyn seeding in vitro.
Conclusions: This study highlights the utility of αSyn-SAA as a screening tool to identify hit compounds able to inhibit seeding and spreading of αSyn aggregates, which is a key event in disease progression. Our findings provide a foundation for further identification and development of αSyn aggregation inhibitors with implications for therapeutic intervention in synucleinopathies.

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SHIFT 02-139

Poster on Board - Shift 02
α-SYNUCLEINOPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
4-5 April 2025

FEPI: INTRANASAL PEPTIDES TO STOP PARKINSON'S DISEASE PROGRESSION

Sofiia Svirska, Maksym Galkin, Volodymyr Shvadchak, Juliane Proft
Institute of Organic Chemistry and Biochemistry of the Czech Academy of Sciences, Prague, Czech Republic

Aims: Parkinson's disease (PD) is the second most common neurodegeneration in the world and currently has no cure. Aggregation of alpha-synuclein into amyloid fibrils plays a central role in driving PD progression. Since these fibrils grow by binding alpha-synuclein monomers to their ends, our goal was to develop a peptide inhibitor that can specifically target fibril ends and block fibril growth. Additionally, we aimed to create a version that can be administered intranasally for easier therapeutic delivery.
Methods: We used the structure of alpha-synuclein fibrils and rational design to create the **f**ibril **e**nd **p**eptide **i**nhibitor (FEPI). The activity of FEPI was tested in both ThT kinetic assays and a FRET-based cellular aggregation assay. To assess stability, we incubated the peptide with mouse brain homogenate and measured the fraction of the intact peptide using HPLC. For intranasal delivery, we evaluated it by administering a fluorescently labeled peptide and measuring fluorescence one hour after administration in the brain homogenates.
Results: FEPI has an IC_{50} of 500 nM, making it nearly 10 times more potent than any inhibitor published so far. Our lead compound is a cyclic 25-amino-acid peptide that is not only highly potent but also stable, with a half-life of over 24 hours. Intranasal administration successfully delivered a therapeutic dose of FEPI to the brains of mice.
Conclusions: We have developed a highly effective peptide inhibitor for alpha-synuclein aggregation that can be delivered intranasally. It is the most potent non-protein inhibitor to date, capable of completely halting alpha-synuclein aggregation both in vitro and in cellulo. This approach can also be used to create inhibitors targeting amyloid-beta aggregation.

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SHIFT 02-143

Poster on Board - Shift 02
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
4-5 April 2025

HIGH-PLEX PROTEOMIC CHARACTERIZATION OF PRECLINICAL MODELS WITH THE NULISASEQ 120-PLEX MURINE PANEL

Xiao-Jun Ma[1], Li Wang[1], Hiyuen Ji[1], Wai Hang Cheng[2], Jianjia Fan[2], Tetiana Poliakova[2], Carlos Barron[2], Andrew Agbay[2], Shweta Iyengar[1], Sean Kim[1], Niyati Jhaveri[1], Xialoei Qiu[1], Bingqing Zhang[1], Cheryl Wellington[2], Yuling Luo[1]
[1]Alamar Biosciences, Fremont, United States of America, [2]The University of British Columbia, Pathology And Laboratory Medicine, Vancouver, Canada

Aims: With the emergence of several preclinical models of neurodegenerative diseases including Alzheimer's Disease (AD), proteomic characterization of these models is needed to better understand their clinical relevance and utility in therapeutic evaluation. Along with amyloid plaques and neurofibrillary tangles, neuroinflammation is an underlying mechanism of disease progression and a multiplex proteomics approach is needed to track the temporal regulation of inflammatory and neurodegenerative processes as well as the degree to which these preclinical models recapitulate the biology of the human disease.
Methods: Previously, we developed a 250-plex Inflammation Panel and 120-plex CNS Disease Panel on the automated ARGO™ HT platform to profile key proteins such as IL6, phospho-Tau, and amyloid beta for profiling of biofluids in human studies. To provide a complementary approach for proteomic profiling in preclinical models, we have developed a 120-plex Murine Panel for detection of cytokines, growth factors and other CNS disease targets. Plasma samples from different mouse strains were assayed at multiple input volumes. CSF and brain lysates were also evaluated. Dilutional linearity, reproducibility and overall detectability were assessed. Additionally, various preclinical models of AD and Traumatic Brain Injury were also evaluated.
Results: Our results demonstrate robust performance with 5% median intra-assay CV and 97.4% detectability in mouse plasma samples from 5 common strains. Additionally, lowering sample input volume from 10µL to 5µL has minimal impact on overall detectability (>95%), reflecting high assay sensitivity. Dilutional linearity further demonstrated good target linearity with signal-to-noise ratio over 2 for 97% of the targets in the panel.
Conclusions: The analytical validation along with the application of the panel across different AD models demonstrates the utility of the multiplex NULISAseq Murine Panel for comprehensive characterization of neurodegenerative and inflammatory markers in preclinical models.

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SHIFT 02-144

Poster on Board - Shift 02
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
4-5 April 2025

INTERACTIONS BETWEEN AMYLOID, ALPHA-SYNUCLEIN, AND TAU IN NOVEL MIXED-PATHOLOGY MOUSE MODELS

Benjamin Rabichow, Lacey Nixon, Katelin Haug, Joe Barnett, David Nascari, Lauren Tallant, Nashali Massa, John Fryer
Mayo Clinic, Neuroscience, Scottsdale, United States of America

Aims: Aim 1: Examine how introducing pathological α-syn, tau, or both affects brain pathology and behavior in APP mice (a) before and (b) after significant amyloid plaque buildup. **Aim 2:** (a) Identify molecular changes in mouse brains with combined pathologies, and (b) compare these findings to data from patients with similar pathologies.
Methods: We administered AAVs to drive neuronal expression of 1) wild-type human α-syn (AAV-asyn), 2) mutant E46K α-syn (AAV-E46K), 3) mutant A152T tau (AAV-tau), 4) mutant tau and α-syn (AAV-tau/asyn), or 5) GFP (AAV-EGFP) in the brains of 2 month old (pre-plaque) and 6 mo (post-plaque), APP(NL-G-F)/MAPT mice and MAPT controls. Open field metrics, weight, and grip strength were assessed at baseline, 3 months post-injection (mpi), and 6 mpi. At endpoint, Y-maze, light-dark, and fear conditioning tests were conducted. Mice were perfused and brain and tissues harvested for ongoing experiments.
Results: Decreased weight gain was observed in AAV-tau and tau/asyn treated mice. AAV-tau and tau/asyn treated APP mice showed increased locomotor activity, decreased rearing, and spent less time in the center at 3- and 6-months post-injection in the open field assay. At 6 mpi, APP mice displayed reduced spontaneous alternation behavior compared to controls. In the light-dark test, 12-month-old APP mice treated with AAV-tau or tau/asyn spent less time in the light. Reduced freezing time in fear conditioning was noted for AAV-tau/asyn APP and control mice.
Conclusions: These results suggest that AAV-tau and AAV-tau/asyn treatments impact behavior and physiology in APP mice, evidenced by increased locomotor activity, altered anxiety-like behaviors, and reduced freezing responses in fear conditioning tests. These findings highlight the potential influence of tau and α-syn co-pathology on motor and anxiety-like behaviors, as well as memory-deficits in amyloid models.

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SHIFT 02-145

Poster on Board - Shift 02
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
4-5 April 2025

ASSESSMENT OF SPATIAL MEMORY DEFICITS IN TG2576 MICE USING A MACHINE LEARNING-BASED ANALYSIS PIPELINE

Johanna Uhari-Väänänen[1], Timo Bragge[1], Taneli Heikkinen[1], Johanna Rokka[1], Pekka Poutiainen[2], Jussi Rytkönen[1]
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Aims: Cognitive tests assessing memory deficits in animal models can be time consuming and prone to observer bias. Novel machine learning approaches to analyze images and videos can provide better opportunities for behavioral analysis with its objective detection, overall speed, and improved data quality. In this study we evaluated spatial memory and learning in Tg2576 mice using video recording of the Barnes maze test and an automated analysis pipeline. Furthermore, the amyloid beta burden in the brain of mice was evaluated with PET imaging.
Methods: Transgenic B6;SJL-Tg(APPSWE)2576Kha (Tg2576) and wild type (WT) mice underwent Barnes maze test, a two-phased test in which spatial learning and memory are assessed in the first phase (acquisition), while the second phase (reversal learning) evaluates cognitive flexibility. An automated analysis pipeline was implemented after DeepLabCut-based tracking of video recordings of animal movement on the test arena. DeepLabCut is a software package for markerless pose estimation based on transfer learning with deep neural networks (Lauer et al. 2022, Nat Methods 19, 496-504). A cohort of the mice were imaged with a small-animal PET scanner (BioPET, Sedecal) for amyloid burden using [^{18}F]-Flutemetamol.
Results: A genotype difference was observed in Barnes maze with Tg2576 mice taking more time to learn the location of the escape box compared to WT counterparts. Interestingly, PET imaging did not show significant differences in different brain regions in the tracer uptake between Tg2576 and WT mice.
Conclusions: We have established an analysis pipeline for assessment of Barnes maze behavioral data. Machine learning does not just streamline and enhance the repeatability of scientific studies, but it also allows us to scale up the amount of data that we can process in an efficient manner.

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SHIFT 02-146

Poster on Board - Shift 02
β-AMYLOID DISEASES / ANIMAL MODELS / TRANSGENIC RODENTS
4-5 April 2025

SPATIAL TRANSCRIPTOMICS REVEALS BRAIN-REGION SPECIFIC CELL-TYPE SIGNATURES IN NOVEL MOUSE MODELS OF ALZHEIMER'S DISEASE

Asli Uyar, Dylan Garceau, Gregory Carter, Michael Sasner
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Aims: Different genetic mutations underlying familial Alzheimer's Disease (fAD) are linked to heterogenous parenchymal and vascular amyloid phenotypes and varying disease progression rates. However, molecular identities and spatial configurations of various cell-types in individual brain regions associated with this heterogeneity is unknown. Here, we utilized spatial transcriptomics to decipher the spatially-informed cell-type and gene expression signatures in novel AD mouse models.
Methods: We engineered three novel App-KI mouse models. The C57BL/6J mouse App locus was edited to humanize three amino acids that differ between mouse and human, and to create combinations of fAD mutations. All models have the Swedish mutation to drive increased BACE cleavage driving increased expression of Abeta species including Abeta-40 and -42. APP^{SAA} model also expresses Arctic and Austrian mutations that drive parenchymal amyloid deposition. APP^{SDI} model also expresses Dutch and Iowa mutations that drive vascular amyloid deposition. APP^{SFL} model also expresses Florida and London mutations to generate wild-type human Abeta peptides. At 9 months of age, brains were collected and spatial transcriptomics of the whole coronal sections was performed using 10X Genomics Xenium platform.
Results: We assessed gene expression signatures associated with microglia- and astrocyte-driven neuro-inflammatory response by a set of genes including Cd68, Siglech, Trem2 and Gfap. All three mouse models showed increased microglia and astrocyte activation. Inflammatory response was more pronounced in APP^{SAA} mice with higher expression of marker genes across hippocampal and cortical regions. We also observed genotype-dependent differences in relative proportions of microglial and neuronal subpopulations across brain regions.
Conclusions: These novel mouse models of AD carrying different combinations of fAD mutations represent spatially-informed cell-type heterogeneity associated with neuroinflammation in the brain, and provide opportunities to improve translational relevance of mouse models in preclinical studies.

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SHIFT 02-148

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
4-5 April 2025

EXPRESSION OF APOE2 IN HEPATOCYTES DOES NOT MITIGATE ALZHEIMER'S DISEASE PATHOLOGY IN THE PRESENCE OF CEREBRAL APOE4

Steve Maclean[1], Lesley Golden[1], Dahlia Siano[1], Xiaojin Wang[2], Gabriela Hernandez[1], Clarity Voy[1], Josh Morganti[3], Scott Gordon[1], Chris Richards[2], Lance Johnson[1]
[1]University of Kentucky, Physiology, Lexington, United States of America, [2]University of Kentucky, Chemistry, Lexington, United States of America, [3]University of Kentucky, Neuroscience, Lexington, United States of America

Aims: Objective: The objective of this study is to test whether liver expressed ApoE2 can mitigate late-onset Alzheimer's disease (LOAD) risk in the presence of cerebral ApoE4. Although hepatocyte-derived ApoE does not cross the blood-brain-barrier (BBB), recent studies have demonstrated the detrimental effects of liver-derived ApoE4 on amyloid accumulation, BBB function, and memory. A critical translational question is whether hepatic ApoE2 expression can reduce pathology in the presence of cerebral ApoE4.
Methods: Methods: Our lab is employing a novel *APOE*4-Switch-*APOE*2 (*APOE*4s2) mouse model using the Cre-LoxP system. Cre is delivered via AAV with a hepatocyte-specific promoter, resulting in mice with ApoE4 expression in the brain but ApoE2 expression in the liver. Western blots on plasma with ApoE isoform specific antibodies and fast protein liquid chromatography (FPLC) were used to validate allele switching. Cognitive function was tested with Y-maze and fear conditioning tasks. Amyloid levels were measured by IHC and ELISAs.
Results: Results: Western blots show efficient (70-99%) and sustained (>12 months) expression of ApoE2 in the plasma of AAV-injected animals and FPLC data revealed changes in lipid profile. However, while still preliminary, our results suggest that expression of ApoE2 in the liver did not improve cognitive function or reduce total amyloid beta levels in 5XFAD mice with CNS ApoE4.
Conclusions: Conclusion: Western blot and FPLC data confirm that our AAV-Cre strategy in *APOE*4s2 mice results in highly efficient and long-lasting recombination in the liver. Our preliminary results suggest that hepatic expression of ApoE2 is insufficient to overcome the detrimental effects of ApoE4 expression in the brain related to cognitive function and total amyloid beta levels. Future studies will investigate BBB integrity and cerebrovascular transcriptomic changes following the hepatocyte-specific ApoE4 to ApoE2 allele switch.

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SHIFT 02-149

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
4-5 April 2025

PROTECTIVE APOE VARIANTS SUPPORT NEURONS BY EXTRACTING PEROXIDATED LIPIDS

Isha Ralhan[1,2], Alison Do[1], Ju-Young Bae[1,2], Femke Feringa[3], Wendy Cai[1], Jinlan Chang[1], Kennedi Chik[1,2], Chris Gerry[4], Rik Van Der Kant[3], Jesse Jackson[1,5], Emily Ricq[4], Maria Ioannou[1,2,5,6]
[1]University of Alberta, Department Of Physiology, Edmonton, Canada, [2]University of Alberta, Group On Molecular And Cell Biology Of Lipids, Edmonton, Canada, [3]Vrije Universiteit Amsterdam, Department Of Functional Genomics, Amsterdam, Netherlands, [4]Kisbee Therapeutics, Cambridge, United States of America, [5]University of Alberta, Neuroscience And Mental Health Institute, Edmonton, Canada, [6]University of Alberta, Department Of Cell Biology, Edmonton, Canada

Aims: During oxidative stress, neurons transfer lipids to glia to protect themselves from toxicity. This process plays an important role in protecting the brain as defects in this pathway cause neurodegeneration. While the mechanisms of this lipid transport pathway are not fully understood, there is a clear role for Apolipoprotein E (ApoE). ApoE is a lipid-transport protein found on lipoprotein particles. There are three main ApoE isoforms: E2, E3 and E4. ApoE4 is a major risk factor for late-onset Alzheimer's disease, while ApoE2 and the Christchurch variant of ApoE3 (ApoE3Ch) are neuroprotective. Little is known regarding how ApoE2 and ApoE3Ch isoforms exert their protective effects and whether this involves facilitating neuron to glia lipid transport.
Methods: We generated 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) particles with recombinant human ApoE2, ApoE3, ApoE4 or ApoE3Ch. We applied these particles to primary rodent neurons, human iPSC-derived neurons, ex vivo intact hippocampi and in vivo rat brains by intraperitoneal injection and assessed lipid efflux and neuronal health and function using super-resolution microscopy, biochemical assays, and electrophysiological recordings.
Results: We discovered that the protective ApoE2 and ApoE3Ch particles attenuate oxidative stress by extracting peroxidated lipids from neurons. This protects neurons from cell death by ferroptosis, a form of cell death driven by lipid peroxidation. While ApoE4 particles increase lipid peroxidation and ferroptosis by disrupting endolysosomal function, this can be rescued by the addition of ApoE2 or ApoE3Ch particles in vitro, ex vivo and in vivo.
Conclusions: Our study reveals new insight into how ApoE2 and ApoE3Ch particles protect the brain from lipid-mediated toxicity and supports the potential therapeutic use of exogenous particles in Alzheimer's disease.

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SHIFT 02-150

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
4-5 April 2025

THE INNOVATIVE NEURON-GLIAL BRAIN ASSEMBLOID MODEL OF ALZHEIMER'S DISEASE REVEALS THE REGULATORY ROLE OF APOE4 IN NEURODEGENERATIVE PATHWAYS

Eliana Sherman[1,2], Lulu Jiang[1,2], Weronika Gniadzik[1,2]
[1]University of Virginia, Center For Brain Immunology And Glia (big), Charlottesville, United States of America, [2]University of Virginia, Department Of Neuroscience, Charlottesville, United States of America

Aims: Exploration of the pathophysiology of Alzheimer's disease (AD) has been hampered by the lack of systems that accurately recapitulate the full profile of disease progression. We developed a three-dimensional (3D) assembloid model with iPSC-induced neurons, astrocytes, and microglia derived from AD subjects to investigate the pathophysiology, protein-protein interactions, cellular mechanisms, and interventional strategies for AD. In the current study, we aim to elucidate the mechanism of the risk isoform ApoE4 in regulating the pathogenesis of AD.
Methods: ApoE4 and its isogenic control ApoE3 iPSC lines were differentiated into neuronal, astrocytic, and microglial progenitor cells in 2D culture. The neuronal cells were seeded with tau oligomers. Subsequently, the three cell types of progenitor cells were mixed together to generate 3D Microglia-Astrocyte-Neuronal spheroids (Masteroids). These Masteroids were challenged with Aβ oligomers on day seven of the 3D culture. Pathological accumulation of tau and Aβ was examined at four weeks after treatment, using immunofluorescence labeling, western blot, and other biochemical methods. Underlying molecular pathways were deciphered using single cell RNA sequencing analysis and validated by knockdown of target genes.
Results: Analysis of the Masteroid cultures after four weeks revealed accumulated β-amyloid deposition, tau pathology, neurodegeneration, astrogliosis, and microglial activation in the conditions challenged with oligomeric tau propagation and/or Aβ oligomers stress. Single cell transcriptomic analysis revealed novel impacts of ApoE4 and its synergistic exacerbation of AD pathology with oligomeric tau.
Conclusions: We generated a novel 3D brain assembloid model that effectively recapitulates key features of AD pathology. This innovative AD model offers an advanced platform to study the cellular and molecular mechanisms of disease progression and reveal distinct signal pathways in which the ApoE4 isoform regulates the pathogenesis of AD and related neurodegenerative diseases.

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SHIFT 02-151

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
4-5 April 2025

APOE4 CARRIAGE IS ASSOCIATED WITH A UNQIUE CEREBROSPINAL FLUID AND PLASMA PROTEOME SIGNATURE

Caitlin Finney[1], Heather Wilkins[2], Jeffrey Burns[2], Russell Swerdlow[2], Chad Slawson[2], Artur Shvetcov[1], Gnpc Global Neurodegeneration Proteomics Consortium[3]
[1]Westmead Institute for Medical Research, Westmead, Australia, [2]University of Kansas Alzheimer's Disease Research Center, Kansas City, United States of America, [3]Global Neurodegeneration Proteomics Consortium, Seattle, United States of America

Aims: The single biggest genetic risk factor for sporadic Alzheimer's disease (sAD) is a variant in the apolipoprotein E gene called ε4 (APOE4). Despite this, little is known about the mechanisms underlying APOE4 carriers' vulnerability to developing sAD. Leveraging the Global Neurodegeneration Proteomics Consortium (GNPC) dataset, we obtained SomaScan 7k assay proteomic data from the plasma and cerebrospinal fluid (CSF) of healthy controls and sAD patients.
Methods: Leveraging the Global Neurodegeneration Proteomics Consortium (GNPC) dataset, we obtained SomaScan 7k assay proteomic data from the plasma and cerebrospinal fluid (CSF) of healthy controls and sAD patients. To identify APOE4-specific proteins (features), we used mutual information. We then used these features in machine learning models to predict APOE4 carriers and non-carriers.
Results: We show that APOE4 carriers have a unique proteome signature across both the CSF and plasma. Functional enrichment analyses revealed that these proteins were associated with apoptosis and inflammation as well as dysregulation in immune system, DNA/RNA processes, mitochondrion organization, and glycolysis. Further, the APOE4 proteome signature was independent of cognitive status, occurring in both healthy controls and sAD patients.
Conclusions: Our findings demonstrate that APOE4 carriage defines both the CSF and plasma proteome profile irrespective of cognitive status. First, this suggests that APOE4 carriers have systemic biological dysfunction that extends beyond the central nervous system. Second, our findings suggest that APOE4 carriers' underlying biological dysfunction may be essential but not sufficient for developing sAD. For example, underlying biological dysfunction makes APOE4 carriers more vulnerable to environmental insults, such as viral infections, and together these factors drive sAD pathogenesis.

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SHIFT 02-152

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APOE
4-5 April 2025

THE IMPACT OF APOE AND APOE CHRISTCHURCH MUTATION ON ATN PATHOLOGY AND ASSOCIATED PATHOLOGICAL PROCESSES IN PRECLINICAL MODEL

Yanyan Wang, Sarah Vanherle, Art Janssen, Bieke Janssen, Chritica Lodder, Jana Hardy, Pablo Botella Lucena, Sofie Kessels, Ilie-Cosmin Stancu, Bert Brône, Yeranddy A. Alpizar, Ilse Dwachter
Hasselt University, Biomed, Neuroscience, Diepenbeek, Belgium

Aims: Apolipoprotein E (APOE) is recognized as the strongest genetic risk factor for sporadic late-onset Alzheimer's disease (LOAD). A recent case report identified a rare APOE variant, APOE3-R136S (Christchurch), which is proposed to protect against early-onset Alzheimer's in a PSEN1-E280A carrier. This study explores the effects of APOE and the APOECh and APOE3Ch variants on amyloid plaques, tau pathology, and the brain's response to these pathologies.
Methods: We generated *Apoe* knockout (KO) mice, *ApoeCh* mice (R146S), and mimic *Apoe3Ch* mice (R146S, R122C), and their crosses with the combined 5xFAD amyloidosis and PS19 tauopathy models (ATN). We used stereotaxic brain injections, immunohistochemistry, biochemical assays, and single-cell RNA sequencing to examine the APOE, APOECh, and APOE3Ch on pathological effects of AD.
Results: APOE deficiency led to diffused plaques, reduced amyloid-induced tau pathology, and decreased disease-associated microglia (DAM) phenotype in the ATN model. We assess here comparative effects of *Apoe* deficiency, *ApoeCh(R146S),* and *Apoe3Ch* mice (R146S and R122C) on amyloid load, tau pathology, neurodegeneration as well as concomitant effects on lipid/cholesterol levels and microglial activation. We furthermore use AAV-GFAP-APOE injections to assess the contributory role of astrocytic APOE and APOE variants in pathology and pathological processes.
Conclusions: These findings highlight the ability of APOE deficiency to influence amyloid and tau pathology while reducing DAM reactivity in ATN models. Using our different models we aim to disentangle different APOE-dependent functions and their relation with pathology progression and pathological processes in the brain in an ATN model.

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SHIFT 02-153

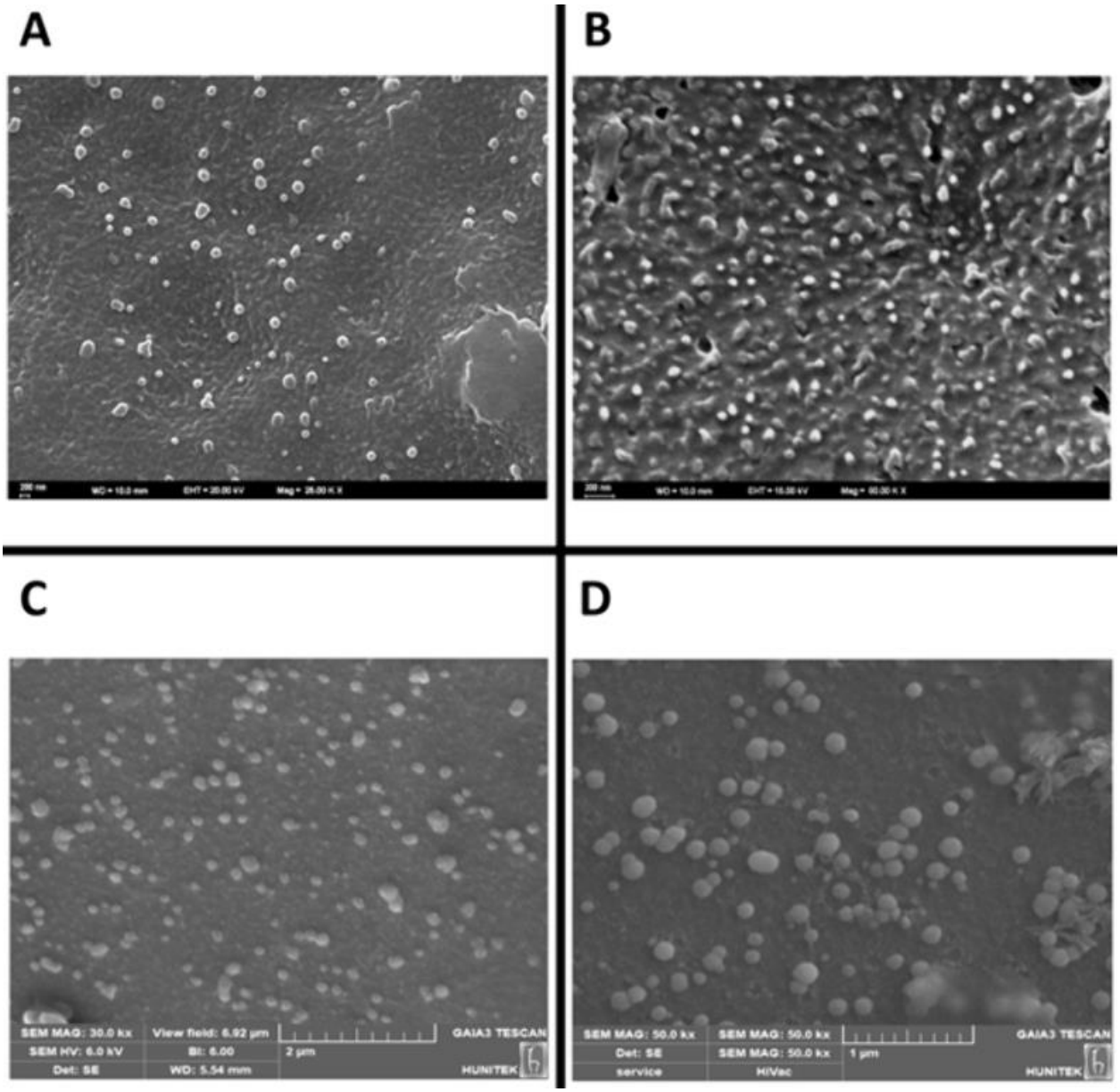
Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
4-5 April 2025

MYEXOSOME® PREVENTS AMYLOID TOXICITY AND IMPROVES CELL HEALTH IN IN-VITRO MODEL FOR ALZHEIMER'S DISEASE

Cenan Öztürk[1], Eren Kahyaoğlu[2], Murat Kantarcıoğlu[3], Mehmet Zülküf Önal[4]
[1]Ankara University, Graduate School of Natural and Applied Sciences, Department Of Biology, Ankara, Turkey, [2]Ondokuz Mayıs University, Graduate School of Education, Department Of Biology, Samsun, Turkey, [3]Güven Çayyolu Surgical Medical Center, Department Of Gastroenterology, Ankara, Turkey, [4]Atılım University, Faculty of Medicine, Department Of Neurology, Ankara, Turkey

Aims: Alzheimer's disease (AD) is the main cause of dementia. AD is disregarded as a pandemic compared with other diseases. To date, there is no effective treatment. Many studies have shown that edible plant derived exosome like nanoparticles (EPDENs) are responsible for beneficial effects on the human body. MyExosome®, the first herbal supplement of its kind is composed of EPDENs derived from coffee, ginseng panax, and gingko biloba. In the literature, the beneficial effects of all three plants on brain health are emphasized. In this study, we aimed to visualize the EPDEN content of MyExosome® and to determine their efficacy on the Alzheimer's cell culture model and microglia cells.
Methods: Scanning electron microscopy (SEM) and Nanoparticle tracking analysis (NTA) were used for morphology of EPDENs. Bicinchoninic acid assay (BCA) for protein content and commercial kit (EXOCET®) for quantification were used. MyExosome® was applied to Alzheimer's cell culture model SH-SY5Y (neuroblastoma) and HMC-3 (microglia) cells three different concentrations for 24 and 48 hours. Cell viability was determined by CCK-8 kit.
Results: MyExosome® content was morphologically compatible with described EPDENs in literature (Figures 1, 2). CA protein analysis and EXOCET® confirmed a high concentration of exosomal proteins, in 10 mg of MyExosome® 6.75e+10 EPDENs were present. In Alzheimer's model, cells treated with MyExosome®, Aβ (1-42)-induced toxicity was reduced, and cell viability significantly increased (Figure 3). Also, microglia cells showed significant proliferative effects (Figure

4).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B
C
D
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SEM HV: 6.0 kV
BI: 6.00
Det: SE
WD: 5.54 mm
2 µm
GAIA3 TESCAN
HUNITEK
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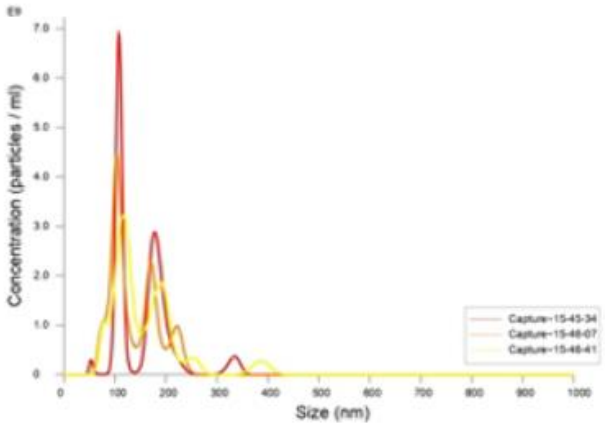
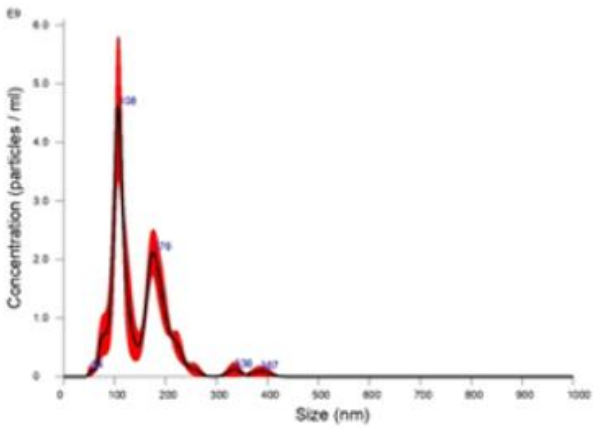
service
SEM MAG: 50.0 kx
HiVac
1 µm
GAIA3 TESCAN
HUNITEK

A



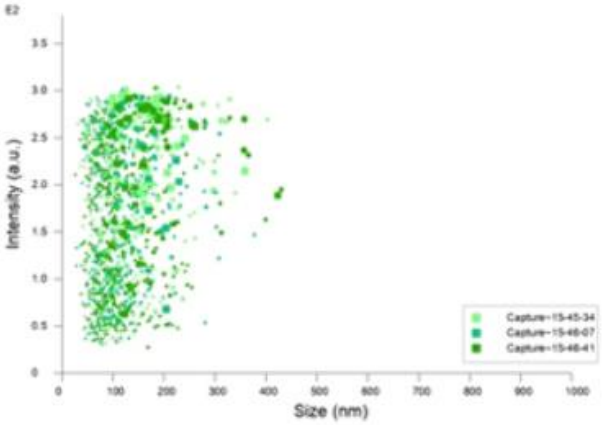
FTLA Concentration / Size graph for Experiment:
Capture 2023-07-21 15-45-21

B



Averaged FTLA Concentration / Size for Experiment:
Capture 2023-07-21 15-45-21
Error bars indicate + / -1 standard error of the mean

C



Intensity / Size graph for Experiment:
Capture 2023-07-21 15-45-21

D

Results

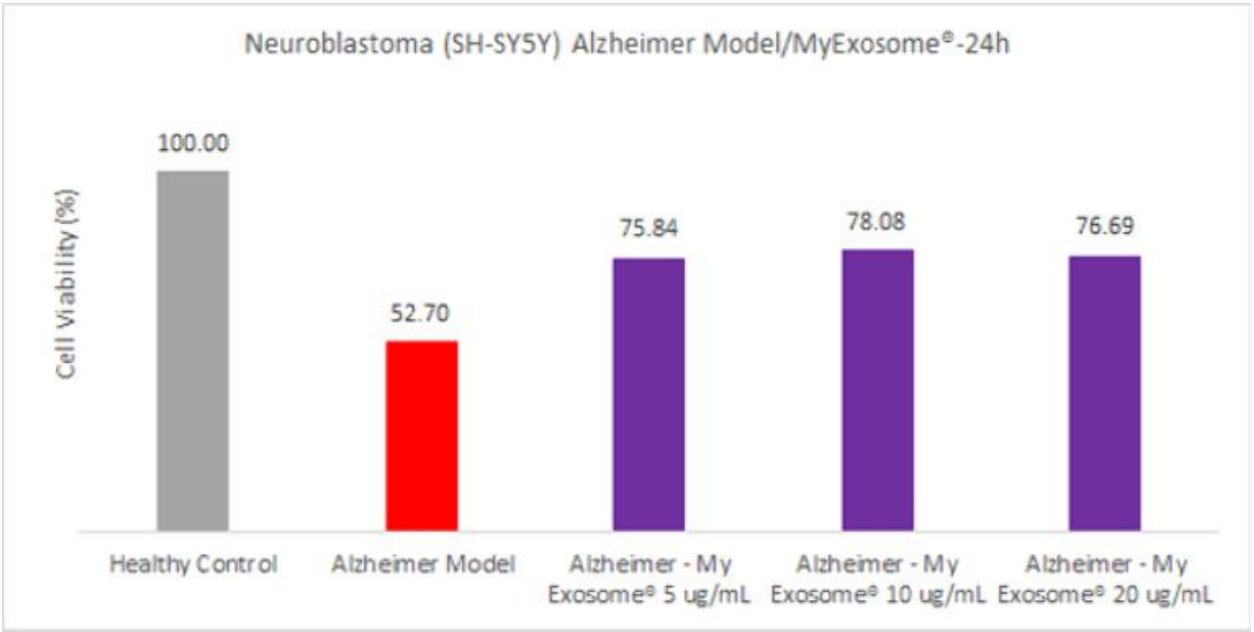
Stats: Merged Data

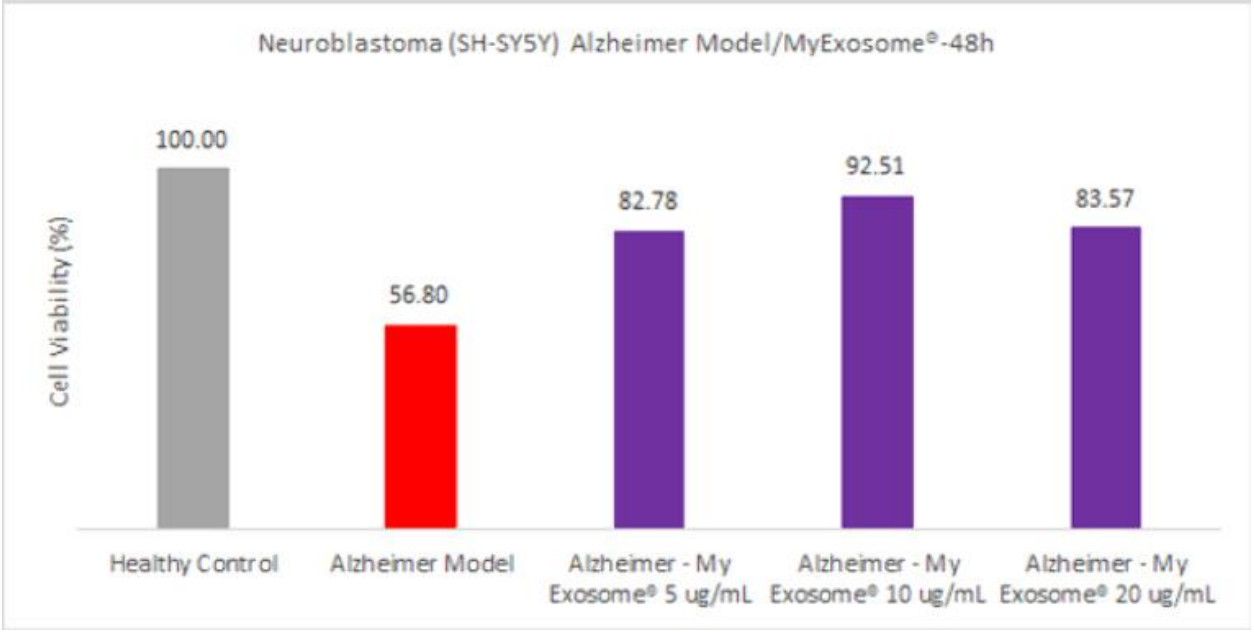
Mean:	149.3 nm
Mode:	107.4 nm
SD:	58.8 nm
D10:	95.0 nm
D50:	129.9 nm
D90:	212.9 nm

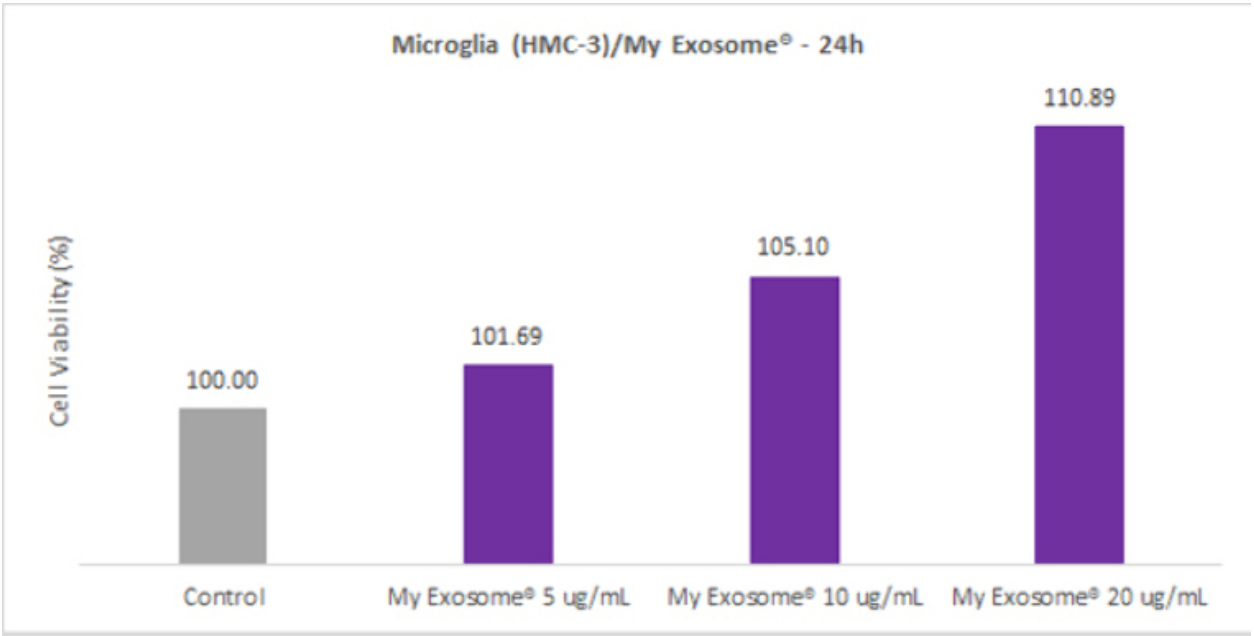
Stats: Mean +/- Standard Error

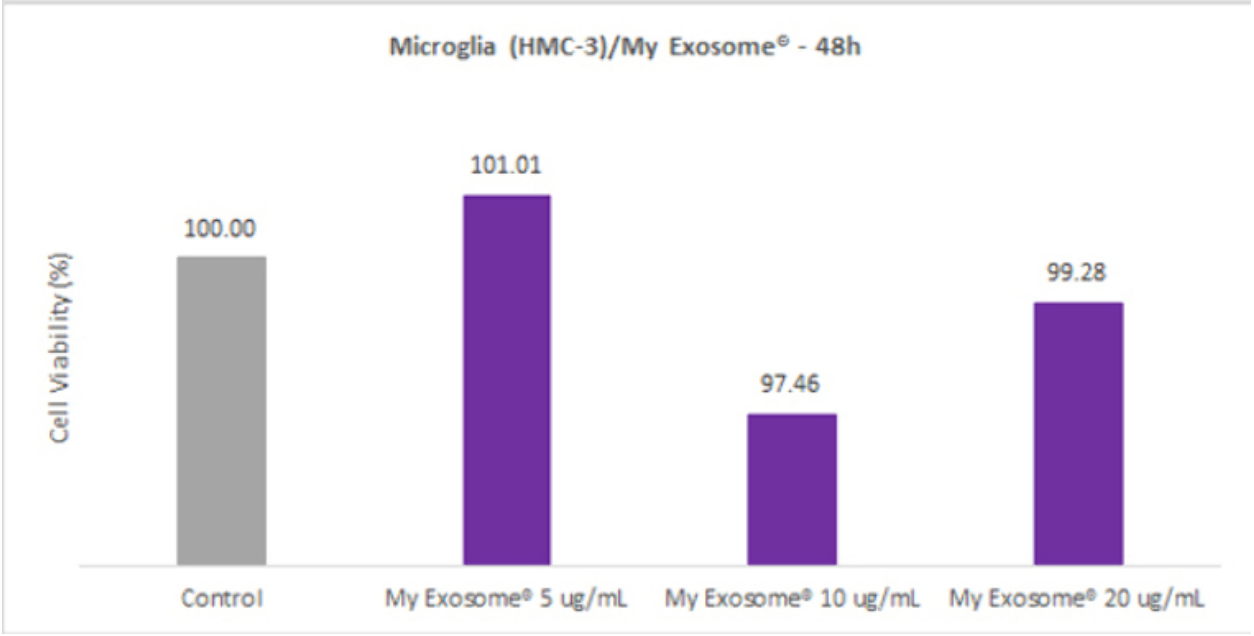
Mean:	149.2 +/- 6.1 nm
Mode:	109.4 +/- 3.7 nm
SD:	57.2 +/- 6.4 nm
D10:	94.3 +/- 4.3 nm
D50:	137.0 +/- 11.1 nm
D90:	214.1 +/- 5.4 nm
Concentration (Upgrade):	2.50e+11 +/- 7.97e+09 particles/ml
	26.8 +/- 1.4 particles/frame
	31.9 +/- 1.0 centres/frame

Concentration measurements may be unreliable
See summary file for more info


Neuroblastoma (SH-SY5Y) Alzheimer Model/MyExosome®-24h
Cell Viability (%)
100.00
52.70
75.84
78.08
76.69
Healthy Control
Alzheimer Model
Alzheimer - My Exosome® 5 ug/mL
Alzheimer - My Exosome® 10 ug/mL
Alzheimer - My Exosome® 20 ug/mL


Neuroblastoma (SH-SY5Y) Alzheimer Model/MyExosome®-48h
Cell Viability (%)
100.00
56.80
82.78
92.51
83.57
Healthy Control
Alzheimer Model
Alzheimer - My Exosome® 5 ug/mL
Alzheimer - My Exosome® 10 ug/mL
Alzheimer - My Exosome® 20 ug/mL





Conclusions: MyExosome® rapidly reduces amyloid beta toxicity in Alzheimer cell culture model and increases microglia viability, wich seems to have a potential therapeutic efficacy for Alzheimer's diseases.

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SHIFT 02-154

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
4-5 April 2025

ALZHEIMER'S DISEASE MODELS IN IPSC-DERIVED GLUTAMATERGIC NEURONS SHOW INCREASED SECRETION OF PATHOGENIC AMYLOID BETA PEPTIDES

Aurora Veteleanu[1], Tony Oosterveen[1], Prachi Bhagwatwar[1], Germano Belli Valletta[1], George Shipley[1], Hannah Garnett[1], Christopher Aruthan[1], Sejla Salic-Hainzl[2], Tilmann Buerckstuemmer[2], Amanda Turner[1], Farah Patell-Socha[1], Karl Firth[1], Oliver Dovey[1], Will Bernard[1], Manos Metzakopian[1], Mark Kotter[1]
[1]Bit Bio, Cambridge, United Kingdom, [2]Bit Bio, Vienna, Austria

Aims: Alzheimer's disease (AD), a complex, multifactorial neurodegenerative disease, is challenging to study in vitro due to a lack of physiologically relevant models. ioGlutamatergic Neurons are deterministically programmed human iPSC-derived excitatory neurons that provide a consistent and scalable model to study such diseases. A panel of AD models in ioGlutamatergic Neurons was developed and characterised to determine the effects of mutations in PSEN1 and APP on amyloid beta (A-beta) production.
Methods: CRISPR-cas9 was used to engineer heterozygous and homozygous PSEN1 M146L, APP KM670/671NL or APP V717I mutations in the parental iPSC-line of the ioGlutamatergic Neurons, which were subsequently programmed using opti-ox technology to generate the disease model cells. The disease models were cultured for 30 days alongside their genetically matched wild type control. Supernatant was collected on days 10, 20 and 30, and concentrations of A-beta38, A-beta40 and A-beta42 were determined using the V-PLEX A-beta Peptide Panel ELISA kit.
Results: ioGlutamatergic Neurons carrying the PSEN1 M146L and APP V717I mutations secreted significantly more A-beta42 compared to their wild type control, showing higher A-beta42:40 ratios at days 20 and 30. Importantly, a clear correlation between genotype and A-beta42:40 ratios was observed, as wild type, heterozygous and homozygous mutants showed a stepwise increase in A-beta42 production relative to A-beta40. ioGlutamatergic Neurons APP KM670/671NL secreted significantly more A-beta38, A-beta40, and A-beta42 than their wild type control but the A-beta42:40 ratio did not increase, as expected.
Conclusions: ioGlutamatergic Neurons with mutations in PSEN1 or APP recapitulate the increase in A-beta42 secretion observed in Alzheimer's patients. This demonstrates their validity as an in vitro model to study AD and for the discovery of drugs targeting the pathogenic A-beta pathway.

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SHIFT 02-155

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
4-5 April 2025

CHARACTERIZATION OF THE ROLE OF THE METALLOPROTEINASE ADAM17 IN ALZHEIMER'S DISEASE

Lena Schaack, Alexander Skupin, Jochen Schneider
Luxembourg Centre for Systems Biomedicine, Belvaux, Luxembourg

Aims: ADAM17 is a transmembrane metalloprotease with protein cleavage activity. As an alpha-secretase, ADAM17 plays a role in the processing of the amyloid precursor protein (APP). Cleavage of APP in the amyloidogenic pathway leads to the production of amyloid beta (Aβ). However, in the alternative non-amyloidogenic pathway involving ADAM17, no Aβ is formed. Furthermore, one of the products of this alternative pathway, sAPPa, is believed to protect neurons by regulating Aβ levels. Decreased ADAM17 activity could thus contribute to the accumulation of Aβ plaques in Alzheimer's disease (AD). Recently, a heterozygous ADAM17 R215I mutation has been implicated in familial late-onset AD. ADAM17 was also associated with Alzheimer's pathology in a GWAS study, but a clear mechanistic understanding is missing. The R215I mutation, located in ADAM17's prodomain—essential for protein maturation and trafficking—likely disrupts membrane localization and proteolytic activity, potentially exacerbating Aβ aggregation and Alzheimer's progression. Given ADAM17's broad substrate spectrum, encompassing over 90 proteins with diverse functions, the dysregulation of ADAM17 could profoundly influence cellular development, differentiation, adhesion, signalling, survival and inflammation. Uncovering the mechanism of ADAM17 dysfunction would offer insights into Alzheimer's complex aetiology.
Methods: This project is using cortical neurons and microglia derived from human iPS cell lines with wildtype ADAM17 and heterozygous R215I mutated ADAM17.
Results: In initial experiments, the R215I mutant cell line shows a decreased ability to differentiate into neurons and has differences in proliferation compared to the isogenic control.
Conclusions: The ADAM17 R215I mutation was found to affect neuronal differentiation and proliferation. Further studies will investigate the effect on microglial activation and demonstrate effects of the R215I mutation on ADAM17 processing an subsequent changes in cleavage activity.

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SHIFT 02-156

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / APP, APLP, ABETA
4-5 April 2025

AMYLOID-BETA INDUCES TOXICITY AND CELL DEATH IN HUMAN IPSC DERIVED NEURONS

Malika Bsibsi, Catalina Gomez-Puerto, Lieke Geerts, Matteo Zanella, Stefan Kostense, Marijn Vlaming
Charles River Laboratories, Leiden, Netherlands

Aims: Alzheimer's is a genetic chronic neurodegenerative disease that typically begins around the age of 60 and progressively impairs cognition and language. A key common hallmark is the accumulation of plaques containing β-amyloid that leads to synaptic failure and, eventually, neuronal death. In recent years, reproducing and studying the mechanisms behind Alzheimer's disease's (AD) pathology and β-amyloid plaques-dependent degeneration have been facilitated by the advent of induced pluripotent stem cells (iPSCs).
Methods: We lately developed a robust AD in vitro model, based on the treatment of iPSC-derived glutamatergic neurons with commercially available β-amyloid aggregates.
Results: Compared to vehicle control and untreated cells, exposure of neurons to β-amyloid for 72 hours induced toxicity, as shown by the destruction of neuronal structures (stained for β-III tubulin) and the reduction of DAPI-positive healthy nuclei. In addition, neurodegeneration was further confirmed by a higher release of Neurofilament Light chain (NfL) in β-amyloid aggregate-treated neurons.
Conclusions: Taken together, these preliminary results support the validity and strength of this model and open the path for future disease-relevant applications, including compound screening, with the goal of establishing effective treatments for AD.

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SHIFT 02-159

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
4-5 April 2025

INFLUENCE OF SHORT TANDEM REPEATS ON DNA METHYLATION IN THE BRAIN

Olena Ohlei[1,2], Ida Happel[2], David Gmelin[2], Valerija Dobricic[2], Laura Parkkinen[3,4], Lars Bertram[2]
[1]University of Münster, Institute Of Epidemiology And Social Medicine, Münster, Germany, [2]University of Lübeck, Lübeck Interdisciplinary Platform For Genome Analytics (liga), Lübeck, Germany, [3]University of Oxford, Oxford Parkinson's Disease Centre, Oxford, United Kingdom, [4]University of Oxford, Nuffield Department Of Clinical Neurosciences, Oxford, United Kingdom

Aims: Quantitative trait locus (QTL) mapping is a powerful procedure to elucidate the genetic basis of complex phenotypes, including molecular traits such as DNA methylation (DNAm). Typically, this type of analysis is performed using single nucleotide polymorphisms (SNPs), while other types of genetic variation, e.g. short tandem repeats (STRs), are often disregarded. To close this gap, we have performed genome-wide methylation QTL (meQTL) mapping in human brain using both SNPs and STRs.
Methods: Genetic (Global Screening Array, Illumina) and DNAm (MethylationEPIC Array, Illumina) data were generated from DNA samples of the entorhinal cortex (EC), collected from probands of the Oxford Brain Bank (n = 145). STRs were imputed from genome-wide SNP data. MeQTL mapping was performed using Matrix-eQTL software for both SNP and STR genotypes. To distinguish STR- from SNP-based meQTL signals we used GCTA-COJO software.
Results: Overall, 1.6M STRs and 5.3M SNPs were tested for association with ~665K CpG probes. This led to 118,368 STR-CpG and 353,484 SNP-CpG associations showing genome-wide significance. For variants in *cis* (i.e. within 1Mb) we observed proportionally more significant SNP-CpG pairs, while for longrange *cis* (i.e. >1Mb on the same chromosome) and *trans* (i.e. different chromosomes) we identified significantly more STR-CpG associations. While many of the top meQTL loci overlapped, there were some notable differences across both types of variants.
Conclusions: Our study shows that STRs confer a sizable fraction of meQTL effects that are independent from SNPs. Together with prior work from us and others, these results emphasize the importance of considering STRs as genetic determinants of complex traits. One practical application of our resource is the characterization of STRs associated with Alzheimer's disease risk (see accompanying abstract by Gmelin et al.)

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SHIFT 02-160

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
4-5 April 2025

CELL TYPE SPECIFIC HISTONE ACETYLATION H3K27AC IN ALZHEIMER'S DISEASE BRAIN

Paulina Urbanaviciute[1,2,3], Joy Ismail[1,2,3], Joe Burrage[4], Barry Chioza[4], Emma Dempster[4], Jonathan Mill[4], Sarah Marzi[1,2,3]

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Aims: Histone acetylation H3K27ac is a well-established epigenetic marker of active gene enhancers. Given the presence of genome-wide patterns associated with Alzheimer's disease (AD) and enrichment of genetic loci linked with disease risk, our research aims to characterize H3K27ac epigenetic landscapes in disease-relevant cell types. As part of the Brains for Dementia Research initiative, we aim to produce the largest cell type-specific gene regulatory map to date in AD and control individuals.
Methods: We fine-tuned experimental variables and analytical approaches by extensive optimization and benchmarking of Cleavage under Targets and Tagmentation (CUT&Tag) sequencing. We profiled H3K27ac by CUT&Tag in neuron, oligodendrocyte, and microglia nuclei isolated from post-mortem tissue of 89 patients and 88 controls, yielding 594 samples in the dorsolateral prefrontal cortex and 79 in other brain regions.
Results: Differential analysis across all three cell populations highlighted widespread histone acetylation differences in AD cases. In microglia, we identified upregulation of genomic regions enriched for interleukin-5 and interleukin-13 production, and downregulation of neuroprotective interleukin-4 in AD. Among the downregulated regions, neuroprotective vitamin B binding was enriched, suggesting a link between a downregulation of its downstream processes and AD.
Conclusions: Our study shows CUT&Tag effectively profiles H3K27ac in brain cells, revealing acetylation changes in Alzheimer's, particularly in microglia, highlighting neuroinflammatory pathways and neuroprotection, offering potential therapeutic targets.

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SHIFT 02-161

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / EPIGENETICS, HISTONE MODIFICATION, DNA METHYLATION
4-5 April 2025

CELL TYPE-SPECIFIC HISTONE ACETYLATION MAPPING IN ALZHEIMER'S DISEASE UNCOVERS MICROGLIAL DYSREGULATION VIA MITF

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Aims: Alzheimer's disease (AD) involves cell-type-specific epigenomic alterations affecting key brain processes. Histone acetylation (H3K27ac), an epigenetic marker linked to gene regulation, plays a crucial role in activating enhancers, particularly in disease-relevant cells. Understanding these changes is critical to uncovering how AD develops at the molecular level and identifying therapeutic targets. We aimed to map histone acetylation across microglia, neurons, and oligodendrocytes in AD patients to identify dysregulated gene regulatory regions and transcription factors that drive this.
Methods: H3K27ac ChIP-seq was performed on cell-type-enriched nuclei (neurons, oligodendrocytes, microglia) from the prefrontal cortex of AD patients and matched controls. Differentially acetylated regions were identified and integrated with AD-associated GWAS loci. We corrected for reference allele mapping bias using WASP and repurposed allelic expression tools MBASED and ASEP to test for imbalances in heterozygous SNPs intersecting H3K27ac peaks, providing insight into regions with differential activity driven by genetic variation. Weighted Gene Correlation Network Analysis (WGCNA) was used to define co-regulated regions, and transcription factor motif enrichment identified key regulators of interest.
Results: We identified transcription factor motifs enriched in AD-dysregulated enhancers and prioritized MITF as a key modulator. MITF-associated peaks showed hyperacetylation and were highly enriched in microglia. Motif matching further confirmed MITF's regulatory role in these hyperacetylated enhancers. Allele-specific imbalances in H3K27ac regions revealed differential enhancer activity linked to genetic variation. These findings suggest MITF may contribute to microglial dysfunction through epigenomic dysregulation and exacerbate disease pathology
Conclusions: This study suggests MITF regulates hyperacetylated enhancers in microglia via H3K27ac alterations. MITF's role in lysosomal function may affect amyloid-β degradation, contributing to neurodegeneration in AD. Insights into allele-specific activity highlight new therapeutic opportunities targeting epigenetic regulators to modulate immune responses and potentially slow AD progression.

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SHIFT 02-170

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4-5 April 2025

KNOWN AND NOVEL POST-TRANSLATIONAL MODIFICATIONS RELATE TO COGNITIVE PERFORMANCE AND ALZHEIMER'S DISEASE NEUROPATHOLOGY

Julia Libby[1], Vladislav Petyuk[2], Philip De Jager[3,4], Vilas Menon[3], Julie Schneider[5], Lisa Barnes[5], David Bennett[5], Timothy Hohman[1,6]
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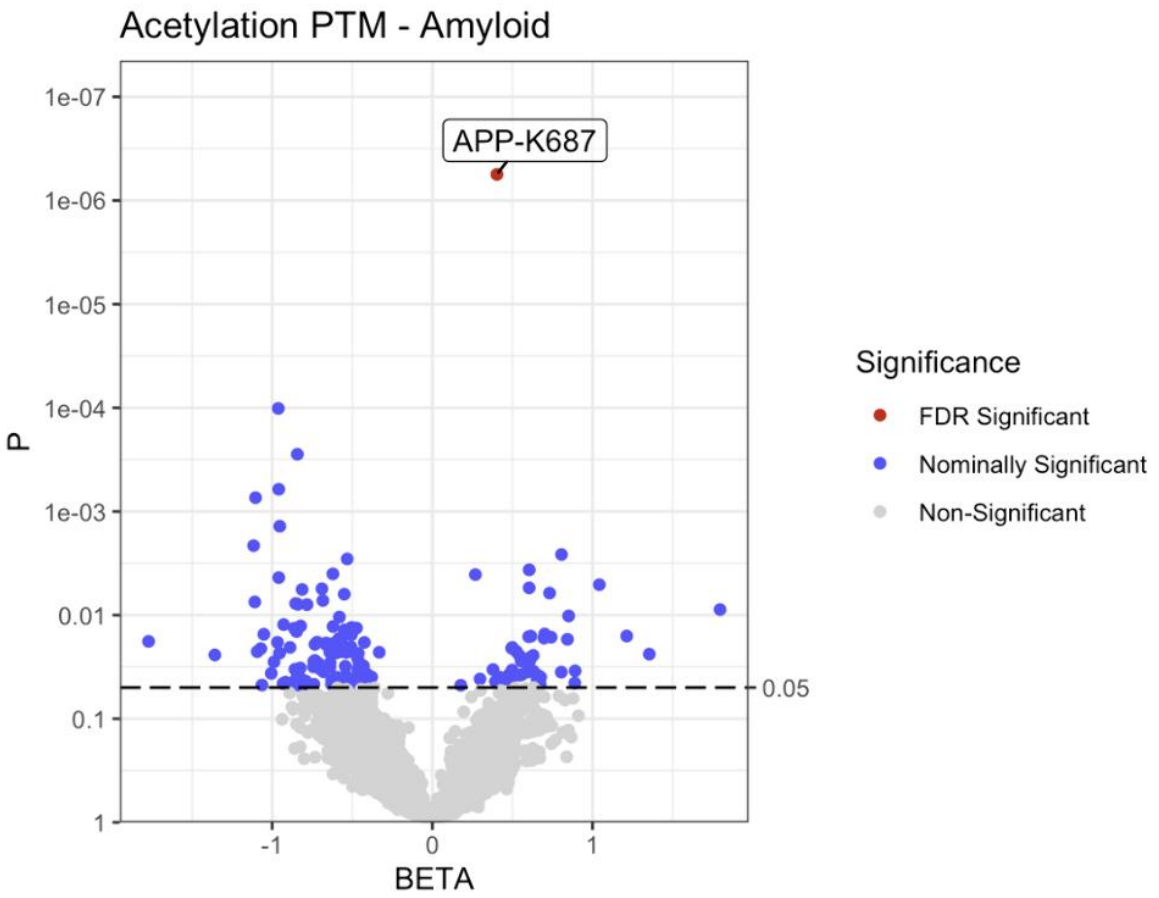
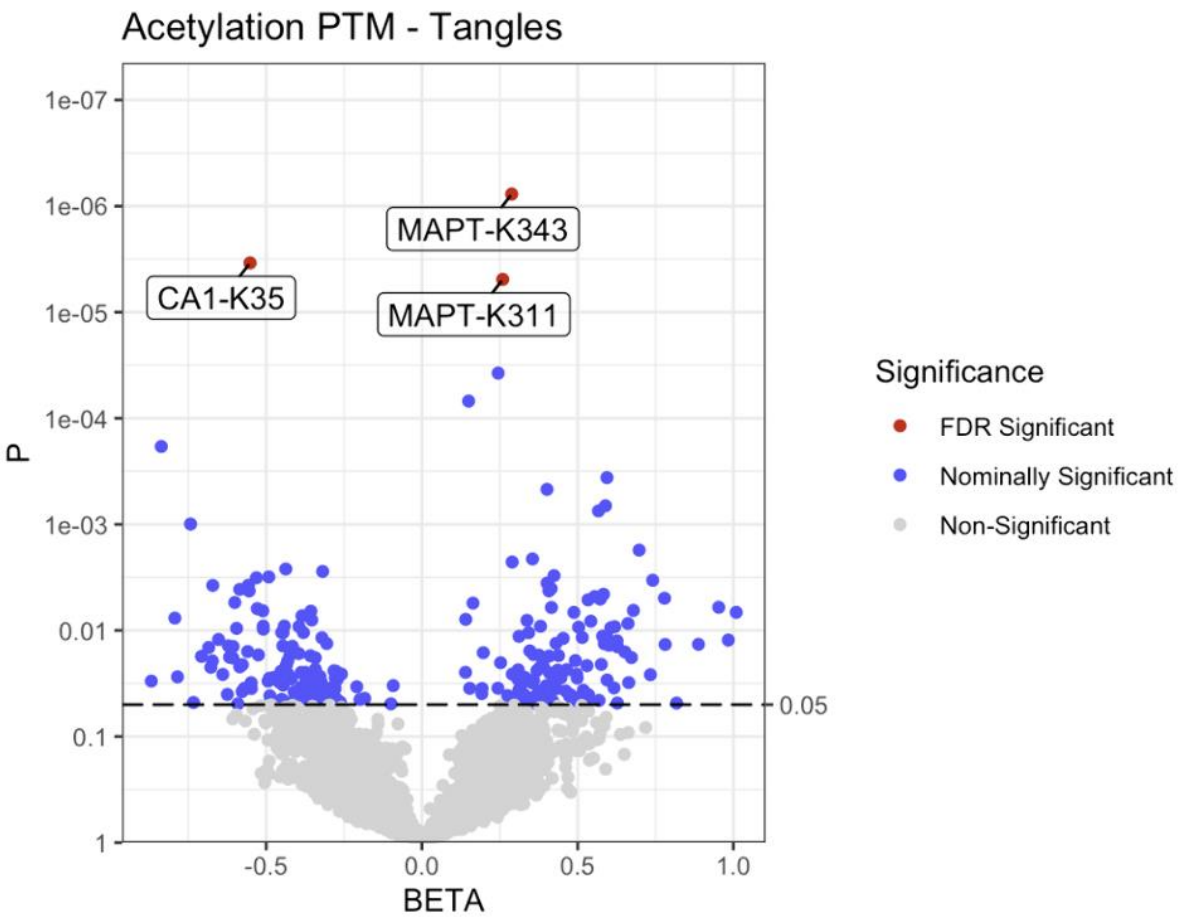
Aims: Proteins undergo various modifications after translation, some of which can have an impact on disease progression. This study explores which post-translational modifications (PTMs) are associated with cognitive performance and Alzheimer's disease (AD) pathology.
Methods: PTMs were quantified with mass spectrometry leveraging tissue from 34 cognitively normal and 69 cognitive impaired participants from Religious Orders Study and Rush Memory and Aging Project (ROS/MAP). 51,654 PTMs across 9,829 proteins were quantified, including acetylation (acet), ubiquitination (ubi), phosphorylation (phos), and cysteine oxidation (cyst). Outcomes included neuropathologically confirmed AD dementia diagnosis, immunohistochemistry measurements of tau tangle density and b-amyloid load, and cross-sectional and longitudinal measures of global cognition. Covariates included sex, age at death, clinical diagnosis at time of death, APOE-e4 carrier status, and post-mortem interval. Correction for multiple comparisons was completed using the false discovery rate (FDR) procedure.
Results: Multiple known proteome-wide PTM sites of MAPT and APP were significantly associated with pathology. Three PTM sites on MAPT contributed to tau tangle density including acet-K343 (β=0.29, P.FDR=0.01), acet-K311 (β=0.26, P.FDR=0.03), and ubi-K298 (β=0.33, P.FDR=0.03). Additionally, acetylation of APP-K687 was associated with higher amyloid burden (β= 0.40, P.FDR=0.01). We also observed multiple novel PTM sites. Multiple sites associated with tau tangle density including acetylation of CA1-K35 (β=-0.55, P.FDR=0.03), and ubiquitination of ARFIP2-K290 (β=0.35, P.FDR=0.008) and PLXND1-K1826 (β=0.55, P.FDR=0.008). Additionally, ubiquitination of LDHB-K91 (β=-0.74, P.FDR=0.02) and TAP2-K245 (β=-0.75, P.FDR=0.02) were associated with cross-sectional global cognitive



performance.



Conclusions: This proteome-wide examination of PTMs in the AD brain highlight known and novel PTMS in MAPT and APP, while also highlighting novel proteins that have PTMs related to amyloid, tau, and cognitive impairment.

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SHIFT 02-171

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4-5 April 2025

COMBINED TRANSCRIPTOME AND PROTEOME PROFILING REVEALS TREM2-DEPENDENT AND -INDEPENDENT GLIAL RESPONSE AND METABOLIC PERTURBATION IN APPNL-G-F MICE

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Aims: Alzheimer's disease (AD) is driven by molecular changes, notably amyloid-beta (Aβ) deposition, which accelerates disease progression. This study aims to elucidate the molecular mechanisms underlying AD pathology by profiling the transcriptome and proteome of *App*$^{NL-G-F}$, a human APP knock-in mouse model, during the early and mid-stages of Aβ pathology. We also investigate the role of TREM2, an AD risk gene, in modulating microglial responses to Aβ deposition.
Methods: Transcriptomic and proteomic analyses were performed on brain tissues from *App*$^{NL-G-F}$ and *App*$^{NL-G-F}$*;Trem2*^{KO} mice at different stages of Aβ pathology. Microglial morphology and the expression of genes related to immune function, lysosome biogenesis and phagocytosis were evaluated. We also assessed microglial impact on Aβ plaque formation and compactness, along with Aβ-associated neuropathology. Lastly, we examined the relationship between Aβ-induced synapse loss and metabolic disruptions in neurons.
Results: Aβ deposition led to significant upregulation of immune-related genes, particularly those involved in the complement system, antigen presentation, phagosome formation, and lysosomal biogenesis. In TREM2-deficient mice, these microglial responses were markedly impaired, resulting in reduced Aβ clearance and exacerbated dystrophic neurite formation. TREM2 was essential for microglial engagement with Aβ plaques and for the formation of compact plaque cores. Additionally, we observed disruptions in energy metabolism and protein synthesis, along with a decline in synaptic protein abundance, which occurred independently of TREM2, indicating a direct impact of Aβ on synaptic integrity.
Conclusions: This study shows that Aβ deposition alters microglial function, with TREM2 playing a critical role in immune and phagocytic responses. Concurrently, Aβ disrupts neuronal metabolism and protein synthesis, contributing to synaptic dysfunction independently of TREM2. These findings suggest that targeting microglial responses and neuronal metabolism could offer new therapeutic strategies for AD.

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4-5 April 2025

CSF PROTEOMIC BIOMARKER ANALYSIS FROM PHASE 2 STUDY SHINE IDENTIFIED EFFECTS OF S2R MODULATOR CT1812 IN ALZHEIMER'S DISEASE

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Aims: In Alzheimer's disease (AD) participants of the SHINE trial (NCT03507790), treatment with sigma-2 receptor (S2R) modulator CT1812 slowed cognitive decline compared to placebo (ADAS-Cog11; 39% slowing in mITT population, 95% slowing in pre-specified p-Tau217 subgroup). Exploratory CSF proteomic analyses were previously performed in smaller cohorts (interim SHINE [SHINE-A] and SPARC). Herein we report findings from the larger SHINE cohort CSF proteomic analysis, identifying CT1812 pharmacodynamic biomarkers of target/pathway engagement and disease modification.
Methods: SHINE (COG0201) was a Phase 2 randomized, double-blind, placebo-controlled study. Participants (N=152) received a daily oral dose of CT1812 (100 or 300 mg) or placebo for 6-months. A CSF proteomic sub-study of 45 participants was performed using tandem-mass tag mass spectrometry (TMT-MS) at baseline and end-of-study. For analyses, CSF from treatment-compliant participants (N=43) were used. Change from baseline was calculated, and differential abundance analysis (combined CT1812 doses vs placebo) was performed, followed by brain protein network and pathway analyses (STRING and Metacore, $p \leq 0.05$).
Results: Brain network and pathway analysis of 113 differentially abundant proteins ($p \leq 0.05$, CT1812 vs placebo) revealed that the impacted proteins enriched modules and pathways related to immune response and synapse biology. The larger SHINE cohort identified 68 new CT1812 pharmacodynamic biomarkers ($p \leq 0.05$, CT1812 vs placebo), including biomarkers dysregulated in AD that were normalized by CT1812 treatment. A subset of pharmacodynamic biomarkers were replicated, including decreased AD genetic risk factor and amyloid-β binding protein CLU/ApoJ.
Conclusions: CSF proteomic analysis of the completed SHINE trial corroborated previously identified biomarkers of CT1812 pathway engagement and disease modification and facilitated identification of novel biomarkers. These data further our understanding of the proteins and pathways CT1812 impacts and help support the observed synaptoprotective mechanism-of-action and continued clinical development of CT1812 for AD.

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β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4-5 April 2025

METABOLOMIC SIGNATURES AND MACHINE LEARNING MODELS FOR DISTINGUISHING ALZHEIMER'S DISEASE AND DEMENTIA WITH LEWY BODIES

Dany Mukesha[1], Maïté Sarter[2], Mélitine Dubray[2], Floris Durand[2], Kilian Henry[2], Anne Hirschfell[1], Kenza Boussahela[1], Lucas Pham-Van[3], Seval Kul[1], Stéphanie Boutillier[3], Hüseyin Firat[1]
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Aims: Alzheimer's Disease (AD) and Dementia with Lewy Bodies (DLB) are difficult to distinguish clinically due to overlapping symptoms, resulting in delayed or incorrect diagnoses. This study uses metabolomic profiles from serum samples and machine learning models to identify key biomarkers that distinguish these conditions.
Methods: Samples from ADDIA study (ClinicalTrials.gov NCT03030586) were prepared for targeted mass spectrometry (LC-MS), non-targeted MS and metabolite profiling was conducted using the Biocrates 400 metabolites panel. We used Principal Component Analysis (PCA) to explore data structure and control for batch effects. We performed ANOVA to examine the influence of age and gender on biomarker levels. Machine learning models, including Lasso, Random Forest, and XGBoost, were then applied to classify AD and Health elderly (HC) groups and evaluated using repeated cross-validation. The role of APOE genotype in improving model accuracy was also investigated.
Results: We identified significant age and gender adjusted biomarkers for AD vs HC, AD vs DLB, and DLB vs HC. The machine learning models achieved AUC values ~0.9 for AD vs HC, with APOE genotype enhancing model accuracy. ROC analysis for the top AD-associated metabolites revealed AUC of 0.714 (95% CI: 0.583-0.828) when discriminating between mild AD and mid-severe AD. The combination of the top three metabolites further improved classification performance, suggesting that integrating multiple biomarkers may enhance differentiation between early and late-stage AD.
Conclusions: These findings offer an advantage for reducing misdiagnosis of AD and emphasize the potential for these biomarkers in clinical applications, demonstrating high classification accuracy. We are extending this work to a large cohort of ~2000 urine samples to validate the data from the ADDIA and ADKIT studies, aiming to develop a non-invasive and cost-effective screening method for neurodegenerative diseases.

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4-5 April 2025

DISTINCT MOUSE MODELS CORRESPOND TO DISTINCT AD MOLECULAR SUBTYPES

Ravi Pandey[1], Kevin Kotredes[2], Michael Sasner[2], Adrian Oblak[3], Bruce Lamb[3], Gareth Howell[2], Gregory Carter[2]
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Aims: Alzheimer's disease (AD) is a complex, multifactorial pathology with high heterogeneity in biological alterations. Mouse models of AD serve as indispensable platforms for comprehensively characterizing AD pathology, disease progression, biological mechanisms, and cognitive performance. Many existing clinical trials that showed promising efficacy in one particular mouse model later do not align with human trial results, assuming that study participants had consisted of a heterogeneous group of participants across many AD subtypes and individual animal models may only recapitulate features of a subgroup of human cases. To improve interspecies translation, it is necessary to comprehensively compare molecular signatures in AD mouse models with subgroup of human AD cases with distinct molecular signatures.
Methods: We performed mulit-omics profiling on whole brain samples from mouse models carrying LOAD risk variants. We utilized multiple human AD data resources to determine the extent to which changes due to genetic perturbations in mice matched those observed in human AD subtypes and disease stages of AD.
Results: We have identified that distinct mouse models match to distinct human AD modules/subtypes in age-dependent and sex-specific manner. Specifically, mouse models carrying human AD risk variants such as *Abca7*A1527G* showed strong correlation with inflammatory AD subtypes, while mouse models carrying risk variant such as *Plcg2*M28L* exhibited transcriptomics changes similar to non-inflammatory AD subtypes.
Conclusions: In this study, we highlighted that mouse model of AD may match to a particular subset of human AD subtypes but not all subtypes simultaneously, and that risk for these subtypes may be influenced by distinct AD genetic factors. Additional work toward validating and better understanding the role of each subtype key regulator in its matching mouse model will provide great value and have a great impact on future studies of AD.

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SHIFT 02-175

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β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4-5 April 2025

PLASMA PROTEOMICS IDENTIFY A 10-PROTEIN PANEL INVOLVED IN EARLY AD

Carmen Peña Bautista[1], Angel Balaguer[2], Luis Raga[1], Lourdes Álvarez-Sánchez[3], Laura Ferré-González[3], Miquel Baquero[4], Consuelo Cháfer Pericas[5]
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Aims: The aim of this study is to study the proteomic profile in plasma samples from patients with AD and controls, in order to provide new potential biomarkers in minimally invasive samples, and analyse the main altered pathways from mild cognitive impairment (MCI) due to AD.
Methods: Sixty patients from the Cognitive Impairment Unit of Hospital La Fe were included. Plasma samples were analysed by LC-MS/MS to obtain their proteomic profile. They were classified into MCI-AD and controls according to standard biomarkers in CSF, neuropsychological assessment and neuroimaging. Discriminant analysis was performed to select a panel of potential biomarkers in plasma from partial least squares (PLS) regression and volcano plot. The main affected pathways were then analysed by String.
Results: A total of 62 of the 1094 proteins analysed showed significant differences between patients with MCI-EA and controls. For discriminate analysis, variables were selected by Volcano plot (n=22) and PLS (N=45). Of these, 10 were common in both analyses (CDC5L, CRIP1, CRTAC1, HYDIN, IGLV4-69, LTBP2, MMP14, PLIN3, REG3A, SHH). All of them showed higher relative levels in MCI-AD with respect to controls, except SHH. In addition, these proteins showed correlation with CSF biomarkers as well as cognitive status. In terms of pathway analysis, biological processes related to stress or stimuli response, immune system, cell adhesion and proteolysis stand out.
Conclusions: The analysis of plasma proteins allows the identification of potential biomarkers for AD. Specifically, we have selected a panel of 10 potential biomarkers that could be useful in early diagnosis taking into account various biological pathways.

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SHIFT 02-176

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β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / METABOLOMICS, TRANSCRIPTOMICS, LIPIDOMICS, PROTEOMICS
4-5 April 2025

A MULTI-OMICS EXPLORATION OF SYSTEMIC AND CENTRAL NERVOUS SYSTEM BIOLOGICAL PATHWAY ALTERATIONS ASSOCIATED WITH GINKGO BILOBA TREATMENT

Miriam Rabl[1], Christopher Clark[1], Julius Popp[1,2]
[1]Psychiatric University Hospital, University of Zurich, Department Of Psychiatry And Psychotherapy, Zurich, Switzerland, [2]Lausanne University Hospital, Old-age Psychiatry Service, Department Of Psychiatry, Lausanne, Switzerland

Aims: Ginkgo biloba extract showed neuroprotective effects in animal studies but little is known about its biological effects in humans. Here, we sought to identify the biological pathways affected by Ginkgo treatment in non-demented older subjects.
Methods: We selected 26 non-demented subjects undergoing a treatment by Ginkgo extract for at least 3 months and 35 subjects without treatment matched for age and BMI from a well-characterised cohort of participants on an Alzheimer's disease biomarker study. Clinical and neuropsychological data, the APOEε4 genotype and albumin ratio were available in both groups. Targeted and untargeted omics approaches were used to quantify analytes in paired cerebrospinal fluid (CSF) and peripheral blood samples. Group comparisons and multivariate ROC analysis were used to identify features differing between groups. Pathway enrichment analysis was performed using hypergeometric distribution tests in the Reactome database.
Results: Group comparisons identified 22 molecules in CSF and 29 in peripheral blood with different concentration levels. The identified neuroinflammatory markers, proteins, minerals and lipids were related to changes in insulin signalling and haemostasis in blood, and to intracellular signalling in the CSF. Multivariate analysis of untargeted metabolomics data analysis in peripheral blood further identified 463 differentially expressed features between groups, mainly related to amino acid and energy metabolism.
Conclusions: Distinct biological alterations in blood and CSF at neuroinflammatory, proteomic, lipidomic, and metabolite levels are associated with Ginkgo treatment. Some of the identified alterations have previously been shown to be associated with dementia and cognitive decline. In further steps, we will relate these alterations to clinical evolution, considering both cognitive and neuropsychiatric symptoms.

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SHIFT 02-180

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
4-5 April 2025

A TOOLBOX OF HUMAN IPSC-DERIVED WILD TYPE, DISEASE MODEL AND CRISPR-READY CNS CELL TYPES FOR COMPLEX ALZHEIMER'S DISEASE MODELLING

Amanda Turner[1], Tony Oosterveen[1], Camilla Fairbairn[1], Philippa Barton[1], Euan Yates[1], Alessandro Abram[1], Richard Hickman[1], Hannah Garnett[1], Lukasz Kowalski[1], Stefan Milde[1], Magdalena Gamperl[2], Barnabas Koenye[2], Samir-Pierre Barbaria[2], Prachi Bhagwatwar[1], Germano Belli Valletta[1], George Shipley[1], Christopher Aruthan[1], Sejla Salic-Hainzl[2], Tilmann Buerckstuemmer[2], Farah Patell-Socha[1], Karl Firth[1], Oliver Dovey[1], Will Bernard[1], Manos Metzakopian[1], Mark Kotter[1]
[1]Bit Bio, Cambridge, United Kingdom, [2]Bit Bio, Vienna, Austria

Aims: In a neurodegenerative disease such as Alzheimer's Disease (AD), the impairment of neuronal functions leads to the gradual loss of cognition and memory. Consequently, a neuron-centric view has prevailed for a long time in AD research, and the role of glia has been under-investigated. In recent years, it has become more evident that amyloid-beta peptides can activate inflammatory responses in astrocytes and microglia as well as cause focal demyelination of axons ensheathed by oligodendrocytes, thereby critically contributing to AD progression. In addition, complex feedback and forward responses between these glial cells may exacerbate neurodegeneration.
Methods: Using deterministic cell programming technology, opti-ox, we generated from iPSCs the key cell types involved in AD progression, and generated genetically matched disease models and CRISPR-ready cells.
Results: iPSC-derived ioMicroglia expressed the classical markers CD45, P2RY12, CD11b, CD14, IBA1, and TREM2, phagocytosed various particles and exhibited a cytokine response to LPS and IFN-gamma stimulation. These cells can be co-cultured with excitatory neurons (ioGlutamatergic Neurons), within which we engineered different AD disease models, highlighting the ability to generate more complex cellular model systems to study AD. In addition, the generation of CRISPR-ready derivatives of both cell types allows the identification and characterisation of genes that drive AD progression in a cell-type specific manner. We have developed co-culture protocols to combine ioGlutamatergic Neurons with other glial cells, including ioAstrocytes and ioOligodendrocyte-like cells, to build more physiological in vitro models to mimic and disentangle the complex cellular interactions during AD.
Conclusions: We generated a versatile toolbox of CNS-related cell types, offering researchers the possibility to combine various wild type and disease model cells. This platform provides a powerful tool for unravelling the molecular processes underlying AD.

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SHIFT 02-181

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
4-5 April 2025

PRESENCE OF MOTILE CILIA-ASSOCIATED PROTEINS IN THE CSF OF ALZHEIMER'S DISEASE PATIENTS SUGGESTS MOTILE CILIA DYSFUNCTION

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Aims: Proper cerebrospinal fluid (CSF) flow is required for the clearance of toxic cellular waste, including amyloid-β (Aβ) plaques and tau tangles. A main driver of CSF flow is the synchronous beating of motile cilia present in ventricular ependymal cells. However, not much is known about motile cilia dysfunction in AD. The aim of this study was to find motile cilia-related proteins dysregulated in AD patients.
Methods: For this study, the European Medical Information Framework Alzheimer's Disease Multimodal Biomarker Discovery (EMIF-AD MBD) cohort was divided into five groups: individuals with normal cognition (NL; n=69), NL with an abnormal Aβ score (NL+; n=18), mild cognitive impairment (MCI; n=102), MCI with an abnormal Aβ score (MCI+; n=92), and diagnosed AD (n=91). Proteomics data from CSF was crosschecked with cilia protein databases to search for cilia-related proteins altered in AD individuals.
Results: We found that 458 (21.5%) of the 2131 proteins detected in CSF were cilia-related, and 97 of these proteins showed significant changes across the five clinical groups. A panel of cilia-related proteins was created based on expression changes between AD, MCI and NL, associations with MMSE score, Aβ ratio, and APOE ε4 locus, immunostaining of multi-ciliated tissues, and RNA expression in ciliated cells. The panel consists of 14-3-3ε (FC=1.8, p<2e-14), 14-3-3ζ (FC=2.2, p<3.7e-14), 14-3-3γ (FC=1.7, p<4.3e-8), DDAH1 (FC= 1.3, p<1.3e-6), GDA (FC=1.6, p<7.9e-6), TXN (FC=1.2, p<0.002), CKB (FC=1.3, p<3.6e-5), and NUTF2 (FC=1.5, p<0.01).
Conclusions: Increased levels of motile cilia-related proteins in the CSF of AD patients suggest enhanced

degradation of motile cilia. These findings indicate that degradation of motile cilia may play a role in AD development, possibly by altering CSF flow and reducing clearance of Aβ plaques and tau tangles.

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SHIFT 02-182

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
4-5 April 2025

QUIESCENCE AND DIFFERENTIATION POTENTIAL IN IPSC-DERIVED NEURAL PROGENITORS AND HUMAN ADULT NEURAL STEM CELLS

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Aims: This study aims to investigate differences in quiescence-associated gene expression between induced neural progenitor cells (NPCs) derived from induced pluripotent stem cells (iPSCs) and adult neural stem/progenitor cells (aNSPCs) isolated from postmortem human brain regions. Our goal is to better understand how quiescence affects the differentiation potential of these two neural cell types. This study has important implications for neural regeneration and neurodegenerative disease research.
Methods: iNPCs were generated from iPSCs reprogrammed from postmortem human dura mater tissue. aNSPCs were isolated from neurogenic regions of the postmortem brain, including the subventricular zone (SVZ) and hippocampus. Bulk RNA sequencing was performed on iNPCs (n=3) and aNSPCs (n=3) to identify differential gene expression, focusing on quiescence and activation-associated genes. Bioinformatic analyses assessed pathways related to cell cycle regulation, quiescence, and differentiation.
Results: iNPCs demonstrated a significantly higher differentiation potential, accompanied by reduced expression of quiescence-associated genes, including ASCL1, ALDOC, HUWE1, ID3, and ILK1. In contrast, aNSPCs displayed a more pronounced quiescent phenotype, with elevated expression of genes linked to stem cell dormancy, suggesting lower capacity for differentiation.
Conclusions: iNPCs, derived from iPSCs, maintain a more active and proliferative phenotype compared to quiescent aNSPCs derived from adult brain tissue. This study highlights the potential of iNPCs in regenerative research and provides insights into stem cell quiescence and activation mechanism in the adult human brain. Future research focusing on modulating quiescence in aNSPCs to enhance their differentiation capacity could advance neurodegenerative disease modeling and our understanding stem cell behavior in aging or disease contexts.

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SHIFT 02-183

Poster on Board - Shift 02
β-AMYLOID DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / OTHER
4-5 April 2025

NON-INVASIVE IN VIVO IMAGING USING DETECTION OF CASPASE-1 ACTIVATION FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE

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Aims: In this study, we aimed to develop an activatable fluorescence probe for visualization of active caspase-1. This caspase-1 activatable probe is
biocompatible, efficiently delivered into cells and tissues, and specifically emits fluorescence upon caspase-1 activation as assessed in in vitro and in vivo models of Alzheimer's disease.
Methods: Cas-1 probe (100 μg/100 μl of saline/mouse) was intravenously injected via tail vein at the indicated time after LPS and ATP treatment. Live mice or lymph nodes collected from sacrificed animals were imaged by an IVIS-Lumina Series III at the indicated time after the probe injection. For Alzheimer's disease model, 5x familial AD (5xFAD) mice were used. T-maze and Y-maze were performed in the animal behavior laboratory in SNU. Collected tissues were applied for biochemical assays.
Results: The alternation ratio in 5-month-old 5xFAD mice evalutated with T- and Y-maze tests decreased when compared with WT, indicating a significant cognitive impairment starting at 5 months in 5xFAD mice. Surprisingly, however, we found a significant increase in fluorescence intensity in 3-month-old 5xFAD mice, which have not yet developed cognitive impairment. Ex vivo imaging consistently showed that caspase-1 activation was significantly increased in the brain and lymph nodes of 3-month-old 5xFAD mice than WT mice. These results suggest that caspase-1 activating probe could be applied for early diagnosis of Alzheimer's disease.
Conclusions: The caspase-1 probe enables detection of neuroinflammation in vivo two months earlier than cognitive impairments occur in Alzheimer's disease model. We detected significant fluorescence emitted from brain tissues, as well as their draining lymph nodes, by macroscopic imaging analysis within 30 min after systemic injection of the probe. This novel synthetic probe could be applied for efficient and rapid detection of caspase-1 activity in a spatio-temporal way by non-invasive imaging.

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SHIFT 02-191

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4-5 April 2025

DO YOU REALLY KNOW YOUR AMYLOID-BETA? THE EFFECT OF AMYLOID-BETA 42 PRODUCTION SOURCE ON ITS AGGREGATION AND TOXICITY

Lei Ortigosa-Pascual[1], Karolina Matulewska-Sobczuk[1], Ewa Andrzejewska[2], Greta Šneiderienė[2], Alexander Dear[1], Dev Thacker[1], Tuomas Knowles[2], Sara Linse[1]
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Aims: The key pathological hallmark of Alzheimer's disease (AD) is the aggregation of amyloid-beta protein (Aβ) into toxic oligomers and fibril plaques. While extensive research has focused on Aβ42, the predominant form in humans, the literature is divided over the use of recombinantly produced AB42 (rAβ42), and Aβ42 produced via peptide synthesis (sAβ42). Previous studies have noted differences between the behaviour of rAβ42 and sAβ42, hinting at the importance of protein choice. In this study, we aim to understand the effects of protein choice on aggregation kinetics, fibril structure and toxicity, and to provide the necessary knowledge for every Aβ42 user to choose their protein source.
Methods: We used a series of aggregation experiments to identify the aggregation mechanism of peptide from the two sources, as well as their seeding capacity. The aggregated fibril structures were compared via cryo-EM. Finally, the toxicity of the variants was compared in terms of oligomer production.
Results: Our results revealed that sAβ42 has a slower aggregation and lower seeding capacity than rAβ42, due to a lower rate of secondary nucleation. This aligns with results showing higher oligomer production and toxicity of rAβ42. Finally, we identify sequence inhomogeneity as the most probable factor contributing to the identified differences.
Conclusions: Overall, we show unequivocal proof of the differences caused by Aβ42 production source, and its consequences on aggregation, fibril morphology and toxicity. This study provides crucial knowledge for a more informed choice of protein source for anyone working with Aβ42.

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SHIFT 02-192

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4-5 April 2025

MICROGLIA, ASTROCYTES AND PERIVASCULAR MACROPHAGES CONTRIBUTE TO THE PERI-AB PLAQUES NEURODEGENERATION IN THE HIPPOCAMPUS OF ALZHEIMER'S DISEASE PATIENTS

Mónica Miranda De La Maza[1,2,3], Gaël Hammer[3,4], Félicia Jeannelle[3,4], Sophie Schreiner[3,4], Michel Mittelbronn[1,2,3,4], David Bouvier[1,3,4]
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Aims: Extracellular β-amyloid (Aβ) plaques, tau neurofibrillary tangles and α-synuclein inclusions are key neuropathological features in various neurodegenerative diseases (NDDs). The hippocampus, crucial for memory formation, is particularly vulnerable in these conditions. The role of glial and immune cells in misfolded protein pathology remains debated. Microglia, brain-resident immune cells, accumulate around Aβ-plaques in Alzheimer's disease (AD), while reactive astrocytes form a glial net around them. We demonstrated that infiltrating perivascular macrophages associate with Aβ-plaques. Given the prominence of amyloid-targeting therapies, understanding the peri-plaque cellular microenvironment is critical. Here, we aim to characterise the glial-immune peri-Aβ plaque microenvironment in human control (CTL) and AD *post-mortem* hippocampus to explore their contribution to disease progression.
Methods: Using multiplex chromogenic immunohistochemistry and digital pathology image analysis, we assess distribution and number of microglia (Iba1), astrocytes (GFAP) and peripheral macrophages (CD163) relative to Aβ-plaques areas in hippocampal subfields (Dentate Gyrus, Cornu Ammonis (CA4, CA3, CA1)) of human CTL and AD *post-mortem* samples.
Results: Microglia were the most prevalent cells associated with plaques in AD compared to astrocytes and macrophages. Their distribution around plaques varied across hippocampal subfields, with higher density of microglia/μm^2 amyloid area in CA3 and CA1 compared to DG. In contrast, astrocytes density/amyloid area was greater in CA4 and CA1. Macrophages were less frequent around plaques in CA4 compared to other subfields. There was a positive correlation between the number of microglia and astrocytes/amyloid area across all subfields. We found a weaker positive correlation for CD163+cells/amyloid area.
Conclusions: Our preliminary data show that glial-immune distribution in the peri-plaque environment in AD varies across hippocampal subfields. Understanding their interactions and contribution to other NDDs will offer valuable insights into peri-plaque degenerative mechanisms across NDDs.

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SHIFT 02-193

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4-5 April 2025

PHOSPHORYLATION-STATE SPECIFIC INTERACTION OF ABETA VARIANTS WITH RAGE

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Aims: Alzheimer disease (AD) is the most common form of neurodegenerative diseases, and deposition of amyloid-β (Aβ) peptides in form of extracellular plaques is a characteristic neuropathological feature in AD brains. Aβ can be phosphorylated at Ser8 (pS8Aβ) and Ser26 (pS26Aβ). The receptor for advanced glycation end products (RAGE) is expressed by brain endothelial cells, and involved in Aβ influx into the central nervous system. Here, we sought to characterize the effect of Aβ phosphorylation on the interaction with RAGE.
Methods: Molecular dynamics (MD) simulations was applied to understand the structural basis of the interactions between the soluble RAGE ectodomain (sRAGE) and the different Aβ phosphorylation-state variants. Furthermore, the effects of RAGE on the aggregation of Aβ variants was assessed by real-time fluorescence spectroscopy.
Results: Here, we show that phosphorylated Aβ variants pS8Aβ and pS26Aβ exhibit increased interaction with sRAGE as compared to non-phosphorylated (np) Aβ. The root mean square deviation and radius of gyration of sRAGE-Aβ complexes show no significant structural deviations throughout the 100 ns MD simulation, which indicate the formation of stable complexes between sRAGE and Aβ variants. The binding free energy predictions calculated through MD simulations showed the differential affinity between sRAGE and different Aβ1-42 variants, with pS26Aβ showing the strongest binding. Comparison of secondary structure transitions indicated that all three Aβ variants formed a Glu22- and Asp23-centered turn and relatively unstructured N-terminal and C-terminal parts. Furthermore, aggregation studies showed inhibitory effects of sRAGE on the aggregation of the different Aβ variants.
Conclusions: Together, our findings provide molecular insight into the interaction of RAGE with different Aβ species, and reveal a novel functional role of RAGE in the modulation of Aβ aggregation.

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Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4-5 April 2025

HIGH-RESOLUTION MULTIMODAL PROFILING OF PROTEIN AGGREGATES IN THE CNS OF ALZHEIMER'S DISEASE MOUSE MODELS

Valeriia Skoryk[1,2], Pablo De Castro Mínguez[1], Ana Rosental[1], Jorge Sánchez[1], Agnes Paulus[1], Iran Da Silva[1], Oxana Klementieva[1,2]
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Aims: Early detection of amyloid plaques and protein aggregates with toxic potential is critical for improving diagnosis and prognosis of Alzheimer's disease (AD) as well as for understanding its pathology. However, current methods often miss complex structural details. This study investigates the use of a **multimodal imaging pipeline** to detect and characterize extracellular and intracellular protein assembles in CNS of AD mouse models taking into account microenvironment condition.
Methods: High-resolution X-ray phase-contrast tomography (XPCT), combined with **optical photothermal infrared spectroscopy (OPTIR)**, provides label-free 3D imaging of protein structures at subcellular resolution (up to 500nm). We applied XPCT on brains and spinal cords from two AD mouse models — 5xFAD and hAPPNL-G-F knock-in. As a next step, we acquire an infrared profile from the same sample, which provides compositional data on lipid, nucleic acid, and protein structures within extracellular and intracellular assembles. It is followed by multiplex immunolabeling to bring compositional validation on infrared and X-ray profiles of variative amyloid appearance and changes in surrounding tissue.
Results: By incorporating all three state-of-the-art techniques, we observed accumulations of higher X-ray intensity voxels aligned with both increased and not increased intensity of infrared spectral peaks for ß-sheet, parallel, and antiparallel structures. On the other hand, some immunolabeled extracellular and intracellular amyloid aggregates did not show a change in X-ray data voxel intensity. Moreover, there were small protein aggregates that only partially overlapped with immunolabeling data. This workflow allowed us to identify different complex amyloid structures within 3D spatial context of surrounding microenvironment changes.
Conclusions: This novel multimodal approach enhances our understanding of amyloid composition and its toxicity by correlating it with changes in the microenvironment. It pushes the boundaries of detection of potentially toxic early-stage AD hallmarks.

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SHIFT 02-195

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4-5 April 2025

ANGIOTENSIN-CONVERTING ENZYME (ACE) GENE INSERTION/DELETION (I/D) POLYMORPHISM IN ALZHEIMER'S DISEASE: BRAIN VOLUME AND HYPERTENSION FROM A RETROSPECTIVE STUDY

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Aims: The angiotensin-converting enzyme (ACE), primarily expressed in lungs and serving to regulate blood pressure, is one of the genes implicated in Alzheimer's disease (AD). The ACE gene has been reported to influence the degradation of beta-amyloid. Regarding ACE insertion/deletion (I/D) polymorphism, D/D genotype is associated with higher protein expression levels and serum activity with better dementia outcomes. Additionally, the impact of I/D polymorphism on AD may be population-specific or influenced by other factors, such as hypertension (HTN)-related cardiovascular comorbidities, which are also risk factors for AD. We aim to investigate the role of ACE gene I/D polymorphism, particularly in relation to HTN, and determine its influence on the brain volume of AD patients.
Methods: This hospital-based, observational study included data from Kaohsiung Municipal Ta-Tung Hospital Dementia Cohort. A total of 77 patients with AD dementia were recruited with diagnosis according to Aging and Alzheimer's Association criteria. ACE I/D genotypes were identified using polymerase chain reaction. The age, biological sex, education years, brain volume, and neuropsychological test scores of patients were analyzed.
Results: A significant difference in total intracranial volume (TIV) was observed among the ACE genotypes (ID, II, DD) in patients with both AD and comorbid HTN (P = 0.05). However, this difference in TIV was not present in AD patients without HTN. No significant differences were found for the other brain volume, such as gray matter, white matter, cerebrospinal fluid, and their normalized ratios, between AD patients with or without HTN.
Conclusions: The ACE gene I/D polymorphism, specifically in the presence of HTN, significantly influences brain volume, particularly TIV, in AD patients, indicating a potential interaction between the ACE polymorphism and vascular comorbidities like HTN in modulating the brain structure of AD patients.

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SHIFT 02-196

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4-5 April 2025

PLASMA SIMOA ALPHA-SYNUCLEIN, AMYLOID-BETA AND TAU AGGREGATE BIOMARKERS FOR DEMENTIA

Woo Yang[1,2], Peter Swann[1], Zengjie Xia[2], Dorothea Böken[2], Jeff Lam[2], Harry Crook[1], John O'Brien[1], David Klenerman[2]
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Aims: Plasma biomarkers have the potential to reflect pathology within the brain. They may provide more information on identifying cases with mixed pathology, defining treatment targets and monitoring therapeutic effectiveness. Here we present a novel approach to identifying disease specific protein aggregates for tau, β-amyloid and α-synuclein.
Methods: Plasma was analyzed using novel single molecule array (Simoa) assays for alpha-synuclein (α-syn), amyloid-beta (Aβ) and tau protein aggregates. In order to ensure that the protein species detected were aggregated, the same antibody was used for capture and detection. The cohort included people with mild cognitive impairment (MCI) (n=11), early stage (clinical dementia rating scale ≤ 1) dementia with Lewy bodies (DLB) (n=8), early-stage Alzheimer's disease (AD) (n=15) and age-matched healthy controls (n=13).
Results: The highest levels of α-syn, Aβ and tau aggregates were present in people with early dementia. Summed together, they could differentiate people with early dementia from controls with an area under the curve (AUC) of 0.89. The assay had a sensitivity of 73% while maintaining 100% specificity in distinguishing dementia from controls. Including people with prodromal dementia (MCI) decreased the AUC to 0.77.
Conclusions: These novel plasma Simoa aggregate assays for α-syn, Aβ and tau show promising results in differentiating early stage DLB and AD from controls. This combined assay had a high specificity, which may be useful in confirming the diagnosis of disease. However, it seemed to only be able to differentiate dementia from controls beyond the MCI stage. This suggests that the protein aggregates detected in the periphery are released from lysed neuronal cells. Further research is required to correlate these plasma biomarkers with other diagnostic methods for α-syn, Aβ and tau pathology.

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SHIFT 02-197

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ABETA AGGREGATION, PROTEIN MISFOLDING
4-5 April 2025

UNRAVELING ALZHEIMER'S COMPLEXITY: NEW AB42 FIBRIL TYPE AND SPECIFIC AV-45 BINDING

Qinyue Zhao, Youqi Tao, Cong Liu, Dan Li
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Aims: We aimed to investigate amyloid fibrils in sporadic Alzheimer's disease (AD) patients, focusing on the soluble fraction and structural variability of Aβ42 fibrils, and their interactions with the Aβ tracer AV-45.
Methods: We extracted amyloid fibrils using the sarkosyl extraction method from the brains of three sporadic AD patients. These patients exhibited similar pathological phenotypes but distinct clinical manifestations. The extraction process isolated fibrils from both the soluble and insoluble fractions.
Results: We found numerous amyloid fibrils in the soluble fraction across all cases, which were more dispersed than those in the insoluble fraction. Additionally, we identified a new type of Aβ42 fibril, termed Type III, exclusively present in the soluble fraction of one patient. Using cryo-electron microscopy (cryo-EM), we determined the structures of Type I and Type III Aβ42 fibrils in complex with AV-45, an FDA-approved Aβ tracer used for AD diagnosis. The AV-45 binding analysis showed that it inserts into an interior ligand-binding channel in the Type I fibril but not in the Type III fibril, which lacks such a channel.
Conclusions: Our discovery of Type III Aβ42 fibril in the soluble fraction suggests a need for revisiting amyloid components isolated by sarkosyl extraction. Moreover, the observed structural heterogeneity among fibril polymorphs across AD patients highlights variability in amyloid pathology. The differing mechanisms of AV-45 binding to Aβ42 fibrils underscore the importance of caution when interpreting Aβ tracer readouts in clinical diagnoses.

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SHIFT 02-201

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
4-5 April 2025

REGULATION OF THE GUT-BRAIN AXIS BY NON-INVASIVE GAMMA SENSORY STIMULATION

Jung Park, P. Lorenzo Bozzelli, Cheng-Yi Yang, Daniela Rodrigues Amorim, Ravikiran Raju, Noah Tan, Daniel Egziabher, Katerina Gusarova, Eric Wang, Nicole Buie, Li-Huei Tsai
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Aims: Declines in intestinal health often precede cognitive and physical deficits in neurodegenerative diseases like Alzheimer's and Parkinson's diseases. Emerging evidence suggests that degradation of the gut-brain axis contributes significantly to disease pathology, revealing new therapeutic targets focused on restoring axis function. With age being the primary risk factor for most neurodegenerative diseases, we investigated how gut-brain axis modifications can improve intestinal health in 24-month-old C57BL/6 mice.
Methods: We employed non-invasive 40hz sensory stimulations – a treatment previously shown to enhance brain activity and ameliorate neurodegenerative pathology in the brain – to observe effects on gut health. 24-month-old C57BL/6 mice were exposed to a three- to four-week regimen of daily audiovisual sensory stimulation.
Results: Chronic gamma sensory stimulation reduced levels of intestinal innate and adaptive immune cells and endogenous alpha-synuclein while increasing mucosal barrier integrity and VIP levels in the gut. Single-nucleus RNA sequencing further revealed increased fat absorption and digestion. To decipher how multisensory gamma stimulation influences the gut, we investigated the role of key components of the gut-brain axis, the insular cortex and the vagus nerve's dorsal motor nucleus (DMX). The 40Hz sensory treatment reduced microgliosis while promoting neuronal activity and integrity in the insular cortex. We also found elevated gamma entrainment in DMX, and increased expression of both ChAT and VIP, indicating enhanced cholinergic and VIPergic signaling. This is consistent with the observed increased VIP signal intensity in the guts of treated mice.
Conclusions: Given the known role of VIP and the vagus nerve in regulating gut immunity, barrier integrity and appetite, these findings suggest that gamma sensory stimulation may hold promise for addressing gut-brain axis dysfunction in aging and neurodegenerative diseases.

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SHIFT 02-202

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
4-5 April 2025

ACCELERATED-AGING IN CEREBRAL ORGANOIDS

Irantzu Perez Ruiz, Tina Loeffler, Izaskun Itxaso, Magdalena Daurer, Livia Breznik, Stefanie Flunkert, Manuela Prokesch
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Aims: Age-related accumulation of senescent cells in the nervous system contributes to neurodegenerative diseases and is being explored in clinical trials as a potential mechanism to treat Alzheimer's disease (AD). Thus, disease models that reflect aging and senescence are crucial. Brain organoids, three-dimensional structures derived from human iPSCs, offer a novel approach to study brain development and disease. The aim of the study was to accelerate aging in organoids to create a model system more accurately reflecting key aspects of neurodegenerative diseases.
Methods: We induced accelerated aging and senescence in brain organoids using D-galactose (d-gal) treatment. Cerebral organoids, derived from a healthy control human iPSC line, were treated with d-gal for 1-3 weeks in presence or absence of sensolytic drugs. To assess their senescence state, organoids were evaluated for p53 and p21 levels on automated western blotting (WES). β-galactose activity to measure senescence using the 4-MUG-based assay is currently performed. In addition, DNA damage and changes in reactive oxygen species or mitochondrial activity in the presence or absence of senolytic drugs will be investigated.
Results: Immediate effects of d-gal treatment such as a reduced growth of organoids of up to 50% were observed, depending on the timepoint and duration of treatment. Additionally, senescence markers, especially p21 were found to be strongly upregulated in d-gal-treated organoids compared to vehicle-treated controls. The effect of different sensolytic drugs in this model is currently investigated.
Conclusions: Overall, d-gal treatment of cerebral organoids leads to increased senescence and accelerated aging of iPSC-derived brain organoids. Thus, these organoids more closely resemble the pathophysiology in brains of neurodegenerative disease patients. Therefore, these artificially aged cerebral organoids can serve as a valuable tool to test potential therapeutics for age-related neurological conditions such as AD.

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SHIFT 02-203

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
4-5 April 2025

ESTIMATING LIFESTYLE, GENETIC AND BIOLOGICAL RISK FACTORS CONTRIBUTING TO ALZHEIMER'S DISEASE AND DEMENTIA

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Aims: Dementia is a global health challenge currently affecting over 55 million people worldwide. The incidence of dementia is decreasing in higher-income countries probably due to healthier lifestyles, suggesting that prevention is possible. Further reduction of dementia incidence can be achieved through structured prevention plans. There are non-modifiable and potentially modifiable risk factors that can contribute to dementia risk. Risk profiling of cognitively unimpaired individuals based on these risk factors can inform personalized and targeted prevention interventions. However, an accurate estimation of the contribution of each of these risk factors accounting for each other in representative populations is still lacking. Additionally, a cumulative risk assessment that combines lifestyle, biological, and genetic risk factors adjusted for each other remain to be developed. This study aims to accurately assess the adjusted hazard ratio of lifestyle, biological and genetic factors on dementia incidence in population-based cohorts of cognitively unimpaired individuals.
Methods: The risk calculation will be conducted as a multi-centric study by analyzing pooled patient-level data sets collected from large population-based cohorts.
Results: This study will provide precise estimations of the adjusted risk of each risk factor which are pivotal for the calculation of the cumulative adjusted dementia risk for individuals.
Conclusions: Our study will be used in the second-generation memory clinics (Brain Health Services) aimed at evidence-based and ethical dementia prevention in at risk cognitively unimpaired individuals. In the scope of the activities of BHS: (i) assessment of risk factors, (ii) risk communication, and (iii) risk reduction with multi-domain interventions; enabling enhancements in the risk profiling of cognitively unimpaired individuals will allow to reduce the global burden of dementia.

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SHIFT 02-204

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
4-5 April 2025

ACCELERATING SENESCENCE IN D-GALACTOSE-TREATED MICE

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Aims: Aging is a complex biological process that leads to a gradual decline in physiological function, and it increases the risk of age-related diseases, such as neurodegenerative disorders, cardiovascular diseases, and cancer. As the global population ages, understanding the mechanisms behind aging has become increasingly important to develop interventions that can extend the healthy lifespan and thus improve quality of life in older adults. Systemic administration of D-galactose (d-gal) is a well-established approach to artificially induce senescence, making it a valuable tool for studying aging mechanisms and evaluating potential anti-aging therapies.
Methods: Two- and six-month-old wild type (B6D2F1/J) mice receive a daily dose of 200 mg/kg of d-gal via drinking water for 20 or 10 weeks, respectively. Behavioral tests, including the pasta gnawing, grip strength, and passive avoidance test, are conducted. Gastric emptying and small intestinal transit time are assessed, and various organs are collected to measure beta-galactosidase activity and cytokine levels.
Results: Analyses are still in progress, but results will provide an insight into the pathology of the inducible senescence accelerating d-gal mouse model across different ages and treatment durations.
Conclusions: Our results could further highlight the potential of this inducible model to address the pressing need for quicker and more cost-effective research on aging.

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SHIFT 02-205

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / AGING
4-5 April 2025

SENOLYTICS IMPROVE COGNITIVE FUNCTION AND ALTER MARKERS OF SENESCENCE IN SAMP8 MICE

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Aims: Current research highlights the therapeutic potential of senolytics in mitigating age-related cognitive decline and cellular senescence. In naturally aged mice, animal models of brain aging and transgenic AD mice, treatment with senolytics showed an improvement in cognitive function, senescence phenotype and pathological hallmarks. Here, we employed senescence accelerated mice (SAMP8), which exhibit an accelerated aging phenotype including cognitive deficits, neuroinflammation and the main pathological hallmarks of AD. We aim to analyze the effects of senolytic treatment in this mouse model, which mimics sporadic Alzheimer's Disease (AD).
Methods: In this study, we administered a senolytic compound to 5-month-old SAMP8 mice, with SAMR1 mice serving as the control group, over a 2-month period. Following treatment, a series of behavioral experiments were conducted to assess cognitive function. Additionally, protein and RNA analyses were carried out using various molecular and biochemical techniques, including immunohistochemistry, qPCR, western blotting, protein fractionation, and ELISAs.
Results: Treated SAMP8 mice exhibited enhanced performance in cognitive tasks such as the open field test and object location test, indicating improved spatial memory and learning capabilities when compared to vehicle treated mice. Additionally, we assessed the effect of the senolytic compound on the expression of different senescent cell markers, including pro-inflammatory cytokines and other senescence-associated secretory phenotype (SASP) factors in the brain. It is currently being investigated whether these changes are also accompanied by an upregulation of neuroprotective pathways and a reduction in oxidative stress markers.
Conclusions: Overall, the senolytic treatment might result in an improvement of the main pathological hallmarks of AD, including a reduction in phosphorylated tau and lower Aβ levels. These findings suggest that senolytic therapies hold promise for alleviating cognitive decline and reducing the senescent cell burden in aged tissues.

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SHIFT 02-208

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4-5 April 2025

AUTOMATED ANALYSIS OF ASTROCYTES, MICROGLIA, AND THE AMYLOID-BETA PLAQUE MICROENVIRONMENT IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Astrocytes and microglia are thought to play a key role in many neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease. Understanding the specific subtypes, roles, and interactions of astrocytes and microglia is important to understand disease mechanisms and to identify and assess therapeutic targets. This study aimed to evaluate the spatiotemporal dynamics of astrogliosis and microgliosis in the amyloid-beta plaque microenvironment in an APP/PS1 transgenic mouse model of Alzheimer's disease.
Methods: We previously developed an automated method to analyze the plaque microenvironment in multiplex immunofluorescence tissue sections, quantifying stain density and characterizing microglia morphology. We have extended this work and implemented a deep learning-based approach to identify, count, and localize astrocytes (Figure 1). Astrocyte morphology was assessed using an explainable machine-learning model to distinguish cells with hypertrophic morphology, indicative of reactivity. We leveraged these methods to measure spatiotemporal cellular changes in the plaque microenvironment in tissue sections stained for Aβ, Iba-1, GFAP, and

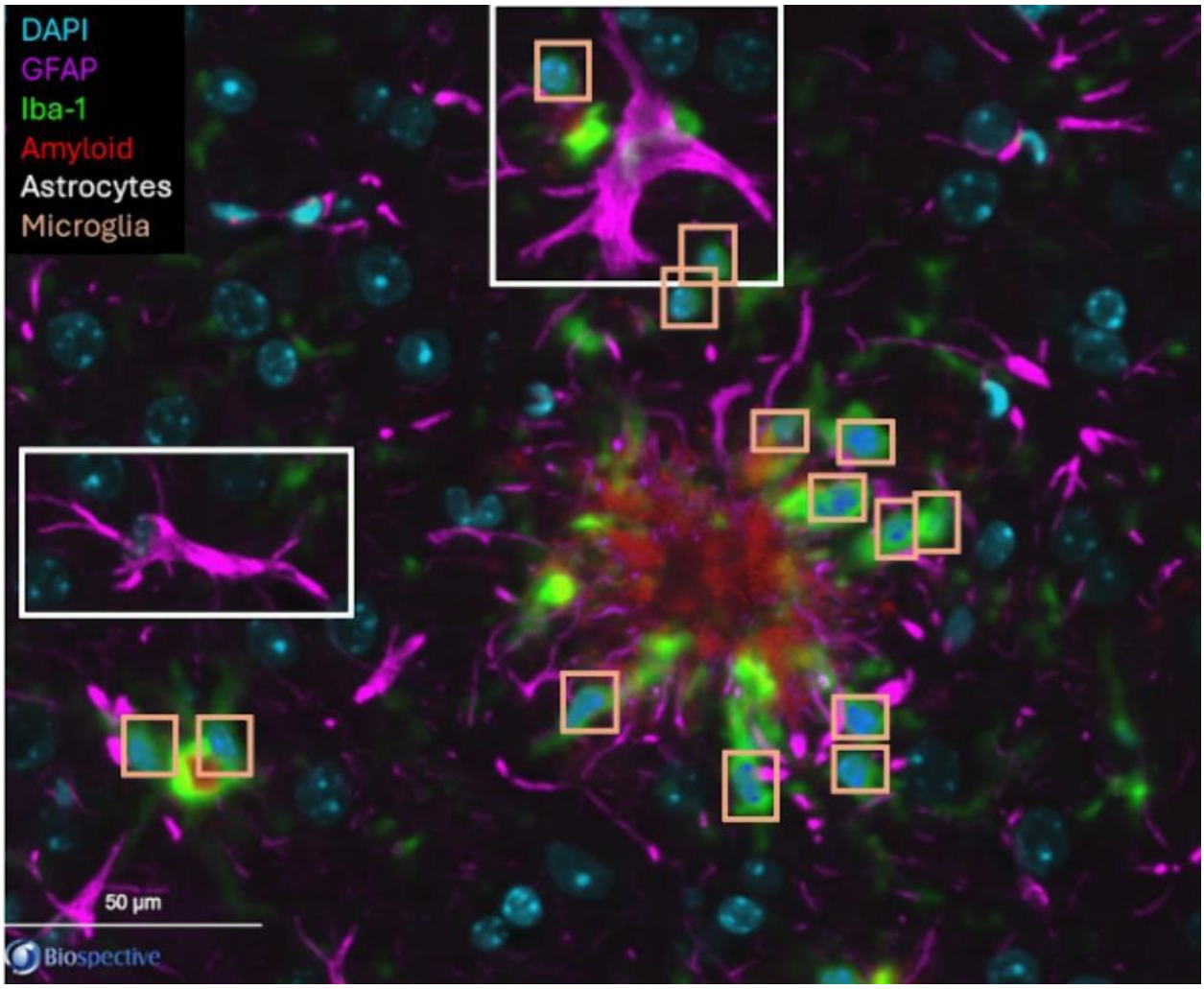
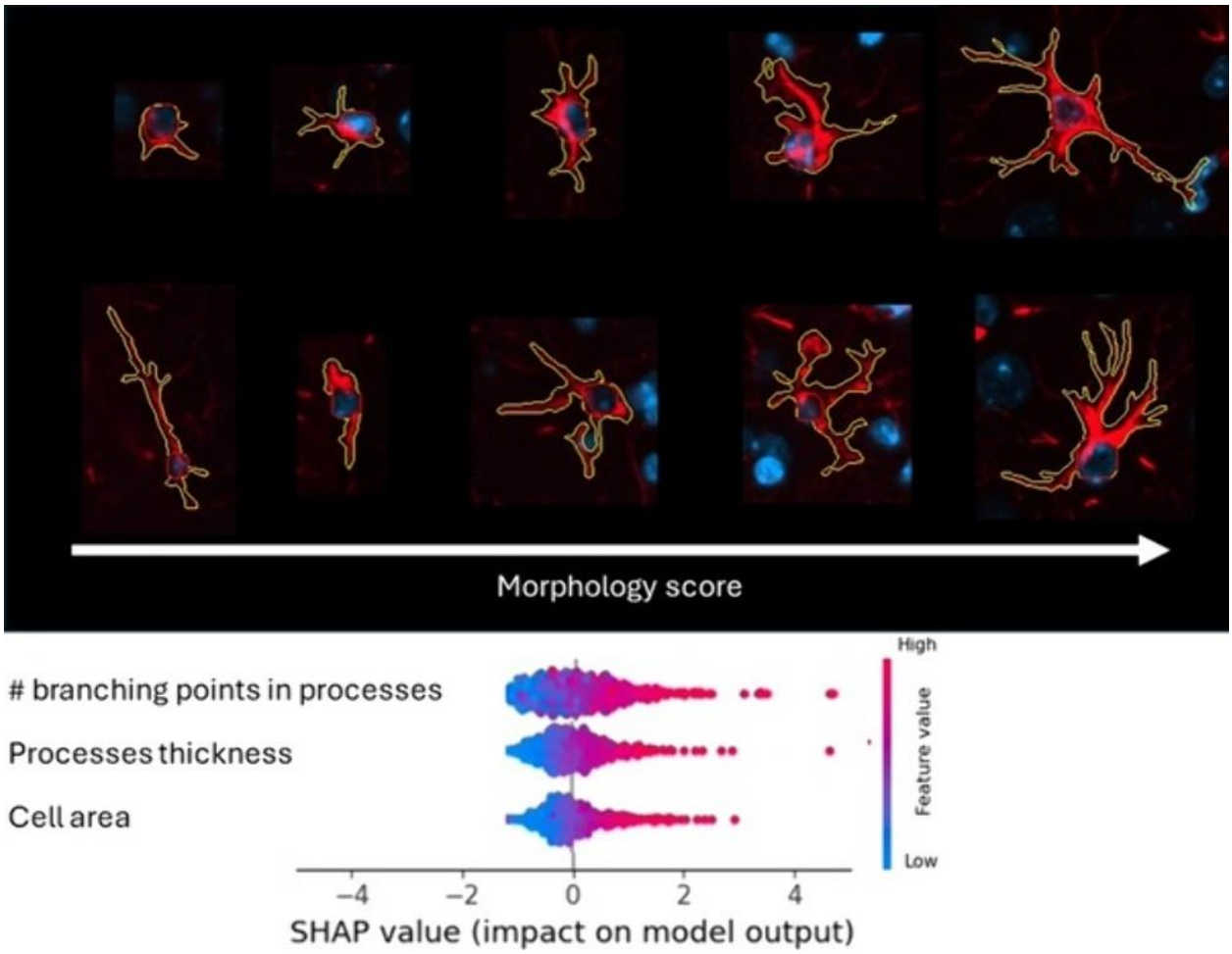


Figure 1 DAPI.

Results: Our model classified reactive astrocytes based on distinctive morphological features, such as thicker, more branched processes (Figure 2). These cells localized to plaques, but more distantly than activated microglia. To study the spatiotemporal pattern, we quantified the density of reactive cells in the microenvironment as a function of plaque size. We found that microglia progressively accumulate as a function of plaque size in the immediate vicinity. In contrast, astrocytes start to accumulate in the microenvironment after microglia (i.e. at larger plaque size) and become more distant as the plaques grow



larger. Figure 2

Conclusions: Assessment of morphological characteristics can provide additional information about the astrocytic phenotype. These features may provide sensitive measures for preclinical assessment of putative disease-modifying therapeutic agents in rodent models of neurodegenerative diseases.

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SHIFT 02-209

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4-5 April 2025

INCREASED CYTOSOLIC CITRATE IN 3T3 CELLS AND ASTROCYTES BY EXTRACELLULAR L-LACTATE

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Aims: Astrocytes are neuroglial cells with many homeostatic functions including brain energy metabolism, where D-glucose can be converted to L-lactate, in a process named aerobic glycolysis. Astrocytes are also the main source of mitochondrial citrate production and secretion into the intercellular space. The concentration of citrate in the cerebrospinal fluid is several tens to several hundred μmol/L, but the role of citrate is unknown. Citrate, which is produced in the Krebs cycle, is involved in the regulation of glycolysis and gluconeogenesis. It has been shown that aerobic glycolysis in astrocytes can be potentially activated through certain GPCR agonists including noradrenaline and L-lactate. Here, we investigate the impact of the stimulation with extracellular L-lactate on the production of citrate and further involvement of intracellular citrate in aerobic glycolysis through GPCR agonists stimulation in astrocytes and 3T3 embryonic cells.
Methods: We used genetically encoded fluorescent biosensors to monitor cytosolic citrate with high temporal resolution in single cells. Cells were stimulated with L-lactate (2 mM) and GPR27 surrogate agonist (1 μM).
Results: Our preliminary results indicate that the extracellular L-lactate significantly increases intracellular citrate in 3T3 embryonic cells and rat astrocytes. Moreover, stimulation of GPR27 with a surrogate agonist also increases intracellular citrate in 3T3 embryonic cells and rat astrocytes.
Conclusions: These results indicate that L-lactate and the GPR27 receptor activation play roles in modulating mitochondrial citrate production, potentially impacting aerobic glycolysis and overall brain energy metabolism.

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SHIFT 02-210

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4-5 April 2025

HOW DOES AMYLOID BETA AND ALPHA-SYNUCLEIN ALTER LEVELS OF INFLAMMATION PARAMETERS IN HUMAN ASTROCYTE CULTURE?

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Aims: Neurodegenerative diseases affect not only neurons but also support cells of the central nervous system. In neurodegenerative diseases, astrocyte responses may influence the initiation and spread of neurodegenerative pathology at least as much as the neuron itself, affecting fundamental mechanisms for neuronal survival. Astrocytes perform several crucial functions in the protection of neurons. Based on this information, this study was designed to determine the general profiles of human astrocytes regarding inflammatory parameters secretion and how this profile is altered in response to α-synuclein overexpression and Aβ1-42 treatment.
Methods: In our study, AD-like pathology was induced by the treatment of Aβ1-42, and PD-like pathology was modeled by the overexpression of α-synuclein in primary human astrocyte cultures. Briefly, a plasmid carrying the human *SNCA*gene was transfected into the cells using a lipid-based transfection agent. Also, the cells were treated with both toxic and non-toxic doses of Aβ1-42 peptide. Changes in the levels of released inflammatory proteins and their receptors were detected using a chemiluminescence-based western/dot blot method with a human inflammation antibody array.
Results: Our preliminary results showed that Aβ treated astrocytes predominantly secretaes IL-6, MCP-1, and TIMP-2 into the culture media. α-synuclein overexpression in human astrocytes increases the release of IL-12-P40, TNFβ, and TNFβ-R proteins into the culture media while it decreases the release of ICAM-1, TGFβ.
Conclusions: We determined that α-synuclein overexpression and Aβ treatment significantly changed the cytokine profile of untreated astrocytes. This is the first in vitro study to investigate the effect of α-synuclein overexpression and Aβ1-42 treatment on inflammatory factors produced in human astrocytes. (The present work was supported by the Research Fund of Istanbul University, Project no: 30666).

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SHIFT 02-211

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4-5 April 2025

IMPAIRED MITOCHONDRIAL ENERGY METABOLISM RELATED TO ASTROCYTE IN THE BRAIN OF ALZHEIMER'S DISEASE

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Aims: This study investigates abnormal brain energy metabolism in Alzheimer's disease (AD) by examining brain tissues from AD patients and APP^{NL-G-F} KI mice. Previous studies using proton magnetic resonance spectroscopy (^{1}H-MRS) revealed elevated lactate in AD patients' brains, indicating disrupted energy metabolism. Here, ^{1}H-MRS and hyperpolarized [1-^{13}C]pyruvate MRS were applied to AD model mice to explore metabolic changes over time.
Methods: Animals: AD model (APP^{NL-G-F} KI) and wild-type mice were studied. For hyperpolarized [1-^{13}C]pyruvate MR, custom headplates were attached. **^{1}H MRS**: Acquisitions were performed on a 7T scanner under anesthesia. **Proteomic Analysis**: Human postmortem posterior cingulate cortex and mouse hippocampal tissues were analyzed via SWATH-MS. **Histochemical Analysis**: Mouse brain sections were immunostained with PDK1 and GFAP antibodies. **Hyperpolarized [1-^{13}C]pyruvate**: [1-^{13}C] pyruvic acid was hyperpolarized with SpinAlingner, and 3T anatomical MRI and ^{13}C imaging were conducted. Mice received awake-condition injections of hyperpolarized pyruvate via tail vein.
Results: Longitudinal ^{1}H MRS in APP^{NL-G-F} KI mice showed increased lactate and myo-inositol in the hippocampus, correlating with disease progression, consistent with findings in AD patients. Proteomic analysis in both AD patients and APP^{NL-G-F} KI mice indicated downregulated oxidative phosphorylation pathways, suggesting mitochondrial dysfunction. Mitochondrial energy-related proteins were reduced, pointing to impaired energy metabolism as a possible disease mechanism. Histochemical analysis showed PDK1, a mitochondrial regulator, localized to astrocytes in late-stage APP^{NL-G-F} KI mice, highlighting astrocyte involvement in metabolic dysfunction. Hyperpolarized [1-^{13}C]pyruvate MRS also showed reduced pyruvate conversion rates in APP^{NL-G-F} KI mice, indicating metabolic shifts in the hippocampus.
Conclusions: These findings suggest impaired mitochondrial energy metabolism and astrocyte dysfunction may underlie AD pathology. Hyperpolarized [1-^{13}C]pyruvate MRS holds promise for the early detection of AD-related metabolic changes and could advance understanding of disease mechanisms and therapeutic strategies.

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SHIFT 02-212

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4-5 April 2025

COMPARISON OF IPSC-DERIVED AND HUMAN PRIMARY ASTROCYTES AS AN IN VITRO MODEL FOR ASTROCYTE ACTIVATION

Matteo Zanella, Malika Bsibsi, Gjis Van Puijvelde, Abeera Popalzij, Lieke Geerts, Stefan Kostense, Marijn Vlaming
Charles River Laboratories, Leiden, Netherlands

Aims: Astrocytes are the most abundant cells in the human central nervous system. This subtype of glial cells has historically been attributed mostly a supportive function, but it is now evident that they perform many active and reactive functions in the healthy and diseased brain. Reactive astrocytes are observed in a variety of neurodegenerative diseases – ALS, Alzheimer's Disease, Huntington's Disease, Multiple Sclerosis, Parkinson's Disease and Prion Diseases – and their modulation may thus provide an avenue for mitigation of pathogenesis.
Methods: As the availability of post-mortem human brain material for isolation of primary astrocytes limits the use of primary astrocytes in large drug development studies, the convenience of a robust and biologically relevant induced pluripotent stem cell (iPSC)-derived alternative is key to advance research towards actual treatment of neurodegenerative diseases. Therefore, we set out to compare and characterize these two model systems and gain a better understanding of their respective responsiveness to an inflammatory trigger.
Results: Using immunocytochemistry, the expression of key astrocyte markers (S100b, EAAT1, GFAP) and absence of microglia and neuronal markers was confirmed in primary human astrocytes isolated from brain tissue provided by the Netherlands Brain Bank and a culture of iPSC-derived astrocytes, indicative of a pure population in both model systems. Ongoing studies focus on the comparison of IL-6 and IL-8 cytokine release upon exposure to various concentrations of activating LPS and inhibition by dexamethasone.
Conclusions: Our research sheds light on the overlap of relevant properties of iPSC-derived vs human primary astrocytes. iPSC-derived astrocytes are suggested as a more accessible model that can be considered in larger target identification and compound screening studies. Subsequent downstream validation in primary astrocytes and a co-culture model is recommended to further enhance the chance of translational success.

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SHIFT 02-213

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / BLOOD-BRAIN BARRIER
4-5 April 2025

BRI2 BRICHOS ENABLES EFFICIENT TRANSPORT OF PROTEINS OVER THE BLOOD-BRAIN BARRIER

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Aims: Bri2 protein, which releases a BRICHOS domain after proteolytic processing, is expressed in the CNS, and recombinantly produced human (rh) Bri2-BRICHOS domain passes the blood-brain barrier (BBB) when injected intravenously in mice. We show here that rh Bri2-BRICHOS coupled to proteins of varied functions and molecular weights pass the mouse BBB and a cell model of the human BBB. We also identify candidates that mediate transcytosis and endocytosis of rh Bri2-BRICHOS.
Methods: An in-vitro model of the human BBB is used to test passage of proteins linked to rh Bri2-BRICHOS, as well as the same proteins on their own. The model consists of human cerebral microvascular endothelial cells (hCMEC/D3) seeded onto inserts. Proteins are added to the apical side of the cells and the passage to the basolateral side is determined. To determine the in-vivo uptake of fusion proteins, WT mice were given a single intravenous injection and sacrificed after two hours. The brains were sectioned for immunohistochemistry. We aim to identify the receptor responsible for mediating the uptake by fusing rh Bri2-BRICHOS to TurboID. Proteins that are biotinylated by rh Bri2-BRICHOS-turboID are identified using mass spectrometry. Cell lines in which candidate proteins have been knocked-out are used to validate the hits.
Results: Rh Bri2-BRICHOS and all tested fusion proteins can pass the hCMEC/D3 monolayer efficiently. The fusion partners without Bri2-BRICHOS show near zero passage. A fusion protein can pass the BBB in mice and is taken up by neurons. Results from screens to identify proteins that mediate rh Bri2-BRICHOS transcytosis are being validated in cell knock-out models.
Conclusions: Recombinantly produced Bri2-BRICHOS can pass the BBB and transport cargo proteins into neurons in mice, a process mediated by endocytosis and specific membrane proteins.

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SHIFT 02-217

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4-5 April 2025

MOLECULAR MODEL FOR TAU OLIGOMERS THAT ACT AS BIOACTIVE PROTEOPATHIC SEEDS

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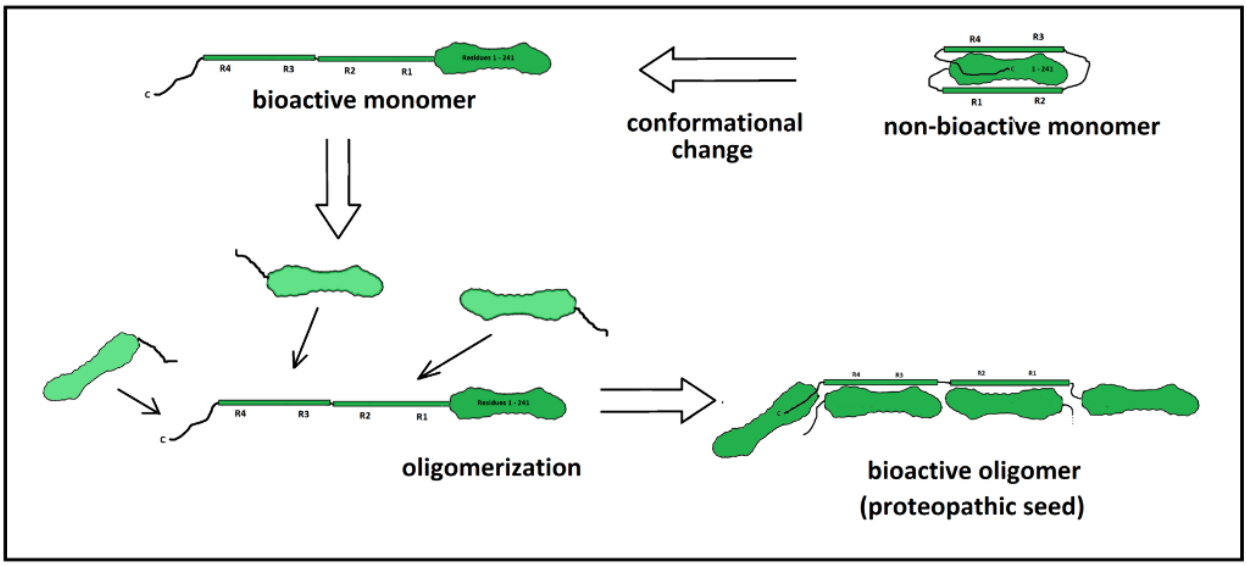
[1]Northeastern University, Department Of Bioengineering, Boston, United States of America, [2]Mass General Hospital/Harvard Medical School, Neurology, Charlestown, United States of America, [3]Massachusetts General Hospital, Boston, United States of America

Aims: The structural characterization of bioactive and non-bioactive oligomers of tau isolated from human brain tissue.
Methods: Oligomers of tau isolated from human brain tissue were separated into bioactive and non-bioactive fractions by anion exchange chromatography. Electron micrographs of immuno-gold-labelled fractions were collected to determine the arrangement of tau molecules in the oligomers.
Results: Bioactive tau oligomers adhered more strongly to the positively charged resin than the non-bioactive oligomers. Linear arrays of 3-4 gold particles spaced roughly 225 Angstroms apart were frequently observed, far more common in the bioactive fraction than the non-bioactive fraction. A preponderance of data suggests that in the inactive fraction, microtubule-binding domains (MTBs) wrap around a compact core comprising the N-terminal 241 amino acids of tau, thereby shielding its negative charges and precluding its binding to the positively charged resin. By contrast, in the bioactive fraction, the MTBs extend away from the N-terminal core domain, leaving it free to interact with the positively charged resin, thereby separating it from the inactive aggregates.
Conclusions: In the inactive form, the MTBs form ***intra***-molecular interactions with the N-terminal core stabilizing a compact form of tau that is un-associative until it encounters a microtubule at which point it undergoes a conformational change resulting in an extended structure with the MTBs lying along a microtubule protofilament. In solution, the active form of tau has an extended conformation analogous to the microtubule-bound form. In this form, MTBs are free to create ***inter***-molecular interactions with the N-terminal domains of other tau molecules, producing an oligomer that has multiple free interaction sites and

is thereby competent to act as a proteopathic seed in catalyzing the progressive oligomerization of other tau molecules.



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SHIFT 02-218

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4-5 April 2025

SELECT TRANSMEMBRANE PROTEINS (STPS) IN THE AMYLOID RESPONSOME DRAMATICALLY INFLUENCE TAU SECRETION AND AGGREGATION

Yong Ran[1], Xuefei Liu[1], Brenda Moore[2], Danny Ryu[2], Yona Levites[2], Christian Beusch[3], David Gordon[3], Matthew Rowan[4], Yenny Yook[4], Kai Hu[2], Todd Golde[1]
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Aims: Comparisons of proteomic changes in human AD brains and Aβ-depositing transgenic mouse brains have identified key conserved and divergent protein networks. These networks highlight a substantial Aβ/Aβ aggregate related "responsome." This led to the development of the "amyloid scaffold hypothesis," which posits that the accumulation of various proteins dependent on amyloid is a key driver of AD pathology. To explore a facet of this hypothesis, we tested whether proteins within two highly conserved modules mediate the crosstalk with tau and tau pathology.
Methods: In these studies, we evaluated how overexpression of select transmembrane proteins (STPs), including but not limited to APP, FLT1, ICAM1, SDC4, and COL25A1, impacts tau dynamics including tau secretion. These STPs, notably, rank among most upregulated proteins in human AD brains.
Results: In 293 cells, overexpression of select STPs with tau led to a substantial increase in tau secretion, over 100-fold in some cases. In contrast in primary astrocytes, overexpression led to reduced intracellular tau levels and aggregation. An initial proteomic analysis further indicates that both tau overexpression and the overexpression of these STPs alter the secretome and intracellular proteome in complex ways. Most of secreted tau induced by the STPs is soluble, but a fraction appears in extracellular vesicles. Ongoing studies of effects of STPs overexpression in neurons will also be presented. Notably, many secreted proteins in the amyloid responsome did not markedly impact tau secretion or aggregation.
Conclusions: STPs induced by amyloid deposition influence tau in cell-type-specific ways. These studies may explain why secreted tau serves as a biomarker of amyloid deposition, and suggest that STP accumulation in AD may have complex effects on AD pathology by promoting tau secretion while reducing intracellular tau and tau aggregate levels.

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SHIFT 02-219

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4-5 April 2025

AMYLOID-BETA SEEDING: IN VITRO AND IN VIVO ASSESSMENT OF HUMAN-DERIVED A-BETA SPECIES

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Aims: In Alzheimer's disease (AD), amyloid-β (Aβ) pathology can localize to the parenchyma and the vessel walls. In AD patients with cerebral amyloid angiopathy (CAA), there is extensive deposition of Aβ in the vessel wall, causing micro-hemorrhages. The disease duration can vary from less than one to more than twenty years. It is hypothesized that different Aβ variants could be responsible for these phenotypic variations. Such Aβ "strains" may have different seeding properties and exert different toxicity. We recently discovered a novel intra-Aβ amyloid precursor protein (APP) mutation (APP_{Aros}) that causes AD pathology and intracerebral bleeding. We aim to investigate differences in the seeding and propagation of parenchymal and vascular Aβ and develop a novel seed amplification assay (SAA) to determine the presence of vascular brain pathology in AD.
Methods: To assess *in vivo* seeding, $App^{NL\text{-}F/NL\text{-}F}$ knock-in mice were intracerebrally injected with human-derived purified Aβ from the APP_{Aros} mutation brain and an AD brain with wild-type (WT) Aβ pathology. Synthetic Aβ peptides were used to establish an *in vitro* Aβ-SAA using Thioflavin-T and novel fluorescent thiophene ligands showing selectivity towards parenchymal versus vascular Aβ as the readouts.
Results: Preliminary data indicate that both Aros Aβ40 and Aβ42 aggregates induce strong seeding reactions on WT Aβ42 monomers, comparable to WT Aβ42 seeds, while WT Aβ40 aggregates have no such effect.
Conclusions: Analyses of the *in vivo* experiments will reveal if APP_{Aros}-related pathologies are preserved upon inoculation in mice. In ongoing studies, the Aβ isoform-selective SAAs will be used to assess Aβ

seeding activity in AD brain and CSF samples. Such assays can potentially be developed into diagnostic tools to discriminate between AD cases with and without CAA.

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SHIFT 02-220

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
4-5 April 2025

IMPLICATION OF RER1 IN THE EXPRESSION AND SIGNALING OF TREM2-DAP12 COMPLEXES

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Aims: The immunoreceptor complex formed by the triggering receptor expressed on myeloid cells 2 (TREM2) and DNAX-activating protein of 12 kDa (DAP12) is expressed on lymphoid and myeloid lineage cells. Both proteins have been linked to neurodegenerative diseases, indicating the importance of this complex. However, how the interaction between TREM2 and DAP12 affects the transport and assembly of both proteins is not fully understood.
Methods: We used macrophage-like differentiated THP-1 cells that endogenously express TREM2 and DAP12, and HEK293 FlpIn cells with transgenic overexpression of different variants of TREM2 and DAP12 to characterize the expression, subcellular trafficking, and assembly of these proteins by molecular, cell biological and biochemical assays.
Results: We found that the degradation of DAP12 was increased upon deletion of TREM2 or when the interaction of both proteins was prevented by site-directed mutagenesis. Unassembled DAP12 was mainly retained in early secretory compartments, including endoplasmic reticulum (ER) and ER-Golgi intermediate compartment (ERGIC), and interacted with the retention in ER sorting receptor 1 (RER1). Mutagenesis analysis revealed the charged amino acid residue D50 within the transmembrane domain of DAP12 is the main determinant for the interaction with RER1 and the retention in the ER. Deletion of RER1 decreased expression of functional TREM2-DAP12 complexes, and strongly reduced membrane proximal signaling and phagocytic activity in THP-1 differentiated macrophage-like cells.
Conclusions: Our combined results indicate TREM2, one of co-receptors of DAP12, stabilizes DAP12 and is necessary for the transport of DAP12 to the plasma membrane. Furthermore, RER1 plays a critical role in the retention of unassembled DAP12 thereby controlling the expression of functional TREM2-DAP12 immune receptor complexes at cell surface, and might be an important regulator in the maintenance of immune cell function.

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SHIFT 02-221

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELLULAR SIGNALLING, KINASES, PHOSPHATASES, CALCIUM
4-5 April 2025

INVESTIGATING THE REGULATION OF WILLIN/FRMD6 AND ITS POTENTIAL ROLE IN ALZHEIMER'S DISEASE

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Aims: The aims of this research were: 1) To predict potential Willin/FRMD6 phosphorylation sites. 2) To use Phos-tag SDS-PAGE to investigate Willin/FRMD6 phosphorylation 3) Use site directed mutagenesis to investigate one potential Willin/FRMD6 phosphorylation site in neurons. 4) Perform phosphoproteomics mass spectrometry to define Willin/FRMD6 phosphorylation sites.
Methods: Phos-tag is a functional molecule which binds phosphorylated serine, threonine and tyrosine. Within polyacrylamide gels, it binds phosphorylated proteins, causing them to move through the gel more slowly 6. This allows separation of proteins based on their phosphorylation status, including number and position of phosphorylated residues. This technique was used to investigate Willin/FRMD6 phosphorylation. Following this, site directed mutagenesis was performed to mutate Willin/FRMD6 Y404, one of the amino acids predicted to be most likely to be phosphorylated. This tyrosine was mutated into a phospho-dead alanine or phospho-mimetic glutamate. Mutants were then expressed in SHSY5Y cells and immunofluorescence, proliferation assay and migration assays were perfomed.
Results: Prediction of phosphorylation sites A number of amino acids in the sequence of Willin/FRMD6 were predicted to be highly likely to be phosphorylated, the majority of these were at the C-terminal end. Phos-tag SDS-PAGE When run on a phos-tag gel, Willin/FRMD6 produces three bands, suggesting it is phosphorylated at at least two distinct sites. These results were seen across mulitple cell types. Mutating Willin/FRMD6 Non-mutant Willin/FRMD6 and Y404E mutants had similar localisation throughout cells, being found at sites of cell-cell contact. In contrast, Y404A mutants were found to aggregate in cells.
Conclusions: These results suggest Willin/FRMD6 is being phosphorylated, at at least two distinct sites. This phosphorylation has an effect on Willin/FRMD6 localisation and may occur at site Y404. Mass spectrometry analysis will add weight to these results.

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SHIFT 02-222

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CHOLINERGIC
4-5 April 2025

ADULTHOOD CHOLINE SUPPLEMENTATION REDUCES CO-MORBIDITIES AND IMPROVES COGNITION IN A DOWN SYNDROME MOUSE MODEL

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Aims: Down syndrome (DS) is the most common cause of early-onset Alzheimer's disease (AD). Dietary choline intake has been proposed as a modifiable factor for AD, as choline regulates multiple cognition-relevant pathways. Although choline can be endogenously synthesized in the liver, this is insufficient for the body's needs and many do not reach adequate daily intake levels. Maternal choline supplementation (Ch+) in the Ts65Dn model of DS (Jackson Strain #005252) protects offspring against basal forebrain cholinergic neuron degeneration and cognitive impairments similar to that seen in AD. Maternal Ch+ also improves AD-relevant outcomes in AD models, and dietary Ch+ throughout adulthood in AD models ameliorates AD pathology and improves cognition. However, the effects of dietary Ch+ throughout the adult life-span in DS has yet to be explored.
Methods: To test whether Ch+ in adulthood improves co-morbidities seen in DS, we fed trisomic Ts65Dn mice and disomic littermate controls (n = 16-18 per diet per genotype, balanced by sex) either a choline normal (ChN; 1.1 mg/kg) or a Ch+ (5 mg/kg) diet starting at 4.5 months, with behavioral testing at 13 months and tissue collection at 14 months.
Results: In contrast to perinatal Ch+ studies, we found that Ch+ in adulthood failed to improve genotype-specific deficits in spatial learning. However, in both genotypes of female mice, Ch+ improved cognitive flexibility in a reverse place preference task in the IntelliCage behavioral phenotyping system. Further, Ch+ reduced weight gain and peripheral inflammation in female mice of both genotypes, and improved glucose metabolism in male mice of both genotypes.
Conclusions: Our findings suggest that adulthood choline supplementation attenuates factors that are associated with the risk of developing AD in DS.

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SHIFT 02-228

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

IMPACT OF APOE E4 CARRIER STATUS ON PLASMA IRISIN LEVELS IN ALZHEIMER'S DISEASE PATIENTS

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Aims: Although irisin has shown neuroprotective effects in animal models of Alzheimer's disease (AD), there is limited data on its role in patients with AD and the influence of the APOE e4 allele on irisin concentration. This study aimed to examine the impact of APOE e4 carrier status on plasma levels of irisin, brain-derived neurotrophic factor (BDNF), and secreted protein acidic and rich in cysteine (SPARC), and to assess correlations between these biomarkers and AD pathology markers in patients with probable AD dementia.
Methods: Sixty patients diagnosed with probable AD dementia were enrolled. Neuroradiological assessments included brain magnetic resonance imaging (MRI) following dementia protocols. Cerebrospinal fluid (CSF) AD biomarkers were categorized using the A/T/N classification. APOE rs429358 and rs7412 polymorphisms were genotyped using real-time PCR with TaqMan assays to determine APOE e2/e3/e4 allele carrier status. Irisin, BDNF, and SPARC plasma levels were measured using enzyme-linked immunosorbent assays (ELISA).
Results: APOE e4 carriers exhibited significantly lower plasma irisin levels compared to non-carriers ($p = 0.021$), while no significant differences were found in BDNF and SPARC levels between the two groups. Correlation analysis revealed a positive association between plasma irisin levels and the Aβ42/40 ratio ($p = 0.030$) and a negative correlation with p-tau 181 levels ($p = 0.048$). Additionally, a significant positive correlation was observed between plasma BDNF and SPARC levels ($p = 0.001$).
Conclusions: This study highlights the potential role of irisin and its involvement in amyloid and tau-related neurodegeneration in AD. These findings align with growing evidence on the neuroprotective role of irisin in AD, particularly among APOE e4 carriers. However, further research is needed to establish its diagnostic potential.

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SHIFT 02-229

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

SEX-SPECIFIC HYPOTHALAMIC PATHOLOGY AND IMMUNE INFILTRATION IN ALZHEIMER'S DISEASE

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Aims: The hypothalamus is integral to regulating numerous physiological processes that are disrupted in Alzheimer's disease (AD). Yet despite its homeostatic importance, the hypothalamus remains critically understudied in AD. We aim to investigate how hypothalamic pathology and blood-cerebrospinal fluid-barrier (BCSFB) dysfunction may contribute to increased peripheral immune infiltration and subsequent neuroinflammation in AD. Additionally, we aim to elucidate how hypothalamic pathology may contribute to underlying sex differences in AD.
Methods: We performed single cell fixed RNA profiling (scFRP) on a cohort of post-mortem human hypothalamus tissues from 64 AD donors (37% male, 63% female) with varying degrees of pathology and 21 controls (33% male, 66% female) without neurological disease. We also performed spatial transcriptomics using the Visium CytAssist protocol on matched hypothalamus FFPE tissue slides from 50 of the same donors in the scFRP dataset**.**
Results: We show that oligodendrocytes, astrocytes, and microglia express the most differentially expressed genes that are associated with estrogen response, hypoxia, and TGF-ß pathways. We also use spatial transcriptomics to locate transcriptional changes in the vicinity of hypothalamic AD pathology. We are currently integrating these two modalities to study transcriptomic changes and cell-cell interactions that associate with AD pathology within the hypothalamus and at the BCSFB.
Conclusions: Our findings aim to elucidate a connection between peripheral immunity and AD pathobiology in the hypothalamus. Ultimately, this research enhances our understanding of how BCSFB function may exacerbate neuroinflammation and potentially influence sex disparities in AD.

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SHIFT 02-230

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

THE INFLUENCE OF APOE4 ON CXCL16 MEDIATED T-CELL RECRUITMENT TO THE BRAIN IN ALZHEIMER'S DISEASE

Jacob Wildeman
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Aims: Neuroinflammation plays an important role in Alzheimer's Disease (AD) pathology. Over recent years, evidence has shown that CD8+ T cell numbers increase in the periphery, with certain T cell populations negatively associated with cognition in AD (1). Specifically, TEMRA cells increase during the mild cognitive impairment stage, reflecting peripheral immune system changes tied to AD progression (2). These increased CD8+ T cells are also observed within the brain, particularly in the AD parenchyma, but their exact role remains unclear (3, 4). A critical area of interest involves the role of microglia, which may produce CXCL16, a chemokine that interacts with CXCR6 to attracts T cells. The CXCL16/CXCR6 signaling axis could be a potential mechanism underlying the infiltration of CD8+ T cells into the brain. Studies in both mouse models and humans suggest that this signaling pathway is implicated in AD. Thus, this study aims to clarify the exact role of the CXCL16/CXCR6 pathway, how CD8+ T cells enter the brain, and whether factors such as the APOE4 genotype and altered lipid metabolism influence this process.
Methods: 1. qPCR on for CXCL16 (and CXCR6?) in different samples. 2. RNA scope for CXCL16/CXCR6 on human APOE4 brain slices (also MS?). Can we find CXCL16 and CXCR6 in brain material, which cells express it and where is the protein eventually located? Does APOE4 or hypoxic conditions change the expression or localization of CXCL16? 3. Migration assays, with different conditions. Exact conditions will depend on experiments 1 & 2. Consider the following: iEC monolayer with APOE4 background, cultured in hypoxic conditions, co-culture with iMG, CXCL16 KO iPSC, changed LDL(R), ...
Results: There are no results to this project yet.
Conclusions: There are no conclusions to this project.

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SHIFT 02-231

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

WESTERN DIET-INDUCED VISCERAL ADIPOSE TISSUE INFLAMMATION CONTRIBUTES TO ALZHEIMER'S DISEASE PATHOLOGY THROUGH PRO-INFLAMMATORY CYTOKINES

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Aims: The aim of this study was to evaluate the relationship between Western Diet (WD)-induced inflammation in visceral adipose tissue (VAT) and Alzheimer's Disease (AD) pathology. Additionally, we aimed to identify the VAT-derived pro-inflammatory cytokines that contribute to neurotoxic effects in mouse brain tissue.
Methods: Male C57BL/6 mice were assigned to either a control chow diet or a WD for 20 weeks. Inflammation in VAT was confirmed through western blot analysis, which measured levels of NLRP3, pNF-kB, and IL-1 beta. We also quantified levels of AD-associated proteins such as amyloid-beta (Aβ) oligomers, beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), and amyloid precursor protein (APP) in brain tissue using Western blot analysis. Cognitive function was assessed using Y-maze and Morris water maze tests. Pro-inflammatory cytokines that were concurrently upregulated in both VAT RNA-sequencing and plasma antibody array analyses were classified as VAT-derived and evaluated for their neurotoxic effect on hippocampal neurons *in vitro*.
Results: Mice fed a WD exhibited elevated levels of NLRP3, pNF-kB, and IL-1 beta in VAT, confirming significant inflammation. These mice also showed increased levels of Aβ oligomers, BACE1, and APP in brain tissue, along with cognitive impairments. Both VAT RNA-sequencing and plasma antibody array analyses consistently revealed upregulation of specific VAT-derived pro-inflammatory cytokines, including CCL5, CCL8, CCL9, CXCL13, and interleukin-18, which were also elevated in brain tissue. Subsequent *in vitro* experiments using a neuron-microglia co-culture system confirmed that these cytokines induce neuronal cell death in mouse hippocampal neurons.
Conclusions: WD-induced VAT inflammation is related with AD pathology. The VAT-derived pro-inflammatory cytokines, elevated in response to a WD diet, exhibit neurotoxic effects on hippocampal

neurons. These findings underscore the potential of targeting VAT inflammation in AD management and prevention.

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SHIFT 02-232

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / INFLAMMATION
4-5 April 2025

MAPPING THE LANDSCAPE OF CEREBROSPINAL FLUID IMMUNE CELL ESTABLISH AN OUTCOME PREDICTING MODEL IN NORMAL PRESSURE HYDROCEPHALUS RECEIVING SHUNT SURGERY

Li Zhang, Hanwen Zhang, Xuhao Fang
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Aims: Normal pressure hydrocephalus (NPH) is a neurological condition marked by gait disturbance, dementia, and urinary incontinence and treated with cerebrospinal fluid (CSF) shunting. This study aimed to map the landscape of immune cells in the CSF of NPH patients and establish a model for predicting treatment response before surgery.
Methods: Single-cell RNA and T-cell receptor sequencing of CSF immune cells was performed in 15 NPH patients who underwent shunting (cohort 1) to study the cellular and molecular basis of NPH. Enzyme-linked immunosorbent assays were used to detect the levels of chemokines and cytokines in the CSF in both cohorts. Multiple machine learning was used to establish a predictive model.
Results: Patients who did not improve after surgery exhibited enrichment of clonally expanded CD8_TRM_CCR5 cells, enhancement of the interferon response, and cytotoxic immune reaction. Significant cellular interactions were identified between $IL1B^{+}$ macrophages and CD8_TRM_CCR5 via CCL3/CCL4-CCR5 signaling, which contributed to enrichment of CD8_TRM cells. A predictive model was developed and further validated in an independent cohort (cohort 2).
Conclusions: Our study mapped the CSF immune cell landscape and suggested cellular and molecular mechanisms underlying the failure to clinically improve after shunt surgery. We also constructed and validated a predictive model for identifying NPH patients who may not benefit from shunt surgery.

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SHIFT 02-236

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES
4-5 April 2025

ASSOCIATION OF PROTEASOME ACTIVITY WITH A/T/N AND COGNITIVE FUNCTIONS IN APOE E4 CARRIERS

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Aims: The proteasome is a multisubunit protease complex, contributing to most intracellular protein degradation and quality control. Although impaired proteasome activity has been reported in various pathophysiological conditions, the association between proteasomes in human blood and Alzheimer's disease (AD) remains largely unknown. Given that the APOE e4 allele is the most potent generic risk factor for AD, we measured plasma proteasome activity and examined its association with the critical pathologic parameters in APOE ε4 carriers.
Methods: This study is an observational cohort study, with participants grouped as cognitively normal (CN), mild cognitive impairment (MCI), and dementia. All study participants underwent [^{18}F]MK-6240 as a tau PET and [^{18}F]flutemetamol as an amyloid PET, 3.0-Tesla MRI, APOE genotyping, and detailed neuropsychological tests. Proteasome activity in the plasma was measured by the extent of hydrolysis of fluorogenic peptides, and its association with other clinical data was evaluated after stratification with APOE ε4 genotypes.
Results: Total number of 148 participants (57 CN, 38 MCI, and 53 dementia) were included. Aamong them, 55 individuals were APOE ε4 carriers and 93 were non-carriers. Proteasome activity was significantly negatively correlated with flutemetamol retention, regional SUVRs of MK-6240 in the brain areas corresponding to Braak stage I/II, and III/IV. Hippocampal volume was also correlated with proteasome activity only in APOE ε4 carriers. Moreover, proteasome activity was positively correlated with global cognitive functions, evaluated with MMSE and CDR SOB, visual and verbal memory functions in APOE ε4 carriers. Whereas, no significant correlation was found in APOE ε4 non-carriers.
Conclusions: Proteasome activity was significantly correlated with cognitive functions, amyloid, tau burden, and hippocampal atrophy only in APOE ε4 carriers, suggesting that proteasome activity could be a non-invasive biomarker for AD with a genotype-specific disease mechanism

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β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES
4-5 April 2025

THE IMPACT OF APOLIPOPROTEIN E4 ON ENDOLYSOSOMAL DYNAMICS IN PRIMARY NEURONS

Emma Nyberg[1], Sabine Konings[2], Nils Lindblom[1], Oxana Klementieva[1], Isak Martinsson[3], Gunnar Gouras[1]
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Aims: APOE4 is the most significant genetic risk factor for developing Alzheimer's disease (AD) and unraveling the key cellular pathways disrupted by ApoE4 can guide us to new therapeutic targets. Alterations in endosomes are among the earliest detectable changes in AD, with endosomal enlargement occurring prior to plaque formation. Both amyloid-beta (Aβ) and ApoE4 have been implicated in affecting endosomal function, but our understanding of how ApoE4 impacts the endosomal system in neurons remains incomplete. We aim to explore how ApoE4 influences the endolysosomal pathway in primary mouse neurons.
Methods: We utilize mixed primary brain cultures (neurons, astrocytes and oligodendrocyte progenitor cells) harvested from ApoE knockout (KO) mice and mice expressing human ApoE3 or ApoE4. Neurons in culture undergo accelerated maturation, and intracellular stress increases with time. We study how ApoE isoforms impact the endolysosomal system at different times in culture, after prolonged neuronal activity, with elevated Aβ levels, and after cholesterol feeding. This allows us to examine the conditions under which ApoE4 alters the endolysosomal system.
Results: Our data show that when neurons reach maturity at 18 days in vitro (DIV), there are no apparent differences in endosome function between the ApoE groups. Moreover, enhancing neuronal activity for 48 hours at 18 DIV causes similar endosome changes between the ApoE groups. However, with time in culture, ApoE4 neurons begin to exhibit reduced degradation of DQ-BSA without altering the appearance of late endosomes/lysosomes.
Conclusions: Our preliminary findings suggest that ApoE4 alters lysosomal function in neurons over time in culture. We are further investigating what causes this reduced degradation capacity with ApoE4 and whether feeding the endosomal system with AD-relevant cargo (Aβ and cholesterol) further exacerbates endolysosomal dysfunction in the presence of ApoE4.

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β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES
4-5 April 2025

ROLE FOR LYSOSOMAL PSEN2/GAMMA SECRETASE IN NEURONAL ORGANELLAR HOMEOSTASIS. RELEVANCE TO ALZHEIMER'S DISEASE PATHOGENESIS

Iván Ramos Calvo[1], Céline Vrancx[1], Anika Perdok[1,2], Wim Annaert[1]
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Aims: While endolysosomal defects, along with mitochondrial and synaptic dysfunction, are early features of AD pathogenesis, they have mostly been studied independently in the context of the disease. We hypothesize that several of these subcellular pathologies could be a consequence of upstream defects in endolysosome homeostasis. To test this, we focused on one of the causal genes in familial AD, presenilin2 (PSEN2), which is found to be restricted in late endosomes/lysosomes. As this work is being conducted in a non-amyloidogenic in vitro model, this would allow us to scrutinize the impact of altered expression of PSEN2, independently of the production of amyloid peptides.
Methods: We have derived primary hippocampal neurons from wild-type, PSEN2 knockout (KO) and PSEN2 N141I knockin (KI) mice and have grown them on both coverslips and microfluidic devices to distinguish somatodendritic from axonal events. These neurons were subjected to functional electrophysiological readouts to evaluate the impact on synaptic function and combined with indirect immunofluorescence and live imaging, using organelle-specific reporters, including for LE/Lys, autophagy and mitochondria. These are supplemented with assays monitoring mitochondrial fitness, such as TMRM or MitoSox. High resolution live imaging is used to in particular investigate the effect of PSEN2 KO or an FAD mutation on the crosstalk between lysosomes and mitochondria.
Results: We observed endolysosomal trafficking impairments in the PSEN2KO and FADPSEN2 axonal compartments. These findings correlated with a reduced synaptic density as well as hyperpolarised mitochondria particularly in axons, that contacted less often but for longer time with endolysosomes. These differences were recapitulated in iPSC-derived human neurons.
Conclusions: These data give a first indication of that PSEN2-related changes in endolysosomal function may instigate downstream defects in mitochondria and synapses.

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SHIFT 02-239

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS, CHAPERONES
4-5 April 2025

UNDERSTANDING THE EFFECT OF EXOGENOUS AMYLOID-B ON AUTOPHAGY IN STEM-CELL DERIVED NEURONAL MODELS USING TRANSPARENT MEAS

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Aims: A recent study in an Alzheimer's Disease (AD) mouse model has shown that faulty autolysosome acidification induces autophagic flux build-up of amyloid-ß (Aβ) in neurons. Furthermore, we have previously shown that Aβ, when added exogenously to cells, can itself be the cause of faulty autolysosome acidification. However, the connection between autophagic dysfunction and Aβ aggregation requires further investigation in human cellular models. In this study, exogenous Aβ was introduced to human induced pluripotent stem cells (hiPSC) derived neurons and its resulting uptake by the neurons and the electrophysiological changes were studied. This work aims to enhance our understanding of the relationship between autophagic dysfunction and Aβ aggregation, providing a foundation for future research into human disease models.
Methods: iPSC-derived neurons were plated on PEDOT:PSS microelectrode arrays (MEAs) as well as 8-well plates. Cells were then treated with varying amounts of exogenous Aβ and its uptake by the neurons was observed using confocal microscopy. In addition, the electrophysiological changes were measured using the MEAs and the autophagic stress will be studied using lysosome-specific dyes.
Results: It has been observed that the addition of laminin to the cell-culture media enhances the viability of the neurons on the MEAs. Exposure to Aβ resulted in a decrease in the electrophysiological activity of the neurons. Additionally, the uptake of Aβ by the neurons resulted in the reduction of the size of nuclei in addition to DNA fragmentation. The intracellular localisation of Aβ within the cell will further be studied using super-resolution microscopy.
Conclusions: The effects of Aβ on the lysosome can lead to a new understanding of AD pathophysiology potentially guiding the development of novel therapeutic approaches.

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SHIFT 02-241

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METABOLISM, INSULIN
4-5 April 2025

METABOLIC DYSREGULATION OF ALTERNATIVE SPLICING DRIVES NEURONAL FATE INSTABILITY IN ALZHEIMER'S DISEASE

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Aims: Directly induced neurons (iNs) retain the biological aging characteristics of their donors, making them a valuable model for studying aging - the primary risk factor for Alzheimer's disease (AD) - in a patient-specific context. In a cohort of sporadic AD patient iNs, we identified a metabolic switch to aerobic glycolysis, resulting in an accumulation of acetyl-CoA. This shift compromises neuronal resilience, rendering AD patient iNs more vulnerable to aging-related stressors like amyloid-β. This project aims to investigate how excess acetyl-CoA impacts neuronal resilience, focusing on its role in protein acetylation.
Methods: We generated iNs from fibroblasts of 13 AD patients and 15 matched controls, demonstrating that iNs exhibit adult neuronal transcriptional identity and AD patient-specific disease signatures of an impaired metabolic state in AD iNs. We used a genetically encoded acetyl-CoA sensor to measure subcellular acetyl-CoA distribution and characterized its influence on protein acetylation using MS-based proteinacetylomics. Furthermore, single-cell long-read RNA sequencing was utilized to detect full-length transcript isoforms and quantify alternative splicing events, both under baseline conditions and following inhibition of nuclear acetyl-CoA production through ACLY inhibition.
Results: AD iNs showed a redistribution of acetyl-CoA, characterized by reduced mitochondrial and increased nuclear acetyl-CoA. This elevation of nuclear acetyl-CoA led to the hyper-acetylation of several splice factors, significantly altering the isoform landscape of genes critical for neuronal identity and resilience. Notably, ACLY inhibition reduced nuclear acetyl-CoA levels and reversed much of the aberrant splicing, restoring a more mature and stable neuronal state.
Conclusions: Our findings reveal an AD-specific metabolic shift that drives changes in alternative splicing, contributing to neuronal instability and increased susceptibility to neurodegeneration. This metabolic regulation of splicing represents a critical link between altered acetyl-CoA metabolism and AD pathogenesis.

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SHIFT 02-242

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METABOLISM, INSULIN
4-5 April 2025

IMPACT OF SRC VARIANTS ON APP METABOLISM

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Aims: Using exome sequencing data from 32,558 individuals, we identified rare variants in the Proto-oncogene tyrosine-protein kinase SRC gene associated with AD risk. This association was mainly due to the localization of rare damaging variants in the SH2 domain of Src. The SH2 domain of Src is known to control the inactive/active forms of the protein and to be involved in its interaction with partners, such as Kindlin2, a genetic risk factor of AD. Moreover, we identified SRC as a strong modulator of APP metabolism. Thus, we hypothesized that SRC variants may modulate APP metabolism and potentially promote synaptic dysfunction.
Methods: We aimed to evaluate the impact of Src variants on APP metabolism by overexpressing each variant in a HEK293 cell line stably overxpressing APP. APP and its byproducts were quantified using WB and Alpha-LISA approaches. To better understand how Src variants may modulate APP metabolism, we studied their impact on Src activity through the quantification of its active and inactive forms using WB. The consequences of Src variants over-expression on neuronal activity were measured using Multi Electrode Array (MEA) in primary neuronal culture.
Results: Compared to the SRC WT, over-expression of the variant V177L was associated with an increase of APP mature and APP-derived byproducts including Aβ peptides. In our neuronal model, we showed that over-expression of V177L leads to a decrease of Src active form, suggesting that the variant alters Src activity. Finally, the over-expression of V177L was associated with altered neuronal activity measured by MEA showing that the variant may impact Src function.
Conclusions: We identified rare damaging variant of Src that modulates APP metabolism and have an impact on the activity of the protein.

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SHIFT 02-243

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / METABOLISM, INSULIN
4-5 April 2025

THE IMPACT OF LOW CIRCULATING CHOLINE ON METABOLIC DYSFUNCTION AND COGNITIVE HEALTH: COMPARATIVE ANALYSIS IN PREDIABETIC HUMANS AND THE 3XTG-AD MODEL OF ALZHEIMER'S DISEASE

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Aims: Dietary choline deficiency affects ~90% of Americans and has been linked to cognitive decline and Alzheimer's disease (AD). The rising prevalence of type 2 diabetes (T2D) and obesity—both significant risk factors for AD—raises concerns about their combined impact on cognitive health. AD affects 6.9 million Americans aged 65 and older and is characterized by amyloid beta (Aβ) plaques, neurofibrillary tau tangles (NFTs), and neuroinflammation, leading to cognitive deficits. Insulin resistance, common in both T2D and AD, disrupts brain glucose metabolism and accelerates neurodegeneration. Deciphering the contributing factors to these connections could pave the way for innovative approaches to address cognitive decline and neurological dysfunction.
Methods: We examined the relationship between circulating choline levels, obesity, and metabolic dysfunction in human participants with obesity (BMIs > 30) and those with normal BMIs (18.5–24.9), alongside mice from the 3xTg-AD mouse model of AD that were fed a choline deficient diet throughout adulthood.
Results: Our analysis revealed that individuals with obesity had significantly lower circulating choline levels compared to healthy weight counterparts. These lower choline levels correlated with increased body fat percentage and higher insulin resistance markers, including HOMA-IR and insulin levels. Elevated inflammatory cytokines in obese individuals were consistent with findings in 3xTg-AD mice on a choline-deficient diet, which showed significant weight gain, altered liver proteins, metabolic dysfunction, mirroring findings in human participants. 3xTg-AD choline deficient mice also showed exacerbated amyloid and tau pathogenesis.
Conclusions: Our results highlight the complex interplay between low choline levels, obesity, insulin resistance, and cognitive decline. Ensuring adequate choline intake and managing weight may help mitigate the risks of T2D and AD, potentially preventing cognitive deterioration and related diseases.

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SHIFT 02-244

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROBIOME
4-5 April 2025

RELATIONSHIP OF GUT MICROBIOTA TO COGNITIVE IMPAIRMENT IN PATIENTS WITH NEUROCOGNITIVE DISORDER

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Aims: Neurocognitive disorders (NCD) are chronic degenerative clinical syndromes characterized by the decrease or loss of cognitive functions; it is a multifactorial disease whose main risk factor is age. Evidence has been found that the gut microbiota composition may mediate or influence NCD status through mechanisms defined by the "microbiota-gut-brain" axis that are not yet fully understood. Evidence is lacking to test whether gut microbiota composition differs between individuals with and without cognitive impairment (CI) in a way that impacts disease presentation. In this study, we proposed investigating the relationship between gut microbiota composition and cognitive impairment in older adults.
Methods: We included 59 individuals (>60 years old) cognitively assessed with the MoCA test. DNA was extracted from stool samples for massive 16s sequencing. Subsequently, sequencing data were processed with the Qiime2 program to obtain α-diversity and ß-diversity, and then we compared the composition with the presence/absence of CI.
Results: Individuals were classified into two groups: without-CI (n=16) and with-DI (n=43). No significant differences were found in phylogenetic diversity (alpha-diversity), however, there was a difference in the percentage of Proteobacteria (Beta-diversity) between individuals in the groups (z= 1.873, p= 0.0307).
Conclusions: Based on this study, it can be inferred that there are differences in the proportions of certain bacterial phyla in patients with CI compared to individuals without impairment.

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SHIFT 02-246

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROBIOME
4-5 April 2025

GUT MICROBIOTA SHAPING COGNITIVE FUNCTION – A NOVEL ROUTE TO COGNITIVE HEALTH – INTRODUCTION TO THE MICROCOGNI STUDY

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Aims: Experimental studies have shown that variation in gut microbiota affects cognitive function, and plays a role in the cerebral accumulation of β-amyloid and tau proteins. Being the first to apply a large population-based cohort, the *Micro*COGNI study seeks to solve whether gut microbiota plays a role in determining cognitive function phenotype in humans via influencing the metabolism of β-amyloid and tau proteins.
Methods: The *Micro*COGNI study is built upon the population-based multigenerational Young Finns Study. The cognitively unimpaired participants (n=2051; age 41-90 years) have been tested using a computerized neurocognitive test battery CANTAB (follow-up time 7 years) and have given plasma and faecal samples. Aβ40, Aβ42, pTau-217, GFAP, and NfL have been measured on the Quanterix Simoa HD-X analyzer. Whole-genome shotgun sequencing is being conducted for the faecal samples. Additionally, extensive longitudinal data e.g., on health behaviors, cardiovascular risk factors and outcomes, socioeconomic status, use of medications and whole genome scans have been collected.
Results: So far, the results from the *Micro*COGNI have confirmed that decrease in cognitive function accelerates with aging in all cognitive domains, and that education may alleviate the decrease with similar but opposite effect size than age. Even in cognitively unimpaired population, higher age is associated with adverse β-amyloid and tau protein concentrations, especially in APOEε4 carriers. Several factors, such as kidney function, obesity, and parental transmission may influence β-amyloid and tau protein concentrations.
Conclusions: The *Micro*COGNI study will provide evidence on the role of gut microbiota determining cognitive function via affecting β-amyloid and tau protein metabolism in humans. If these links are revealed, it would lead to a novel outlook to the determinants shaping cognitive function, and thereby, offer novel routes for cognitive health promotion.

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SHIFT 02-247

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROBIOME
4-5 April 2025

STRAIN-SPECIFIC EFFECTS OF GUT BACTERIA ON MACROPHAGE UPTAKE OF AMYLOID-BETA PEPTIDES

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Aims: Gut bacteria can affect Alzheimer's disease (AD) in mice by modulating microglia that clear amyloid peptides and plaques from the brain. Here, we use a functional assay to investigate how gut bacteria isolated from AD and control gut microbiota regulate the amyloid clearing capacity of macrophages *in vitro*.
Methods: A total of 288 bacteria were isolated from two AD patients, two age-matched controls, and two young controls in an anaerobe environment. The donor samples were analyzed with 16S sequencing. RAW264.7 macrophages were stimulated with bacteria culture supernatants for 24h and then challenged with fluorescently labeled amyloid-β-42 peptides for 4h. Amyloid uptake was assessed with flow cytometry and bacteria supernatants were analyzed with metabolomics.
Results: The isolated bacteria represented several major branches of the phylogenetic tree of each donor. Macrophage stimulation with supernatants showed that 30 out of 70 unique isolated bacteria significantly stimulated the macrophage's ability to take up amyloid-β-42 (4 independent experiments), up to 2.7 times of the control. Interestingly, one of four strains of *Holdemania filiformis*, one of two strains of *Parabacteroides merdae*, one of two strains of *Intestibacter barletti* and one of three strains of *Escherichia coli* significantly stimulated amyloid uptake even though the other strains of the same species did not. Metabolomics of supernatants from the 4 strains of *H. filiformis* revealed that four metabolites were significantly higher levels in the stimulating strain compared to the non-stimulating strains, including N6-methyladenosine, N-acetylneuraminate, 2,8-quinolinediol sulfate and N-acetylglucosamine.
Conclusions: We conclude that despite near-identical 16S genes, bacteria of the same species may still have differential immunomodulatory effects, with implications in AD. This study underlines the importance to consider strain-specific effects of gut bacteria in AD.

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SHIFT 02-251

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

EXTRACELLULAR ATP AND P2X7 RECEPTORS AS MAIN DRIVERS OF NEUROINFLAMMATION IN ALZHEIMER'S DISEASE

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Aims: Growing evidence suggests that neuroinflammation plays a crucial role in Alzheimer's disease (AD) genesis and progression. Our project aims at investigating, along disease progression, whether and how the extracellular ATP (eATP)/P2X7 receptor (P2X7R) signalling axis influences glia activation, neuroinflammatory pathways and neuronal Ca^{2+} excitability in an AD mouse model (B6.152H) expressing human PS2-N141I and APP Swedish mutations.
Methods: We conducted an Imaris-based morpho-functional analysis of microglia and astrocytes in the somatosensory cortex (SSCx) at different time points. We also characterized the inflammatory state of AD mouse brains by Western blot, ELISA and real-time PCR. To assess the consequences of glial cell alterations on neuronal Ca^{2+} activity, we combined electrical stimulation with 2-photon Ca^{2+} imaging in brain slices. Moreover, to verify whether brain eATP is higher in AD with respect to WT mice, we performed *in vivo* eATP measurements in the whole brain of anaesthetized mice by exploiting a luminescent genetically encoded ATP probe.
Results: We found that AD brains show an early inflammatory state, occurring at 2 months of age before Aβ-plaque deposition, with increased eATP concentrations, reactive microglia, inflammasome activation and cytokine production. Of note, at this early AD stage, reactive microglia show an increased synapse and extracellular matrix phagocytosis accompanied by neuronal Ca^{2+} hyperexcitability. Strikingly, by using AD mice knock-out (KO) for the P2X7R, we obtained a complete rescue of microglia alterations.
Conclusions: Our data reveal an unexpected early neuroinflammatory state and activation of microglia that are rescued in AD/P2X7RKO mice. Studies are ongoing to verify whether the normalization of microglia function is paralleled by a decrease in brain eATP levels and neuronal activity is restored.

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SHIFT 02-252

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

MAPPING MICROGLIAL AGGREGATE SUBTYPES WITH HIGH-CONTENT NEUROPATHOLOGY AND SPATIAL PROFILING UNVEILS DISTINCT IMMUNE AND NEURODEGENERATIVE SIGNATURES IN ALZHEIMER'S DISEASE HIPPOCAMPUS

Mónica Miranda De La Maza[1,2,3], Sonja Fixemer[1,3], Gaël Hammer[3,4], Félicia Jeannelle[3,4], Sophie Schreiner[3,4], Jean-Jacques Gérardy[3,4], Naguib Mechawar[5], Michel Mittelbronn[1,2,3,4], David Bouvier[1,3,4]
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Aims: Microglial distribution throughout the brain parenchyma is frequently disrupted in Alzheimer's disease (AD), where they undergo spatial reorganization and form cellular aggregates often associated with amyloid-β (Aβ), termed plaque-associated microglia (PaM). Using high-content neuropathology, we discovered another type of microglial aggregates, unrelated to Aβ, found in the pyramidal layer of the CA2/CA1 regions of the hippocampus in AD patients and predominantly attached to tau tangles and neurons containing phosphorylated α-synuclein. Because of their peculiar conformation we have named them Coffin-like microglia (CoM). This study aims to define the structural, pathological and molecular signatures of hippocampal PaM and CoM in AD patients and to explore their involvement in disease progression.
Methods: We used Nanostring GeoMx Deep Spatial Profiling (DSP), multiplex chromogenic, confocal microscopy and digital pathology analysis to characterise and compare the structural, proteomic and transcriptomic profiles of CA1 PaM, CoM and their direct microenvironments in *post-mortem* AD patients and age-matched controls (CTLs).
Results: CoM exhibit specific protein and transcriptomic signatures associated with STING, protein degradation, TGF-β, and NF-κB signaling pathways. In contrast, PaM signatures were associated with complement components, ErbB signaling, metabolic and neurodegenerative activities. We also observed a clear enrichment of phosphorylated mixed lineage kinase domain-like protein (pMLKL) and severe tau pathology encapsulated by PaM. We found no direct association of CD8+ T cells with PaM or CoM, although there was a slight, non-significant increase in number of cells in AD compared to CTLs. CD163+ peripheral macrophages were frequently found incorporated into PaM.
Conclusions: This study provides new insights into the molecular profiles of microglia, their association

with infiltrating immune cells and identifies specific neurodegenerative hotspots within the hippocampus in AD, underscoring their critical role in hippocampal deterioration.

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SHIFT 02-253

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

THE DIFFERENTIAL AND TEMPORAL EFFECTS OF A SINGLE OR DUAL INFLAMMATORY INSULT ON MICROGLIA ACTIVATION STATES

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Aims: Neuroinflammation is a key defence mechanism in the brain, primarily orchestrated by microglia, which play an essential role in responding to injury and infection. However, a prolonged or excessive response by microglia to inflammation can exacerbate neuronal damage and impair synaptic plasticity, significantly disrupting brain function and contributing to the progression of neurodegenerative diseases, such as Alzheimer's and Parkinson's disease. Inflammation in the brain is typically a dynamic, multi-phase process, often involving multiple inflammatory triggers. Interferon gamma (IFNg), which has been found in the brains of Alzheimer's patients, acts as a "primer" of microglia, so when a secondary inflammatory trigger occurs, it can lead to an intensified microglial activation state. Here, we investigated the dual effect of IFNg and lipopolysaccharide (LPS) on the inflammatory activation cascade of microglia.
Methods: We used human iPSC-derived microglia in monoculture to investigate the "priming" effect of IFNg alone or in combination with LPS. We utilised several techniques, including Quantitative Polymerase Chain Reaction (qPCR), Immunocytochemistry and Bulk RNA-sequencing.
Results: Our data revealed not only a differential effect on the gene expression of several inflammatory related markers, but we also discovered temporal changes in inflammation and morphological and motility changes in microglia exposed to either a single or a dual inflammatory insult. RNA sequencing analysis of the microglia also revealed a robust and varied effect on several different molecular functions and biological processes.
Conclusions: Taken together, these findings emphasise the importance of understanding the temporal effects, the differential response of pro-inflammatory cytokines and the diverse impact of single or combined inflammatory stimuli on the activation state and biological response of microglia during inflammation.

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SHIFT 02-254

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

UNRAVELING THE ROLE OF LYSOSOMAL EXONUCLEASE PHOSPHOLIPASE D3 IN THE ACTIVATED RESPONSE MICROGLIA PHENOTYPE IN ALZHEIMER'S DISEASE

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Aims: The high regional specialisation and complexity of the brain provides microglia with a range of diverse signals, requiring different responses. One of these includes the activated response microglia (ARM) phenotype which is acquired by microglia surrounding amyloid plaques in Alzheimer disease (AD) brains. The late-onset AD risk factor Phospholipase D3 (PLD3) is systematically upregulated in ARMs. PLD3 is a lysosomal exonuclease that regulates inflammatory responses by degrading single-stranded DNA; i.e., the substrate of toll-like receptor 9. In neurons, PLD3 loss-of-function majorly impacts lysosomal proteostasis, suggesting PLD3 could play a role at the crossroad between inflammation and the microglial degradative capacity.
Methods: To study the effect of PLD3 in an in vivo situation, we created a knockout mouse in a C57Bl/6J background using RNP-CRISPR/Cas9 technology and further crossed it with APPN-L-GF knock-in mice; enabling the investigation of the role of PLD3 in an AD background. Histological assessments were performed at 3, 6 and 9 months.
Results: In an initial characterization of the mouse models, we observe that the loss of PLD3 results in an altered amyloid plaque organisation towards fewer plaques of larger size, and a redistribution of microglia which cluster less efficiently around plaques. We observe reduced microglial activation as well as an altered degradative compartment within these microglia.
Conclusions: Further investigation will determine the extent of the phenotypic change in these microglia and to which degree this affects microglial functions. The acquired knowledge will unveil a functional link between a dysfunctional exonuclease/PLD3 activity and microglial activities, and how this impacts the AD pathology.

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SHIFT 02-255

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

DIFFERENTIAL INTERACTION OF STREM2 WITH MODIFIED ABETA SPECIES

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Aims: Recent exome sequencing studies allowed for the identification of rare variants of the triggering receptor expressed on myeloid cells 2 (TREM2) as genetic risk factors for the sporadic form of Alzheimer's Disease (SAD). Previous studies indicated that TREM2 interacts with Aβ peptides. Therefore, we sought to characterize the interaction of TREM2 with Aβ variants in different aggregation- and phosphorylation-state.
Methods: By using the purified soluble ectodomain of TREM2 (sTREM2) for in vitro experiments we were able to investigate its binding affinity towards differently modified Aβ species in a variety of biophysical and biochemical assays including dot-blot, solid-phase assay, immunoprecipitation, bio-layer interferometry and surface-binding to TREM2 reporter cell line. Additionally, the effects of sTREM2 on the aggregation of Aβ variants was assessed by real-time fluorescence spectroscopy. Finally, cell biological studies were performed to identify functional effects of the differential binding on microglial intracellular signalling, Aβ uptake and neuronal toxicity.
Results: Our data indicate that TREM2 interacts preferentially with oligomeric assemblies of Aβ. In addition, we find that phosphorylated variants of Aβ exhibit increased binding to TREM2 in comparison to its non-phosphorylated form. Cell biological studies further indicate that TREM2 modulates the differential binding and uptake of phosphorylated and non-phosphorylated variants of Aβ. However, the interaction of Aβ variants did not significantly stimulate canonical TREM2 dependent intracellular signaling pathways. Notably, sTREM2 decreased the aggregation of different Aβ species into fibrillary assemblies.
Conclusions: These findings support the interaction of Aβ with TREM2, which is modulated by the phosphorylation- and aggregation-state of Aβ. Thus, it will be important to further assess the interaction of TREM2 with different Aβ variants during the pathogenesis of AD.

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SHIFT 02-256

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

MICROGLIA RESPONSE TO LASER CAPTURE MICRODISSECTED AMYLOID BETA (AB) PLAQUES FROM THE BRAINS OF ALZHEIMER'S DISEASE (AD) PATIENTS

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Aims: Microglial interactions with Aβ deposits in the brain are highly dynamic, affecting both microglial activity and the formation/maturation of Aβ deposits. The molecular mechanisms driving this crosstalk remain poorly understood, largely due to the lack of appropriate models. *In vivo* studies in mouse brains rely on complex and low-throughput live imaging techniques while Aβ aggregates purified from AD brains lose their morphological diversity and composition, which may be key to these interactions. To address these limitations, we developed a novel *in vitro* model by culturing iPSC-derived human microglia with Aβ deposits isolated from AD brains using Laser Capture Microdissection (LCM).
Methods: Aβ deposits were identified in frozen AD brain sections using Thioflavin S (ThS) staining and isolated via LCM. iPSC-derived microglia were incubated with LCM-captured Aβ deposits. ThS negative regions from the same AD brain, and tissue from non-demented subjects, were used for comparison. Microglial engagement with LCM-Aβ deposits and controls were monitored via live imaging over 48 hours. Bulk RNA sequencing was performed to investigate microglial response. Aβ deposits-induced differentially expressed genes (DEGs) were identified through transcriptome analysis and validated using immunofluorescence.
Results: Microglia actively migrated and interacted with Aβ deposits and control regions. LCM-captured Aβ deposits induced significant changes in the expression of multiple genes, including AD risk genes known to be expressed in microglia.
Conclusions: The platform developed in this work provides a valuable tool for studying microglial interactions with Aβ deposits observed in AD brains, and defining the role of AD risk genes in these interactions. This model can be enriched by including other brain cell types, such as neurons and astrocytes, allowing for a more comprehensive analysis of cellular responses within the Aβ-deposit niche.

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SHIFT 02-257

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

MICROGLIAL CONTACT WITH PLAQUES IS ESSENTIAL FOR GENE REGULATION IN HUMAN ALZHEIMER'S DISEASE

Jack Wood[1,2], Georgia Ppasia[1], Naciye Magusali[3], Damian Cummings[1], Dervis Salih[3], Jörg Hanrieder[2,4], Frances Edwards[1]
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Aims: Confirm the dependence of microglial contact with plaques on the upregulation of Alzheimer's disease (AD)-associated genes in humans, validating previous observations in mice (Wood et al., 2022).
Methods: Human hippocampal samples from Alzheimer's disease (AD) and non-AD cases were donated by the Netherlands Brain Bank, with a low postmortem interval (≤7 hours) and matched for sex and ApoE status. The 8 µm FFPE sections were initially stained for microglia (IBA1 antibody), Aβ plaques (Amytracker dye), and hybridized with whole transcriptome RNA-targeting probes. Using the GeoMx Digital Spatial Profiler, whole-slide images of the tissue were captured. Probes were then collected from microglial regions in direct contact with plaques, near plaques (within 50 µm), and far from plaques (more than 100 µm), before being sent for sequencing. Analysis was performed whole transcriptome using the Deseq2 package in R.
Results: Microglial contact with plaques led to the upregulation of 41 genes compared to microglia distant from plaques and 34 genes compared to microglia in periplaque regions. Many of these genes, such as *TREM2*, *TYROBP*, *CTSZ*, *CTSB*, *C1QA*, and *C1QB*, were previously identified as Alzheimer's disease (AD)-associated in mice and have been shown to be plaque-contact dependent in an AD mouse model (Wood et al., 2022). Ongoing analysis will investigate differences dependent on sex and APOE genotype.
Conclusions: The primary conclusion is that microglia rely on plaque contact to upregulate Alzheimer's disease (AD)-associated genes. Secondly, this study translates findings from mouse models to human tissue, supporting the effectiveness of these models in studying AD. Lastly, with the additional power provided by a planned increase in sample size, results on sex and ApoE genotype-dependency are expected to offer further insights into the role of microglia surrounding Aβ plaques.

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SHIFT 02-258

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

SINGLE-CELL TRANSCRIPTOMIC ATLAS OF ALZHEIMER'S DISEASE MIDDLE TEMPORAL GYRUS REVEALS SEX SPECIFICITY OF GENE EXPRESSION IN MICROGLIA WITH NOVEL GENETIC RISK FOR MERTK IN FEMALE

Le Zhang
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Aims: Alzheimer's disease (AD), the most common age-related neurodegenerative disease, is closely associated with both amyloid-ß plaque and neuroinflammation. Two thirds of AD patients are females, and they have a higher risk of developing the disease. To investigate the impact of sex differences on AD risk and neuroinflammation, and to achieve an accurate and unbiased assessment of sex-specific and cell-type-specific changes associated with AD, we transcriptionally profiled AD brains and age- and sex-matched controls at the single cell level, focusing on the middle temporal gyrus, a brain region strongly affected by AD.
Methods: We conducted single nucleus RNA sequencing with brain samples from AD patients and age- and sex-matched controls, focusing on the middle temporal gyrus. We analyzed excitatory neuron populations and assessed reactive astrocyte and microglia signatures of AD brains at the single cell level. We combined single cell transcriptomic data with genome-wide association studies (GWAS) to identify novel sex-specific genetic risk factors for AD.
Results: We identified a subpopulation of selectively vulnerable layer 2/3 excitatory neurons that were RORB-negative and CDH9-expressing. Disease-associated, but sex-independent, reactive astrocyte signatures were also present. In clear contrast, the microglia signatures of diseased brains differed between males and females. Combining single cell transcriptomic data with results from GWAS, we identified *MERTK* genetic variation as a risk factor for Alzheimer's disease selectively in females.
Conclusions: Taken together, our single cell dataset revealed a unique cellular-level view of sex-specific transcriptional changes in AD micorglia, illuminating GWAS identification of sex-specific AD risk genes. These data serve as a rich resource for interrogation of the molecular and cellular basis of AD, providing a novel tool for analyzing single cell hints using GWAS data to identify sex-specific risk genes for AD.

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SHIFT 02-259

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

INVESTIGATING THE IMMUNOPROTECTIVE ROLES OF HIGH-DENSITY LIPOPROTEINS ON MICROGLIA: A FOCUS ON PARTICLE SUBCLASS HETEROGENEITY

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Aims: High-density lipoprotein (HDL) particles are known primarily for their role in cholesterol removal from the arterial wall, however, HDL also play multiple roles in the immune system and are starting to be recognized for their potential involvement in Alzheimer's disease (AD). Recent evidence shows that peripheral HDL particles cross the blood-brain-barrier, and both high and low HDL-cholesterol concentrations are associated with increased risk for AD. There are multiple subclasses of HDL, and the effects of these different subclasses on immune cell function in the context of AD have not been examined.

The objective of this project is to determine how different subclasses of HDL interact with microglia, with the purpose of discovering mechanistic targets to regulate neuroinflammation in AD.
Methods: We used ultracentrifugation followed by size-exclusion chromatography (SEC) coupled with UV, multi-angle light scattering (MALS), dynamic light scattering (DLS), and differential refractive index (dRI) to isolate and measure the diameter, particle concentration, and molecular weight of 6 HDL subclasses – HDL-large,-medium, small, and dense-HDL-large,-medium,-small. Microglia stimulated with LPS and amyloid beta oligomers (AbO) were treated with isolated HDL subclasses and cytokine release, gene expression, and phagocytosis function were measured.
Results: Some HDL subclasses exhibited strong anti-inflammatory properties, while others showed less anti-inflammatory or even pro-inflammatory effects. Specific genes related to pro-inflammatory pathways demonstrated reduced expression in cells treated with certain HDL types. Some HDL subclasses attenuated the loss of phagocytosis function better than other HDL subclasses.
Conclusions: These results demonstrate that different HDL subclasses have varying potential to regulate neuroinflammation, highlighting the need for further research on interventions that can modify HDL subclass distribution to reduce AD risk.

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SHIFT 02-260

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

INVOLVEMENT OF RER1 IN THE LIPID METABOLISM OF THP-1 CELLS

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Aims: Lipid droplets (LDs) are dynamic cytoplasmic stores of triacylglycerols (TGs) and cholesterol esters (CE). Dysfunctional LD metabolism is associated with different diseases, including obesity, diabetes, atherosclerosis, and neurodegenerative disorders. Here, we investigated the role of RER1 in lipid metabolism of monocytic and macrophage-like cell models.
Methods: Wild type (wt) and RER1 knock out (ko) monocytes and macrophage-like differentiated THP-1 cells were analyzed by cell biological and biochemical methods including western immunoblotting, immunocytochemistry, and flow cytometry, RNA sequencing (RNA seq), gas chromatography flame ionization detection (GC-FID) and gas chromatography–mass spectrometry (GC-MS).
Results: We found a strong accumulation of LDs in RER1 ko monocytes and macrophage-like differentiated THP-1 cells. Sterol analysis in monocytes revealed that the cholesterol precursors lanosterol and desmosterol were significantly increased while lathosterol, was strongly decreased in RER1 deleted monocytes. However, the total amount of cholesterol was not significantly changed. Levels of free cholesterol tended to be slightly increased, while that of cholesterol esters tended to be slightly decreased in RER1 ko as compared to wt THP-1 monocytic cells. In macrophage-like differentiated THP-1 cells, precursors of cholesterol and total cholesterol were significantly decreased in RER1 ko as compared to respective control cells. However, the percentage of free cholesterol was significantly increased, while that of cholesterol esters was significantly decreased in RER1 ko macrophage-like cells as compared to wt cells. RNA sequencing data showed that RER1 deletion results in upregulation key genes involved in lipid metabolism.
Conclusions: Our data indicates an important role of RER1 in the lipid metabolism of monocytes and macrophage-like cells. Thus, RER1 might play a crucial role in lipid metabolism of immune cells. It will be interesting to further dissect the underlying molecular mechanisms.

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SHIFT 02-261

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

ALZHEIMER'S DISEASE-ASSOCIATED PRESENILIN 2 INFLUENCES THE LIPIDIC PROFILE.

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Aims: Alzheimer's disease (AD) is the most common form of neurodegenerative dementia. Presenilins (PSs) 1 and 2 – the catalytic subunits of γ-secretase – are major players in amyloid-β (Aβ) production and amyloid pathology. Mutations in PSs found in familial forms of AD (FAD) are believed to exert a partial loss-of-function effect on PSs whose pathogenic role extends beyond Aβ production. PS2 in particular is critical in mitochondrial function and cell bioenergetics. We aim to explore the role of PSs in cellular lipid metabolism.
Methods: WT, PS1- and PS2-*knock-down* SH-SY5Y cells were cultured in normal or lipid-depleted media and the lipidic profile was assessed using the PhenoVue Nile Red lipid stain. In parallel, WT and PS2-*knock-out* primary neurons were cultured in a lipid-deficient media, supplemented or not with a lipid concentrate, and the same lipid staining was performed. The effect of the *PSEN2N141I* FAD mutation was studied by lentiviral infection of both SH-SY5Y cells and primary neurons. Finally, the production of extracellular vesicles (EVs) was assessed using Nanoparticle Tracking Assay (NTA).
Results: The intracellular lipidic content was increased in PS2KD SH-SY5Y cells, but not in PS1KD. This increase was lost in a lipid-deficient environment. This phenomenon was also observed in primary neuronal cultures. EVs production was decreased when cells were cultured in lipid-depleted media but did not seem to vary depending on the genotype.
Conclusions: These data suggest a role for PS2, but not PS1, in the endogenous production of lipids. The absence of PS2 would favor the uptake of extracellular lipids from the environment, except in a lipid-depleted media where cells do not accumulate intracellular lipids. PS2 N141I mutation might have more nuanced influences on the lipidic profile, currently under investigation in lipidomic analyses.

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4-5 April 2025

FRAGMENTATION OF THE GOLGI APPARATUS INDUCED BY CHRONIC OXIDATIVE STRESS EXACERBATES ALZHEIMER'S DISEASE PATHOLOGY

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Aims: The Golgi apparatus, essential for cellular homeostasis and protein trafficking, is increasingly recognized for its role in Alzheimer's disease (AD) pathology. This study explores the impact of chronic oxidative stress on Golgi fragmentation and its contribution to the overproduction of beta-amyloid and hyperphosphorylated tau, hallmark proteins of AD.
Methods: iPSC-derived neurons were exposed to chronic oxidative stress through H2O2 treatment (aound 100mM) every three days for 15 days. Cellular phenotypes, including Golgi fragmentation, beta-amyloid secretion, and hyperphosphorylated tau accumulation, were assessed via western blotting, ELISA, and immunocytochemistry. A Golgi-targeting antioxidant nanoparticle was applied to directly investigate the role of oxidative stress on Golgi integrity.
Results: Sub-lethal doses of H2O2 (100μM) induced a significant increase in beta-amyloid secretion and hyperphosphorylated tau accumulation, coinciding with a marked rise in neurons displaying fragmented Golgi apparatus. These fragmented Golgi structures co-localized with beta-amyloid and APP, indicating a direct link between Golgi disruption and AD pathology. Treatment with a Golgi-targeting antioxidant nanoparticle successfully reduced both Golgi fragmentation and the levels of beta-amyloid and hyperphosphorylated tau.
Conclusions: The study demonstrates that Golgi fragmentation plays a critical role in exacerbating AD pathology by promoting the overproduction of beta-amyloid and tau. The findings underscore the importance of Golgi integrity in mitigating disease progression and suggest that targeting oxidative stress in the Golgi could be a novel therapeutic approach for slowing AD development.

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SHIFT 02-263

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

THE ROLE OF ASTROCYTIC PHOSPHOLIPASE D1 IN RECOGNITION MEMORY AND ITS POTENTIAL IMPLICATIONS IN ALZHEIMER'S DISEASE PATHOLOGY

Hyein Song[1], Heejung Chun[2]
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Aims: Phospholipase D1 (PLD1) is an enzyme that catalyzes phosphatidylcholine hydrolysis to phosphatidic acid (PA), facilitating critical cellular signaling processes. Previous studies report that PLD1 is upregulated in reactive astrocytes and caveolae-enriched membrane domains in Alzheimer's disease (AD) brains, where it associates with amyloid precursor protein (APP) and amyloid-beta (Aβ) plaques. This suggests a potential role for dysregulated PLD1 in AD-associated cognitive decline, yet the specific role of astrocytic PLD1 in cognitive function remains unclear.
Methods: We investigated the role of astrocytic PLD1 in cognition through astrocyte-specific PLD1 knockout (KO) models in mice. Whole-brain astrocytic PLD1 KO mice (hGFAP-CreERT2+PLD1$^{flox/flox}$) were used to assess recognition memory via the object location test (OLT) and the novel object recognition test (NORT), with additional assessments of locomotor activity and depressive-like behavior. To examine PLD1's regional role in cognition, we generated a hippocampal-specific astrocytic PLD1 KO model by delivering Lenti-pGFAP-CRISPR-PLD1gRNA (or NT)-GFP to the CA1 region of C57BL/6J mice.
Results: Our findings demonstrate that whole-brain astrocytic PLD1 KO mice exhibited significant recognition memory impairment in the OLT and the NORT, while no effects were observed on locomotor activity or depressive-like behavior, indicating that astrocytic PLD1 is essential for recognition memory. Interestingly, hippocampal astrocytic PLD1 KO mice showed cognitive deficits, highlighting the critical role of hippocampal astrocytic PLD1 in cognitive function.
Conclusions: These findings establish a foundational understanding of astrocytic PLD1's involvement in cognition, suggesting that its dysregulation may contribute to AD pathology. Investigating PLD1's involvement in Aβ interactions within AD could further clarify its role in AD progression, presenting a potential therapeutic target for AD-related cognitive impairment.

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SHIFT 02-264

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

STEAROYL-COA DESATURASE INHIBITION LEADS TO FATTY ACID NORMALIZATION AND IMPROVED DENDRITIC SPINE DENSITY IN THE HIPPOCAMPUS OF THE 5XFAD MOUSE MODEL

Marta Turri[1,2], Myriam Aubin[1], Laura Hamilton[3], Annick Vachon[2], Anne Aumont[1], Mélanie Plourde[1,2], Karl Fernandes[1,2]
[1]University of Shebrooke, Medicine And Health Sciences, Sherbrooke, Canada, [2]Centre de Recherche sur le Vieillissement, C, Canada, [3]CRCHUM, Neuroscience, Montréal, Canada

Aims: Alterations in brain lipids are a central feature of Alzheimer's disease (AD), nevertheless therapeutic strategies targeting brain lipid metabolism are still lacking. Our lab recently reported that a pharmacological inhibitor of the fatty acid enzyme, stearoyl-CoA desaturase (SCD), led to recovery of hippocampal synapses with associated improvements in learning and memory in the slow-progressing 3xTg-AD mouse model. Here, we used the 5xFAD rapidly progressing AD model to further delve into lipid metabolism disruptions in AD, and into the effect of the SCD inhibitor (SCDi) on fatty acid (FA) alterations and synapse loss.
Methods: Hippocampi from 5xFAD and non-carrier (NC) littermate control mice were collected at 5 and 8 months old (MO) for FA profiling by gas chromatography–flame ion detection (GC–FID) and for IHC for β-amyloid, GFAP (astrocytes) and Iba-1 (microglia). SCDi or vehicle was infused via intracerebroventricular osmotic pumps for 28 days in 5 MO 5xFAD and NC mice, and their hippocampi were processed for GC-FID and Golgi staining for dendritic spine quantification.
Results: FA alterations were apparent in female hippocampus at 5 MO (together with plaque pathology and gliosis) and worsened by the age at 8 MO, while males first showed FA alterations at 8MO. The C16:1/C16:0 desaturation index, parameter associated to SCD enzymatic activity, showed a significant increase in 5xFAD mice at 8 MO, but starting at 5MO in females. Treating 5xFAD females' mice with SCDi improved dendritic spine density and normalized FA levels.
Conclusions: These data demonstrate that SCD inhibitor treatment in a second AD mouse model, the more aggressive 5xFAD model, has beneficial effects on FA alterations and hippocampal dendritic spines. These findings add to accumulating data supporting SCD inhibition as a promising novel therapeutic target for AD.

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β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
4-5 April 2025

LABEL-FREE FUNCTIONAL CHARACTERIZATION OF HUMAN IPSC-DERIVED NEURONS AT SUBCELLULAR RESOLUTION

Ouissame Mnie-Filali, Silvia Oldani, Zhuoliang (Ed) Li, Xiaohan Xue, Fraser Mccready
MaxWell Biosystems, Zurich, Switzerland

Aims: Brain models derived from pluripotent stem cells have become a fundamental tool for studying common neurological disorders, such as epilepsy, Alzheimer's disease, and Parkinson's disease. The ability to measure the electrical activity of human iPSC-derived neurons in real time and label-free can provide much needed insights into the complexity of their neuronal networks.
Methods: With MaxWell Biosystems high-density microelectrode array (HD-MEA), we can perform in vitro extracellular recordings of action potentials at different scales, ranging from network through single- neuron to subcellular features.
Results: In this poster, we show the advantages of having an HD-MEA system featuring 26'400 electrodes per well, which are key to increase the statistical power of the data collected from iPSC-derived neurons over multiple days/weeks and to capture the smallest neuronal signals. We also present the AxonTracking Assay, a tool for automated recording and analysis of individual axonal arbors of many neurons in parallel.
Conclusions: Our HD-MEA platforms and the extracted metrics provide an extremely powerful and user-friendly approach for in vitro disease modelling. Nevertheless, our software modules suite for large-scale data handling allow to streamline your research process and enhance your results.

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Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
4-5 April 2025

RELATIONSHIP BETWEEN SYNAPTIC DYSFUNCTION AND GLIAL RESPONSE THROUGH THE ALZHEIMER'S DISEASE CONTINUUM AND AGEING

Mariana Muñoz García[1], Yuetiva Deming[2], Sterling Jonhson[2], Sanja Asthana[2], Cynthia Carlsson[2], Ozioma Okonkwo[2], David Perez-Martinez[1], Alberto Villarejo-Galende[1], Kaj Blennow[3], Henrik Zetterberg[3], Barbara Bendlin[2], Estrella Morenas-Rodriguez[1]
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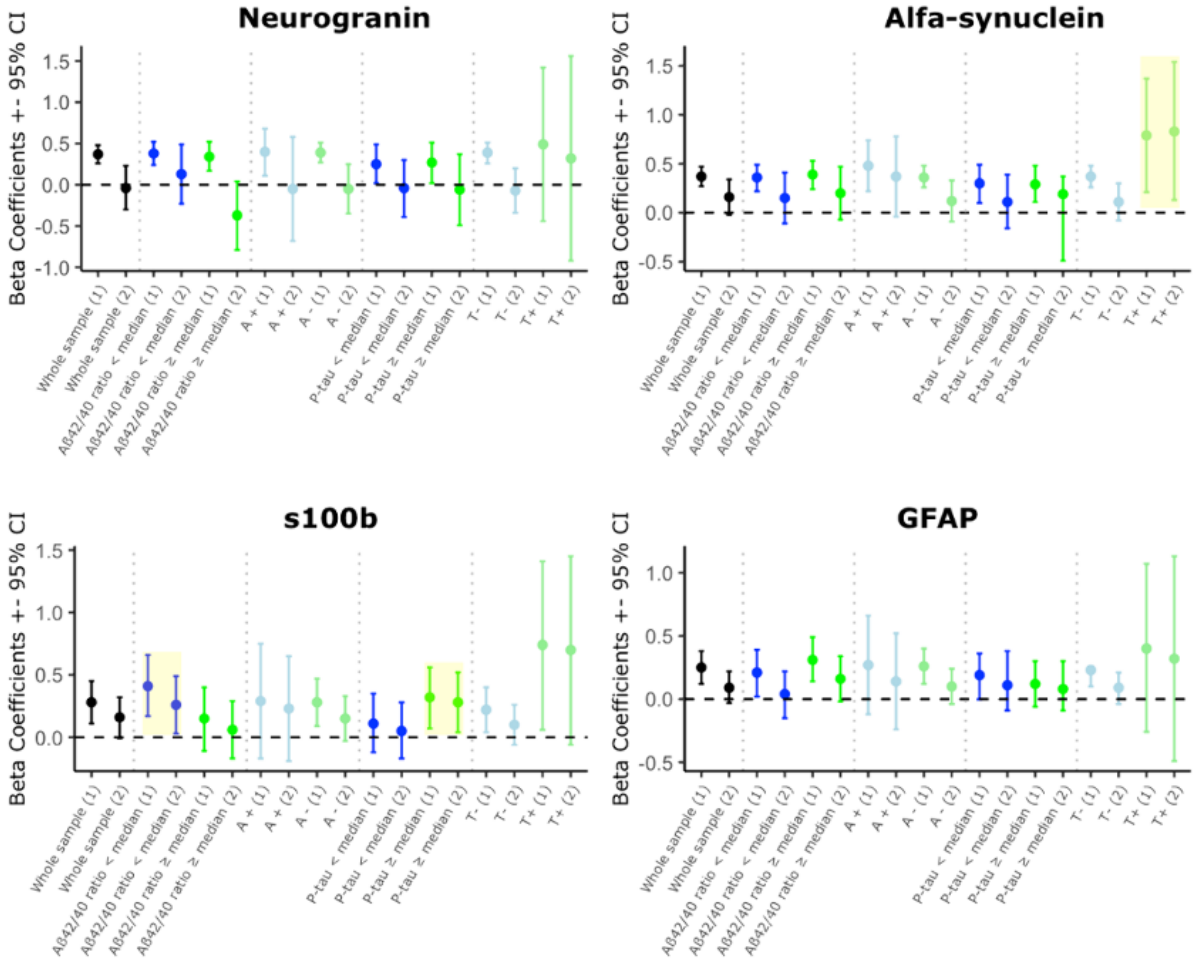
Aims: Synaptic homeostasis, maintained by microglia & astroglia, is disrupted early on in neurodegenerative diseases. Our aim was to study the relationship between TREM2-dependent microglial activation, astroglial response and synaptic dysfunction in a longitudinal cohort of asymptomatic volunteers, and whether this relationship is influenced by AD core biomarkers.
Methods: We studied cross-sectional (n=239) and longitudinal (n=116) associations between cleaved soluble TREM2 (cTREM2), astroglial (GFAP, s100b) and synapse-related biomarkers (neurogranin, α-synuclein) in cerebrospinal fluid (CSF) from asymptomatic volunteers. cTREM2 was measured by an in-house MSD-based immunoassay, while synapse-related, astroglial and AD core markers were quantified by the Elecsys® platform. We performed linear regression and linear mixed models unadjusted and adjusted by Aβ42 and p-tau. We defined subgroups according to the AT classification, and medians of p-tau, and Aβ42/Aβ40 ratio.
Results: Models adjusted by Aβ42 and p-tau showed an association between cTREM2 and s100b in participants with Aβ42/Aβ40 ratio below the median, and in participants with p-tau above the median (figure 1). We found an independent association between cTREM2 and α-synuclein in the T+ group. Also, baseline levels below median of neurogranin and α-synuclein, and levels above median of s100b independently predicted a higher longitudinal increase of cTREM2 (Figure 2, β=-0.02, p-value=0.01; β=-0.02, p-value=0.01, β=0.02, p-value=0.03, respectively). Additionally, higher baseline levels of CSF cTREM2 were independently associated with a lower longitudinal increase of neurogranin (β=-0.03, p-

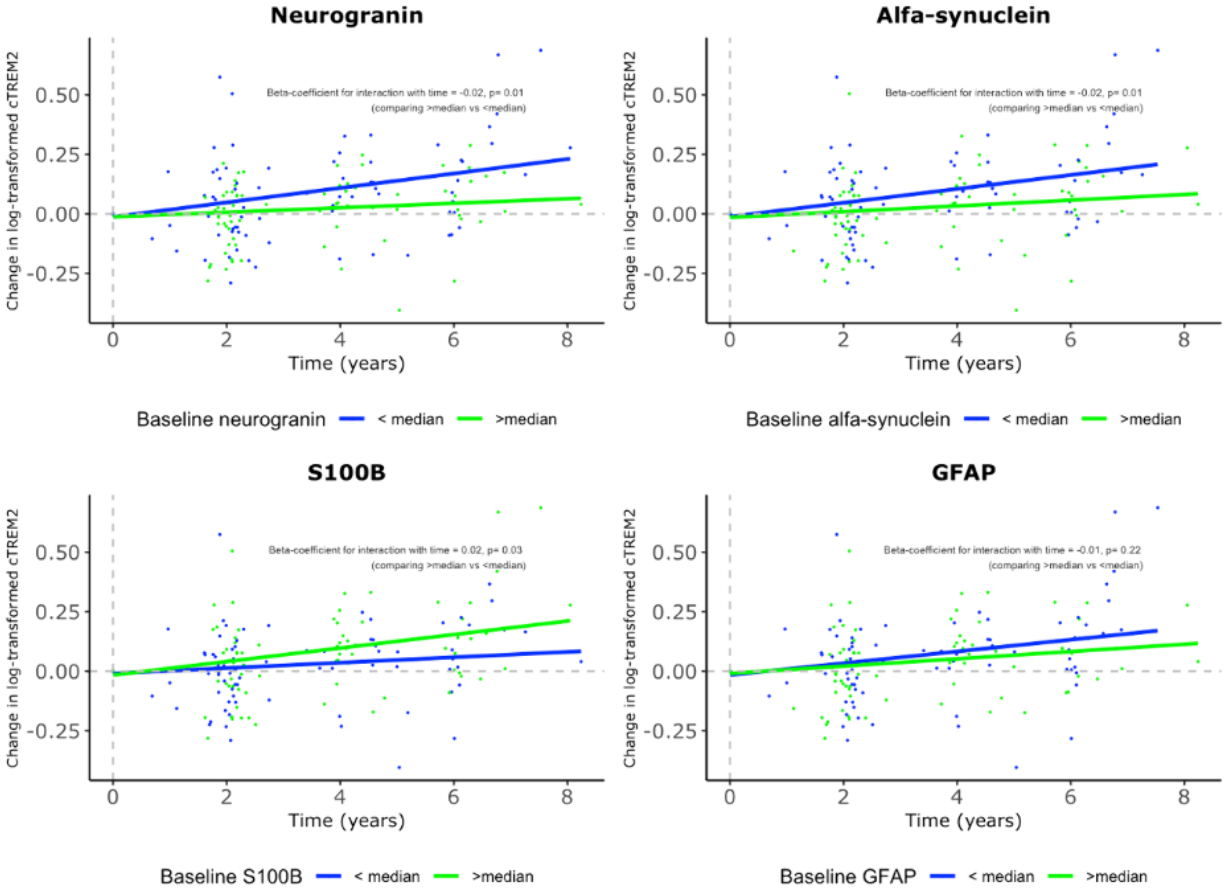
Figure 1. Cross-sectional associations between biomarkers and cTREM2.



Model 1: adjusted by age and gender. Model 2: adjusted by age, gender, AB42 and p-tau.

value=0.001).

Figure 2. Longitudinal associations between baseline biomarkers and cTREM2.



Models are adjusted by age, gender, AB42 and p-tau.

Conclusions: Synaptic dysfunction markers at baseline influence the longitudinal dynamics of CSF cTREM2 independently of AD-pathology related biomarkers. In turn, higher baseline cTREM2 is associated with more stable neurogranin levels over time. These results support an independent interaction between synaptic dysfunction and TREM2-dependent microglial activation throughout aging and neurodegeneration beyond AD pathology.

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SHIFT 02-267

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
4-5 April 2025

ALTERED SYNAPTIC INTEGRITY IN THE LATE-ONSET ALZHEIMER DISEASE (LOAD2) MOUSE MODE

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Aims: Alzheimer's disease (AD) is a neurodegenerative disorder characterized by cognitive decline. Structurally and functionally, synapses are essential for neurotransmission and for maintaining normal cognitive functions. Among AD patients, Late-Onset Alzheimer disease (LOAD) is the most common type of dementia. Here we sought to investigate whether synaptic integrity and synaptic transcriptomic signatures are altered in the brain of the LOAD2 mouse model (a triple homozygous expressing the *APOE4*, *Trem2*R47H*, and *hA*β risk variants), which was created by the MODEL-AD Center.
Methods: Brain subcellular fractions were prepared from LOAD2 mice to obtain synaptic and extra-synaptic sites to assess the expression of multiple proteins associated with synaptic function and relevant changes associated with age. We also evaluated gene expression using NanoString multiplex nucleic acid hybridization technology to investigate changes of expression in genes associated to neuropathology.
Results: LOAD2 mice exhibited changes in the expression of both presynaptic and postsynaptic proteins. Whereas synaptophysin and PSD95 were not altered 12- or 18-month-old (mo) LOAD2 mice, SV2A a presynaptic vesicular protein, showed significant changes in LOAD2 mice that were age-dependent. Importantly, we found significant changes in subunit composition of NMDA and AMPA receptors at the post-synaptic sites in LOAD2 mice. Alterations of gene expression were found mostly at 4-mo but not 12- or 18-mo.
Conclusions: The MODEL-AD Center has created novel mouse models with humanized, clinically relevant genetic risk factors to study progression of late-onset Alzheimer's disease (LOAD) more accurately. Here we show that LOAD2 mice showed synaptic alterations, which is relevant given that synaptic degeneration is a key feature of AD in both in humans and preclinical models, and it has been considered the most predictive pathological feature associated with cognitive decline in AD.

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SHIFT 02-268

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPTIC PLASTCITY & SYNAPSE PATHOLOGY
4-5 April 2025

EXCITATORY AND INHIBITORY SYNAPTIC DIFFERENCES IN ALZHEIMER'S DISEASE PROGRESSION IN MTG NEURONAL CELLS, A RNASEQ SINGLE CELL ANALYSIS

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Aims: Alzheimer's disease (AD) is a neurodegenerative disorder and the main cause of dementia worldwide. Synaptic dysfunction in the middle temporal gyrus (MTG), an area involved in language and memory, has been associated with main behavioral symptoms. Our group has previously described that regional disturbances in excitatory (E) and inhibitory (I) synapses may contribute to disease progression. However, it is not known which cell types are major drivers of E/I imbalances in the MTG. We hypothesize that vulnerable cell types present E/I imbalance as measured by the ratio of gene expression of excitatory and inhibitory postsynaptic proteins and their corresponding receptors.
Methods: Thus, we used single cell RNAseq data from human MTG provided by the Seattle Alzheimer's Disease Brain atlas (SEA-AD), to investigate the differences across AD disease stages along different neuronal subclusters.
Results: We will present our findings describing differential changes of E/I ratio depending on the cell type and their supertypes. Interestingly, non-neuronal cells expressed postsynaptic receptors that change with disease progression. We also observed differential changes in the E/I ratio of excitatory and inhibitory neurons that may correlate with the hyper- and hypoexcitability observed in AD. In the case of somatostatin cell types which are more vulnerable to AD stages, we observed a general decrease in the E/I ratio in highly affected donors, with some exception in specific supertypes. These cells are responsible to exert their inhibitory effects over excitatory neurons. The increase in the inhibitory component at later stages would reduce their neuronal firing, contributing to an increase of excitability in the brain circuit.
Conclusions: Thus, differences at the transcriptomic level in synapsis present useful information of the disease progression setting the basis to identify AD in early stages.

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SHIFT 02-271

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
4-5 April 2025

TRANSCRIPTIONAL REGULATORY NETWORKS IN PS19 MOUSE MODEL REVEALED BY MULTIOMICS ANALYSES

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Aims: This study is based on the hypothesis that distinct phenotypes of the PS19 mice result from cell-type specific changes at the molecular level, primarily changes in chromatin accessibility and, thus, changes in gene expression.
Methods: We used cortices and hippocampi from PS19 and WT mice at nine months and performed multiome (snRNA seq + snATAC seq) single-nuclei sequencing. Sequencing data were aligned using mouse reference genome (mm10) and 10X cell ranger pipeline; the integration of gene expression and chromatin accessibility was done using Seurat and Signac bioinformatics R tools.
Results: We identified nine major cell type clusters and sub-clusters for excitatory and inhibitory neurons determined by the expression level of known marker genes. snATAC-seq analysis revealed an abundance of distal intergenic peaks followed by those in intronic regions. DAVID and REVIGO were used to summarize Gene Ontology terms. They provided insights into their unique functional characteristics with implications for TAU-related neurodegeneration in a mouse model expressing dysfunctional protein tau. Cell Ranger ARC pipeline was used to produce Feature linkage to identify cell type- and disease-specific *cis*-regulatory elements (CREs) and their target genes by correlating gene expression with chromatin accessibility across all nuclei in the dataset within 1kb upstream and 100 bp downstream from the transcription start site. The results revealed a positive correlation, suggesting that higher accessibility is associated with increased gene expression in most cell types in PS19 mice. We performed transcription factor footprinting analyses to understand the differences and differential gene expression further, and the differences revealed complex cell-type-specific interconnected transcriptional activities
Conclusions: Our data provide comprehensive insights into differential gene expression and chromatin accessibility across various cell types in the PS19 mouse model

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SHIFT 02-272

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
4-5 April 2025

MIRNA PROFILE IN BRAIN EXTRACELLULAR VESICLES: MIR-484 AND MIR-193B-3P ARE DOWN-REGULATED IN ALZHEIMER'S DISEASE PATIENTS

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Aims: Extracellular vesicles (EVs) have a role in the delivery of proteins, lipids and nucleic acids, including microRNA (miRNA), and contribute to cell communication. In neurodegenerative diseases, they are supposed to be involved in the transport of misfolded proteins, contributing to the propagation of the disease. The aim of our study is to get insights into the role of EVs and identify dysregulated miRNA involved in the pathogenesis of dementias.
Methods: EVs were purified from brain samples obtained from patients with Alzheimer's disease (AD, n=10), frontotemporal dementia (FTD, n=10) and dementia with Lewy bodies (DLB, n=10), and from non-demented subjects (n=10). The expression of 754 miRNAs was quantified into the EVs using TaqMan™ Array Human MicroRNA A+B Cards (Thermo Fisher). The expression of 86 miRNA target-genes was studied in brain lysates by custom-designed microfluidic TaqMan Array Card (Thermo Fisher). The ΔΔCq method was used for miRNA and mRNA expression analyses. To identify potential target-genes of differentially expressed miRNAs, TargetScan, miRTarBase, and Tarbase repositories were consulted. ClueGO was employed to elucidate enriched KEGG/REACTOME pathways/biological processes.
Results: The miRNA expression analysis showed that miR-484 and miR-193b-3p are significantly down-regulated in AD compared to controls. The expression analysis of miRNA target-genes showed an up-regulation of genes involved in WNT pathway, zinc and calcium transport, and APP processing.
Conclusions: To our knowledge, this is the first time that the dysregulation of miR-484 and miR-193b-3p is

reported in brain EVs from AD patients. These miRNAs regulate the expression of genes playing key roles in AD pathogenesis. The analysis of the miRNA target-genes suggests that miR-484 and miR-193b-3p may contribute to AD pathogenesis by affecting WNT pathway, zinc and calcium transport, and APP processing.

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SHIFT 02-273

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS
4-5 April 2025

LOSS OF MMP9 LEADS TO ALTERED INFLAMMATION IN A MOUSE MODEL OF CEREBRAL SMALL VESSEL DISEASE

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Aims: Vascular contributions to cognitive impairment and dementia (VCID) are a leading cause of dementia. Hyperhomocysteinemia (HHcy)-induced cerebral small vessel disease (cSVD) results in astrocytic end-foot degeneration as well as increases in matrix metalloproteinases (MMPs), which remodel the basement membrane, promoting growth factor activation and inflammation. This study investigates the role of MMP9 in cSVD using MMP9$^{-/-}$ mice on a HHcy diet.
Methods: Six-month-old C57Bl6/J mice and MMP9$^{-/-}$ mice were placed on a diet deficient in B vitamins and enriched in methionine or a control diet with normal levels of B vitamins and methionine for 12 weeks. The left hemibrain was fixed in PFA while the right brain was dissected for biochemistry. RNA was extracted from the frontal cortex and analyzed using NanoString's Mouse Neuroinflammation panel. Microhemorrhage assessment via Prussian blue staining as well as Dp71, AQP4, and GFAP detected by immunohistochemistry were performed on the left hemisphere.
Results: Gene expression data from MMP9$^{-/-}$ mice on a control diet showed significant decreases in inflammation-associated genes (Cd14, Slamf8, Prkcq, Lag3) and lower expression of the microglia marker P2ry12 compared to wild-type mice. In response to a HHcy diet, wild-type mice increased expression of Cpa3, Reln, and the glial transcription factor EOMES, while MMP9$^{-/-}$ mice increased expression of PECAM1, Hira, Myd88, and Pink1. MMP9$^{-/-}$ mice trended toward fewer microbleeds, but this was not statistically significant.
Conclusions: Our findings suggest that MMP9 plays a key role in the inflammatory response associated with HHcy-induced cSVD. The absence of MMP9 led to reduced expression of several inflammation-related genes, though differences in gene expression profiles between wild-type and MMP9$^{-/-}$ mice highlight distinct molecular pathways. Further studies are needed to fully understand MMP9's role in cSVD progression.

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SHIFT 02-274

Poster on Board - Shift 02
β-AMYLOID DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / VASCULATURE, MICROBLEEDS, HYPERTENSION, ANGIOGENESIS
4-5 April 2025

APOE4 MICE SHOW REDUCED GLYMPHATIC CLEARANCE AND IMPAIRED NEUROVASCULAR COUPLING

Cheng-Yi Yang, Mitchell Murdock, Md Rezaul Islam, Katerina Gusarova, Nicolas Lavoie, Martin Kahn, Mingus Zoller, Jung Park, Li-Huei Tsai
Massachusetts Institute of Technology, The Picower Institute For Learning And Memory, Cambridge, United States of America

Aims: To investigate the impact of the Alzheimer's-disease associated APOE4 allele on glymphatic clearance and its response to multisensory stimulation.
Methods: We used 6-months old mice expressing humanized ApoE with either the control APOE3 or the Alzheimer's-associated APOE4 allele. To assess glymphatic clearance, we measured both CSF influx from the arterial perivascular spaces into the brain parenchyma and arterial vasomotion with *in vivo* 2-photon imaging through a cranial window positioned over the frontal cortex. CSF influx and vasomotion were determined in mice under Ketamine-Xylazine (KX) anesthesia and also in awake mice before and during audiovisual stimulation with a light flickering and a sound clicking at 40 Hz. After 2-photon imaging, mice were sacrificed and aquaporin-4 (AQP4) channel polarization to astrocytic endfeet determined through immunofluorescence staining.
Results: During KX anesthesia, APOE4 mice showed decreased CSF influx into the brain parenchyma compared to APOE3 mice, as well as less arteriolar vasomotion at ultraslow frequencies below 0.1 Hz and reduced AQP4 channel polarization to astrocytic endfeet positioned on arterioles. Multisensory stimulation at 40 Hz robustly increased CSF influx and ultraslow vasomotion in awake APOE3 mice but had only mild effects on those processes in awake APOE4 mice.
Conclusions: The APOE4 allele has previously been implicated in altered vascular integrity and vasomotion during Alzheimer's disease. Our results show that glymphatic function in APOE4 mice is reduced even at a young age, before Alzheimer's-related symptoms become apparent. In addition, glymphatic function in APOE4 mice is poorly responsive to multisensory stimulation, suggesting an impairment in neurovascular coupling.

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SHIFT 02-275

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / AGGREGATION INHIBITORS
4-5 April 2025

THE SMALL MOLECULE GAL-201 UNDER DEVELOPMENT FOR AD-TREATMENT: MODULATION OF AMYLOID-BETA AGGREGATION DIRECTLY INFLUENCES SYNAPTIC PLASTICITY BUT ALSO AFFECTS NEUROINFLAMMATION

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Aims: As Aβ-oligomers represent the major toxic species leading to neurodegeneration in AD, an inhibition of the Aβ-aggregation process at source might be promising. GAL-201, a small molecule currently under development as an oral therapy for AD binds to misfolded, aggregation-prone Aβ monomers with high selectivity and affinity thereby preventing the formation of toxic oligomers. Here, we further investigate its mode of action.
Methods: By using Fluorescence Activated Cell Sorting we examine the potential impact of GAL-201 on neuroinflammation. In addition, we visualize plaques with a methoxy staining and test the efficacy of GAL-201 on different Aβ-isoforms using long-term potentiation.
Results: We show that GAL-201 prevents an $A\beta_{1-42}$ induced increase of proinflammatory microglia and reactive astrocytes. Furthermore, we demonstrate that the effect of GAL-201 is irrespective of Aβ cleavages and posttranslational modifications, present in $A\beta_{1-40,}$ 3NTyr (10)-Aβ and AβpE3. In addition, we observe changes in plaque morphology, suggesting that the mode of action is more consistent with modulation of Aβ aggregation, rather than its complete inhibition.
Conclusions: These new data show that the modulation of the Aβ-aggregation process at source by GAL-201 does not only impact on synaptic plasticity and behavior, but also on Aβ-induced neuroinflammation, which is an important component of the Aβ-cascade leading to neurodegeneration. As the binding motif of GAL-201 lies within the KLVFF-region, different Aβ isoforms can be targeted. Therefore, GAL-201 represents a promising drug candidate with a superior mode of action against Aβ-derived pathophysiology.

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SHIFT 02-276

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / AMYLOID CLEARANCE
4-5 April 2025

AI-DRIVEN OPTIMIZATION OF ANTI-AMYLOID ANTIBODY TO MINIMIZE NON-SPECIFIC PLASMA BINDING

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Aims: Recent anti-amyloid therapies like lecanemab show promise for Alzheimer's treatment but are limited by reduced half-life due to plasma protein binding, particularly with fibrinogen. To address this, we developed optimized anti-amyloid antibodies that reduce plasma binding by at least 60% while maintaining activity. Using AI-driven maturation, we engineered antibodies with substantially reduced plasma interactions compared to lecanemab. We aim to confirm the 60% reduction in binding and compare pharmacokinetics in non-human primates to determine if lower plasma binding improves half-life. This study seeks to enhance anti-amyloid treatment profiles with extended half-life and bioavailability.
Methods: We utilized an AI-based machine learning approach to generate 20,000 antibody variants from our proprietary sequences. Through in silico affinity maturation, we narrowed these to 200 candidates, with the top 30 ranked antibodies selected for expression and testing in the lab. Experimental methods included ELISA and surface plasmon resonance (SPR) for on-target binding (Aβ40, Aβ42, PyroE3), as well as SPR assessment for off-target binding in human plasma and serum samples, using lecanemab biosimilar as a benchmark control in all experiments. Additional tests included antibody-dependent phagocytosis of amyloid aggregates, plasma stability assays, and a comprehensive pharmacokinetics and pharmacodynamics (PK/PD) profile using a single 15 mg/kg dose in non-human primates.
Results: Among the 30 antibody sequences tested, we identified three clones with affinity to monomeric and oligomeric Aβ comparable to lecanemab. Of these, two clones demonstrated over 60% reduction in plasma protein binding in head-to-head comparisons with lecanemab. Non-human primate data are currently under analysis.
Conclusions: AI-driven antibody maturation yielded candidates with comparable Aβ affinity to lecanemab and significantly reduced plasma binding, indicating potential for improved pharmacokinetics in Alzheimer's therapy. Further non-human primate data will clarify in vivo efficacy.

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SHIFT 02-277

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / AMYLOID CLEARANCE
4-5 April 2025

IDENTIFICATION OF CSF PROTEINS THAT CORRELATE WITH COGNITIVE OUTCOMES IN PARTICIPANTS OF PHASE 2 STUDY SHINE EVALUATING EFFECTS OF CT1812 IN PATIENTS WITH ALZHEIMER'S DISEASE

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Aims: In Alzheimer's disease (AD) participants of the SHINE clinical trial (NCT03507790), treatment with sigma-2 receptor (S2R) modulator CT1812 resulted in slowed cognitive decline compared to placebo (ADAS-Cog11; 39% slowing in mITT population, 95% slowing in pre-specified p-Tau217 subgroup). To understand molecular changes underlying this favorable effect, an exploratory unbiased proteomic CSF biomarker analysis was performed.
Methods: SHINE (COG0201) was a Phase 2 randomized, double-blind, placebo-controlled study. Participants (N=152) received a daily oral dose of either CT1812 (100 or 300 mg) or placebo for 6-months. A CSF proteomic sub-study of 45 participants was performed using tandem-mass tag mass spectrometry (TMT-MS) at baseline and end-of-study. For analyses, CSF from treatment compliant participants (N=43) were used. Change from baseline (CFB) was calculated, and Pearson correlation analysis was performed with CFB levels of proteins to CFB in ADAS-Cog11 scores. STRING pathway analysis was performed on significantly correlated proteins ($p \leq 0.05$ or $p \leq 0.01$).
Results: Sixty-five proteins correlated with ADAS-Cog11 CFB ($p \leq 0.05$, $r \geq |0.5|$). These proteins showed enrichment for synapse-related Biological Process GO terms, such as "Synapse organization" and "Learning or memory" (FDR≤0.05). AD-related proteins were among the most strongly correlated proteins ($p \leq 0.01$, $r \geq |0.5|$). Proteins involved in amyloid biology were also correlated ($p \leq 0.01$) with ADAS-Cog11 CFB, including APP (r= -0.47) and APOE (r= -0.41), and proteins comprising the S2R complex, PGRMC1 (r= -0.44) and prion protein (PRNP, r= -0.52).
Conclusions: CT1812 PD biomarkers that correlated with favorable ADAS-Cog11 change were identified. Correlation analysis results were consistent with the impact of CT1812 on synaptic protection and mechanisms in amyloid biology. These exploratory biomarker analyses, together with CT1812-associated trends in slowing cognitive decline, particularly in a pre-specified p-Tau217 subgroup, support the clinical development of CT1812 for AD.

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SHIFT 02-278

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / IMMUNOTHERAPY
4-5 April 2025

INTERIM RESULTS FROM THE PHASE I IBC-01-01 STUDY: THE FIRST IMMUNE CHECKPOINT INHIBITOR THERAPY IN PATIENTS WITH EARLY ALZHEIMER'S DISEASE

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Aims: Growing evidence of the role of immune cells in Alzheimer's disease (AD) pathology has paved the way for novel therapeutic approaches. IBC-01-01 is a Phase I clinical study investigating the safety, tolerability, and preliminary efficacy of IBC-Ab001, a novel immunomodulatory agent designed to harness peripheral immunity by targeting the inhibitory immune checkpoint PD-L1 in patients with early AD.
Methods: This randomized, placebo-controlled, dose-escalation study aims to enroll 40 patients aged 50–80 with early AD, regardless of ApoE genotype status. Participants receive a single intravenous dose of IBC-Ab001, with escalating doses across five cohorts. The study plans for participants to receive up to four doses, administered every 12 weeks. Primary and secondary endpoints are safety, tolerability, and pharmacokinetics of IBC-Ab001. Exploratory endpoints include changes in biomarkers of neuroinflammation and neurodegeneration in cerebrospinal fluid (CSF) and blood, as well as changes in cognitive function assessed by the Cognitive Functional Composite (CFC).
Results: Interim results following a single administration of IBC-Ab001 or placebo and three months of observation will be reported. Preliminary findings from the initial cohorts demonstrate a favourable safety and tolerability profile of IBC-Ab001 in patients with early AD, along with evidence of peripheral target engagement.
Conclusions: IBC-01-01 adopts an innovative approach in AD treatment by targeting an immune checkpoint inhibitor for the first time in dementia therapy. This first-of-its-kind treatment represents a unique approach to targeting AD by leveraging the physiological role of the immune system in brain repair.

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SHIFT 02-279

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / MEDICINAL CHEMISTRY APPROACHES, DRUG REPURPOSING
4-5 April 2025

SYNERGISTIC DRUG INSIGHTS: LEVERAGING KNOWLEDGE GRAPHS IN ALZHEIMER DRUG REPURPOSING

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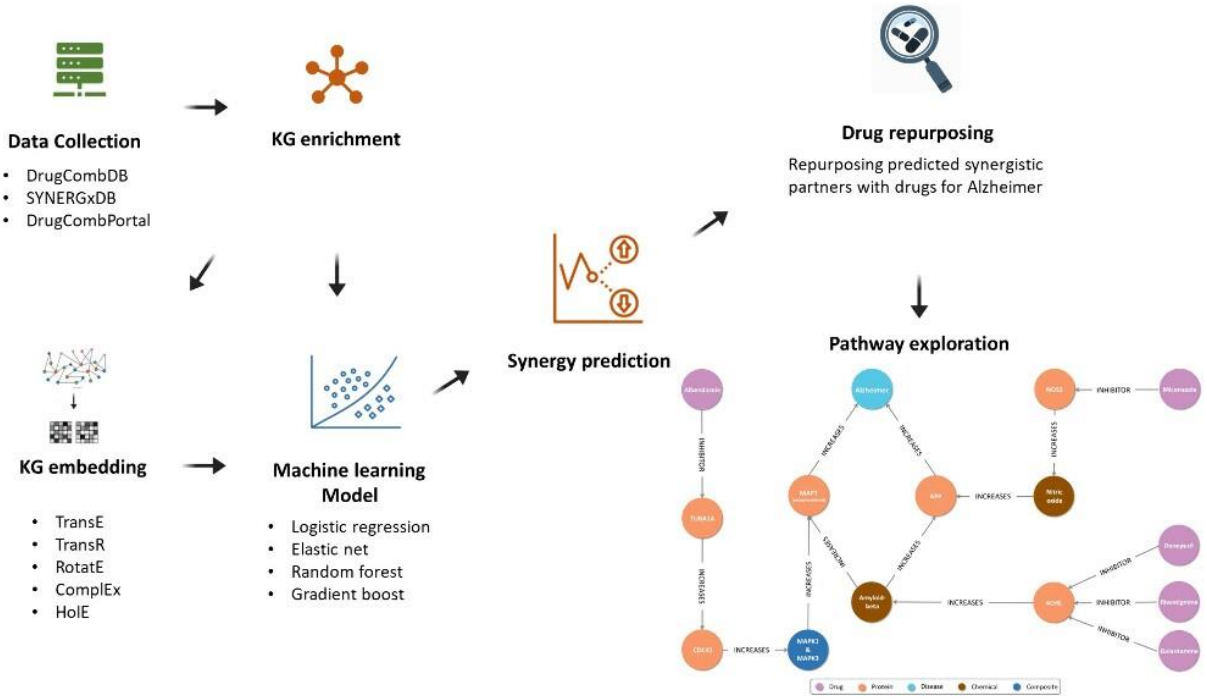
Aims: Most drug repurposing investigations rely on the physicochemical similarities among drug entities and their binding to common targets. However, the availability of extensive biological databases has catalyzed the development of innovative computational methodologies. These approaches depend on the intricate networks connecting various proteins or genes related to the disease within a knowledge graph (KG), thereby facilitating knowledge reasoning. Nevertheless, existing KGs are built solely on semantic relationships among drugs, diseases, and targets. To expand this perspective, we developed another approach that leverages a KG enriched with drug combination effects, to repurpose drug candidates for Alzheimer's disease (AD).
Methods: Drug combination effect was extracted from databases, e.g., SYNERGxDB, transferred into subject-predicate-object triples, and used to enrich a KG (The Human Brain Pharmacome). After extraction of vector embeddings of drug pairs from enriched KG, they were classified using machine learning models into synergism, or antagonism with focus on synergistic drug partners for commonly prescribed medications for AD. The exploration of pathways connecting these partner agents to relevant target proteins or genes forms the basis for proposing them as monotherapies for



AD.

Results: Our drug repurposing methodology has identified many candidates for AD, such as miconazole and albendazole, which had a clear inhibitory pathway to AD. The literature review of the identified candidates confirmed the activity of these drugs against AD in animal and cell culture models. On the other hand, some candidates exhibit insufficient pathway clarity or lack supporting literature for their application.

Conclusions: We provide researchers with a powerful resource for repurposing clinically approved drugs for AD. Utilizing more specialized knowledge graphs and diverse drug combination datasets will aid in repurposing more drugs for the better management of AD.

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SHIFT 02-282

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEUROPROTECTIVE & MITOCHONDRIAL COMPOUNDS
4-5 April 2025

FINAL DATA FROM A PHASE 1 SINGLE AND MULTIPLE-ASCENDING-DOSE TRIAL OF 50561, A SMALL MOLECULE INHIBITING RAC1 ACTIVITY FOR TREATMENT OF ALZHEIMER'S DISEASE

Mengnan Wu, Weiwei Ma
Beijing Joekai Biotechnology LLC, Rm401, Synnex, Beijing, China

Aims: 50561 is a novel selective inhibitor of Rac1, a synaptic plasticity protein dysregulated in Alzheimer's disease (AD) and might cause accelerated forgetting. 50561 had an IC_{50} of 87nM in cells and reduced rac1 activity in hippocampus of AD models. It also improved memory deficits after dosing 10 mg/kg daily for 7 consecutive days. Our study aims to assess the safety, tolerability, and pharmacokinetics (PK) of oral 50561 in Chinese healthy volunteers.
Methods: Our phase I study included two randomized, double-blind, placebo-controlled trials. The first was a single ascending dose (SAD) study with doses from 8 mg to 384 mg. The 8 mg cohort included 4 subjects, with 2 receiving 50561 and 2 receiving placebo. Subsequent cohorts included 8 subjects each, with a 3:1 randomization ratio of 50561 to placebo. The second was a multiple ascending dose (MAD) study with 64 mg, 128 mg, and 256 mg administered once daily (QD) for 7 days. Each cohort included 8 subjects, with the same 3:1 randomization. An independent Safety Review Committee (SRC) reviewed safety, tolerability, and PK before dose escalation.
Results: In the SAD study, 52 subjects were enrolled and received the investigational drug, with 38 receiving 50561. In the MAD study, 24 subjects were enrolled, with 18 receiving 50561. No grade 3 or higher adverse events (AEs) or serious adverse events (SAEs) were reported in neither study. No AEs led to early withdrawal nor death. The incidence and types of AEs showed no significant dose dependency. The in vivo exposure levels of 50561 demonstrated a generally proportional increase with escalating doses.
Conclusions: 50561 tablets showed good safety and tolerability in phase I clinical studies.

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SHIFT 02-283

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
4-5 April 2025

MACHINE LEARNING MODEL ENABLES ACCELERATED ENROLLMENT TIMELINES IN PARKINSON'S DISEASE CLINICAL TRIALS

Carolyn Murray, Run Zhuang, Coco Kusiak, Jonathan Walsh
Unlearn AI, San Francisco, United States of America

Aims: 90% of clinical trials in Parkinson's disease (PD) fail to enroll patients within the target timeline. Here, we demonstrate how the use of a machine learning model combined with advanced statistical methods accelerates enrollment timelines. This method reduces the number of patients required for the control group and increases the chance that patients will be randomized to the active arm.
Methods: Using historical data from previously completed PD clinical trials and observational studies, we trained a machine learning model using a novel architecture. This model generates digital twins of patients which are longitudinal predictions of clinical outcomes, labs and vitals for each patient. We used 5-fold validation over an integrated dataset from the National Institute of Neurological Disorders and Stroke (NINDS), Parkinson's Disease Biomarkers Program (PDBP), and Parkinson's Progression Markers Initiative (PPMI) to train the model and evaluate performance. The dataset contains over 2000 patients with subpopulations off dopamine agonists (N=875), on dopamine agonists (N=672) and with early PD (N=808). A prognostic covariate was derived from each digital twin and combined with Bayesian methods to estimate sample size reduction when used for two endpoints: MDS-UPDRS Parts I-III total (Subscore) and Part III (Motor Score).
Results: Reduction in sample size of the control group was by 35% for MDS-UPDRS Subscore and 38% for MDS-UPDRS Motor Score. Reduction in the overall sample size was 21% for MDS-UPDRS Subscore and 24% for MDS-UPDRS Motor Score. This approach increases the probability of being randomized to the active arm by up to 45%.
Conclusions: Utilizing digital twins of patients with Bayesian statistical methodology can accelerate enrollment timelines in early-stage clinical trials by reducing the number of patients and increasing active arm assignment.

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Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
4-5 April 2025

ALZHEIMER'S DISEASE (AD) AND INFLAMMATION: BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS IN A PHASE-2 STUDY OF XPRO1595 IN EARLY AD

Parris Pope[1], Therese Blomberg[1], Kim Staats[1], Genevieve Wills[2], Melanie Buitendyk[2], Sarah Barnum[3], Judith Jaeger[3], R. J. Tesi[1], C. J. Barnum[1]
[1]INmune Bio, Inc,, Boca Raton, United States of America, [2]Allucent, Cary, United States of America, [3]Cognition Metrics LLC, Stamford, United States of America

Aims: XPro1595 (XPro™) is a selective, brain penetrant, dominant-negative neutralizer of soluble tumor necrosis factor (solTNF). XPro™ was rationally designed to selectively inhibit neurotoxic neuroinflammation while preserving cellular processes involved in natural maintenance and repair of neuronal tissue. The MINDful trial aims to evaluate the cognitive and clinical benefits of XPro™ in patients with Early Alzheimer's Disease (AD) and systemic inflammation (ADi).
Methods: MINDFuL (NCT05318976, EUCT2023-505396-71-00) is a phase 2, randomized, double blind, placebo-controlled, 24-week clinical trial. The primary endpoint is change from baseline (CFB) on the Early and Mild Alzheimer's Cognitive Composite (EMACC). Other outcomes on cognitive, functional and behavioral measures, and changes in blood biomarkers of AD pathology and AD-related neuroinflammation, are also included.
Results: Well characterized patients with mild cognitive impairment (MCI) or mild AD (NIA-AA Clinical Stage 3-4, respectively), and biomarker evidence of both amyloid pathology (Aβ) and systemic inflammation, were enrolled at sites in Australia, Canada, the UK and EU. Full enrollment (N=208) was achieved in November 2024. Blinded baseline demographics, disease characteristics and biomarker status of enrolled patients will be presented. Psychometric properties of the EMACC will also be explored.
Conclusions: Innovative study designs are required for determination of treatment effects in early-stage AD. These include patient enrichment strategies and the use of treatment-sensitive endpoints. The MINDful trial is enriched for patients with biomarker confirmed neuropathological AD and systemic inflammation deemed likely to benefit from treatment with XPro™. The EMACC is an objective measure with the sensitivity necessary for detection of cognitive changes in short-term clinical trials in Early AD. The study is ongoing, with top-line results expected in Q3 2025.

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SHIFT 02-285

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β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NEW CLINICAL TRIAL DESIGNS, SIMULATION OF PROGRESS-DIGITAL TWINS
4-5 April 2025

DESIGN OF 50561-II-01: A PHASE 2 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED POC STUDY TO EVALUATE THE EFFICACY AND SAFETY OF 50561 TABLETS IN ALZHEIMER'S DISEASE PATIENTS

Mengnan Wu, Ruichen Ni, Xuena Zhao, Tiantian Wang, Weiwei Ma
Beijing Joekai Biotechnology LLC, Rm401, Synnex, Beijing, China

Aims: We aim to investigate the efficacy and safety of 50561 tablets, a first-in-class small molecule for the treatment of mild to moderate Alzheimer's Disease (AD). The primary objective is to assess the preliminary efficacy of 50561 over 24 weeks, while the secondary objectives focus on safety, tolerability, and pharmacokinetics (PK).
Methods: This randomized, double-blind, placebo-controlled study will enroll 60 participants. The study will enroll subjects with mild to moderate AD dementia (age 50-85, MMSE 11-25, CDR 1-2), in good general health, diagnosed with AD according to the 2011 NIA-AA criteria. Subjects will be randomly assigned to one of three groups—low-dose 50561, high-dose 50561, or placebo—in a 1:1:1 ratio. The study consists of screening (up to 2 weeks), lead-in (4-5 weeks), baseline (D-3 to D0), double-blind treatment (24 weeks), and safety follow-up (2 weeks). Primary and secondary efficacy endpoints include ADAS-cog/13, CDR-SB, MMSE, ADCS-ADL, and NPI scores. Safety and tolerability will be assessed with clinical and laboratory tests. PK of 50561 and its metabolite in plasma and CSF will be measured. Pharmacodynamic (PD) profile including inflammatory markers, Aβ, Tau, and Nfl in blood and CSF will also be evaluated, if feasible. An Independent Data Monitoring Committee (IDMC) will oversee the trial to ensure safety. ClinicalTrials.gov Identifier: NCT05811442
Results: With measurable efficacy, safety, PK, and PD results, the study is well-positioned to provide proof of concept (PoC) for 50561's clinical impact, safety and drug exposure.
Conclusions: This trial aims to establish PoC for 50561, offering insights into its dose-response relationship and safety profile, and provide evidence for future development.

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SHIFT 02-287

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
4-5 April 2025

BMI TRAJECTORIES AND DROPOUT IMPACT AMONG EARLY ALZHEIMER'S DISEASE TRIAL PARTICIPANTS: INSIGHTS FROM THE CRITICAL PATH FOR ALZHEIMER'S DISEASE CONSORTIUM

Teresa León Colombo[1], Sharon Cohen[2], Nils Skajaa[1], Alex Mourer[1], Alice Clark[1], Masaru Mimura[3]
[1]Novo Nordisk A/S, Søborg, Denmark, [2]Toronto Memory Program, Toronto, Ontario, Canada, [3]Center for Preventative Medicine, Keio University, Tokyo, Japan

Aims: Understanding the natural weight evolution among patients with early (e) Alzheimer's Disease (AD) may provide insights into the impact of therapies on this population's health and well-being, but evidence is lacking. Leveraging the Critical Path for Alzheimer's Disease (CPAD) repository, we investigated the natural body mass index (BMI) trajectory over time in eAD clinical trial participants and examined the impact of BMI on trial dropout.
Methods: We included participants aged 55–85 years with a documented AD diagnosis (limited data on amyloid status), a Mini-Mental State Examination (MMSE) score of 21–30 and ≥2 BMI measurements. The percentage BMI change over time was computed and depicted with locally weighted smoothing overall and in patient subgroups. Cox regression was used to examine the impact of baseline and time-varying BMI on trial dropout (composite outcome of trial dropout or death).
Results: Data from 1908 participants were included. Of these, 55% were women, median age was 71 years, median BMI was 24 kg/m^2 and 81% had an MMSE score of 21–25. The percentage BMI change increased slightly over 2.5 years from trial baseline, mainly in women, participants with underweight or normal weight, and those concomitantly using anticholinesterases. During the 2.5-year follow-up, 207 (10.8%) participants dropped out and 5 (0.3%) died; 753 (39.5%) had missing information. For those with information, the 1.5-year cumulative incidence of the composite outcome was 19.8% (95% CI 17.3, 22.4). The adjusted cumulative incidence and the adjusted hazard ratio revealed no statistically significant association between BMI (baseline or time-varying) and trial dropout.
Conclusions: In eAD clinical trial participants, BMI increased slightly over time. BMI had no impact on trial dropout in this CPAD repository data analysis.

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SHIFT 02-288

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
4-5 April 2025

MYEXOSOME® AS AN INNOVATIVE SUPPLEMENT FOR THE TREATMENT AND PREVENTION OF MILD COGNITIVE IMPAIRMENT

Mehmet Zülküf Önal[1], Cenan Öztürk[2], Eren Kahyaoğlu[3], Murat Kantarcıoğlu[4], Suat Yılmaz[5]
[1]Atılım University, Faculty of Medicine, Department Of Neurology, Ankara, Turkey, [2]Ankara University, Graduate School of Natural and Applied Sciences, Department Of Biology, Ankara, Turkey, [3]Ondokuz Mayıs University, Graduate School of Education, Department Of Biology, Samsun, Turkey, [4]Güven Çayyolu Surgical Medical Center, Department Of Gastroenterology, Ankara, Turkey, [5]NeuroUp Clinic, Ankara, Turkey

Aims: Mild Cognitive Impairment (MCI) is an early stage of cognitive decline, often considered a precursor to Alzheimer's disease (AD). There is no current treatment for MCI and AD. Edible plant-derived exosome-like nanoparticles (EPDENs) are shown to play a crucial role in intercellular communication. MyExosome® is a dietary supplement composed of highly purified EPDENs from organic coffee, Ginkgo biloba, and Panax ginseng, produced without chemical preservatives. Preliminary studies suggest these plant-derived EPDENs may enhance neurocognitive functions, including memory and attention. This study aims to evaluate the potential effects of MyExosome® on cognitive function in MCI patients.
Methods: A group of patients (N=17) were evaluated retrospectively (Figure 1). All were diagnosed with MCI. None of the selected participants were using any related medications during the study period. Informed consent was obtained from all participants and their caregivers. Over one month, participants received one capsule of MyExosome® daily without altering their routine medication. A comprehensive battery of neuropsychological assessments evaluated cognitive function at baseline and after one month of treatment.

N=17		
Sex, n(%)	Female	13 (76.5)
	Male	4 (23.5)
Age, Mean±SD		77±11
Median (Q1-Q3) (Min-Max)		79 (71-84) (57-97)
Diagnosis, n (%)	Mild Cognitive Impairment	17 (100)

Results: A statistically significant improvement in cognitive function was observed following the use of MyExosome® (Figure 2). This indicates its promise as a dietary supplement for supporting the treatment of MCI and potentially other neurodegenerative

		Test N=17 Mean±SD Median (Q1-Q3) (Min-Max)	Retest N=17 Mean±SD Median (Q1-Q3) (Min-Max)	p
Attention Tests	Mental Control Test	8.29±5.19 11.00 (3.00-13.00) (0.00-14.00)	8.59±5.55 10.00 (4.00-13.00) (0.00-15.00)	0.480*
	Forward Digit Span Test	5.76±1.20 6.00 (5.00-6.00) (3.00-8.00)	6.18±1.01 6.00 (6.00-7.00) (4.00-8.00)	0.138*
	Backward Digit Span	3.65±1.22 4.00 (3.00-5.00) (2.00-5.00)	3.94±1.03 4.00 (3.00-5.00) (2.00-5.00)	0.059*
Memory Tests	Logical Memory Encoding	8.94±5.51 10.00 (4.00-13.00) (0.00-17.00)	11.24±6.48 12.00 (8.00-16.00) (0.00-21.00)	**0.008***
	Logical Memory USB	10.65±7.63 11.00 (5.00-15.00) (0.00-24.00)	13.00±8.05 12.00 (8.00-20.00) (0.00-23.00)	**0.028***
	Visual Memory Encoding	5.88±4.55 5.00 (3.00-8.00) (0.00-14.00)	7.59±5.18 7.00 (4.00-13.00) (0.00-14.00)	**0.005***
	Visual Memory USB	4.35±5.60 1.00 (0.00-8.00) (0.00-14.00)	5.59±5.73 3.00 (0.00-11.00) (0.00-14.00)	**0.007***
Memory Tests VM	Immediate Memory	2.71±1.76 2.00 (2.00-4.00) (0.00-7.00)	4.53±3.24 3.00 (2.00-6.00) (2.00-12.00)	**0.002***
	Total Learning Score	74.00±32.85 63.00 (49.00-101.00) (29.00-134.00)	88.35±34.87 81.00 (58.00-123.00) (42.00-139.00)	**0.004***
	USB Spontaneous Recall	4.53±4.46 3.00 (0.00-9.00) (0.00-14.00)	6.53±4.19 8.00 (3.00-10.00) (1.00-13.00)	**0.004***
	USB Total Recall	12.35±2.71 13.00 (11.00-15.00) (7.00-15.00)	13.65±1.41 14.00 (12.00-15.00) (11.00-15.00)	**0.035***
Visual and Spatial Functions	Line Orientation Test	15.29±8.72 18.00 (10.00-22.00) (0.00-26.00)	17.24±8.90 22.00 (11.00-23.00) (0.00-29.00)	0.068*
	Benton Facial Recognition Test	17.29±7.30 19.00 (17.00-23.00) (0.00-24.00)	17.94±7.68 21.00 (17.00-23.00) (0.00-25.00)	0.325*
	Figure Copying	2.76±1.52 4.00 (2.00-4.00) (0.00-4.00)	2.88±1.45 4.00 (2.00-4.00) (0.00-4.00)	0.603*
	Boston Naming Test	28.24±3.83 30.00 (27.00-31.00) (17.00-31.00)	27.82±3.50 28.00 (26.00-31.00) (20.00-31.00)	0.618*
Stroop Test	Interference Time	66.00±57.00 68.00 (0.00-120.00) (0.00-149.00)	63.88±61.16 55.00 (0.00-94.00) (0.00-195.00)	0.875*
Verbal Fluency Tests	Phonemic Fluency	24.82±16.27 20.00 (12.00-38.00) (6.00-55.00)	27.53±16.79 26.00 (16.00-36.00) (6.00-75.00)	0.176*
	Semantic Fluency	16.18±7.93 16.00 (9.00-23.00) (4.00-30.00)	17.59±7.78 16.00 (12.00-24.00) (7.00-31.00)	0.139*
	Fruit Name Task Switching	4.76±3.65 4.00 (2.00-8.00) (0.00-11.00)	5.00±3.48 5.00 (2.00-7.00) (0.00-12.00)	0.436*

Wilcoxon Signed Rank Test

conditions.

Conclusions: MyExosome® demonstrates potential as a novel supplement for cognitive enhancement in patients with MCI. The observed improvements indicate promising benefits, meriting further investigation. A multicenter, placebo-controlled, prospective trial involving Alzheimer's patients is currently being conducted.

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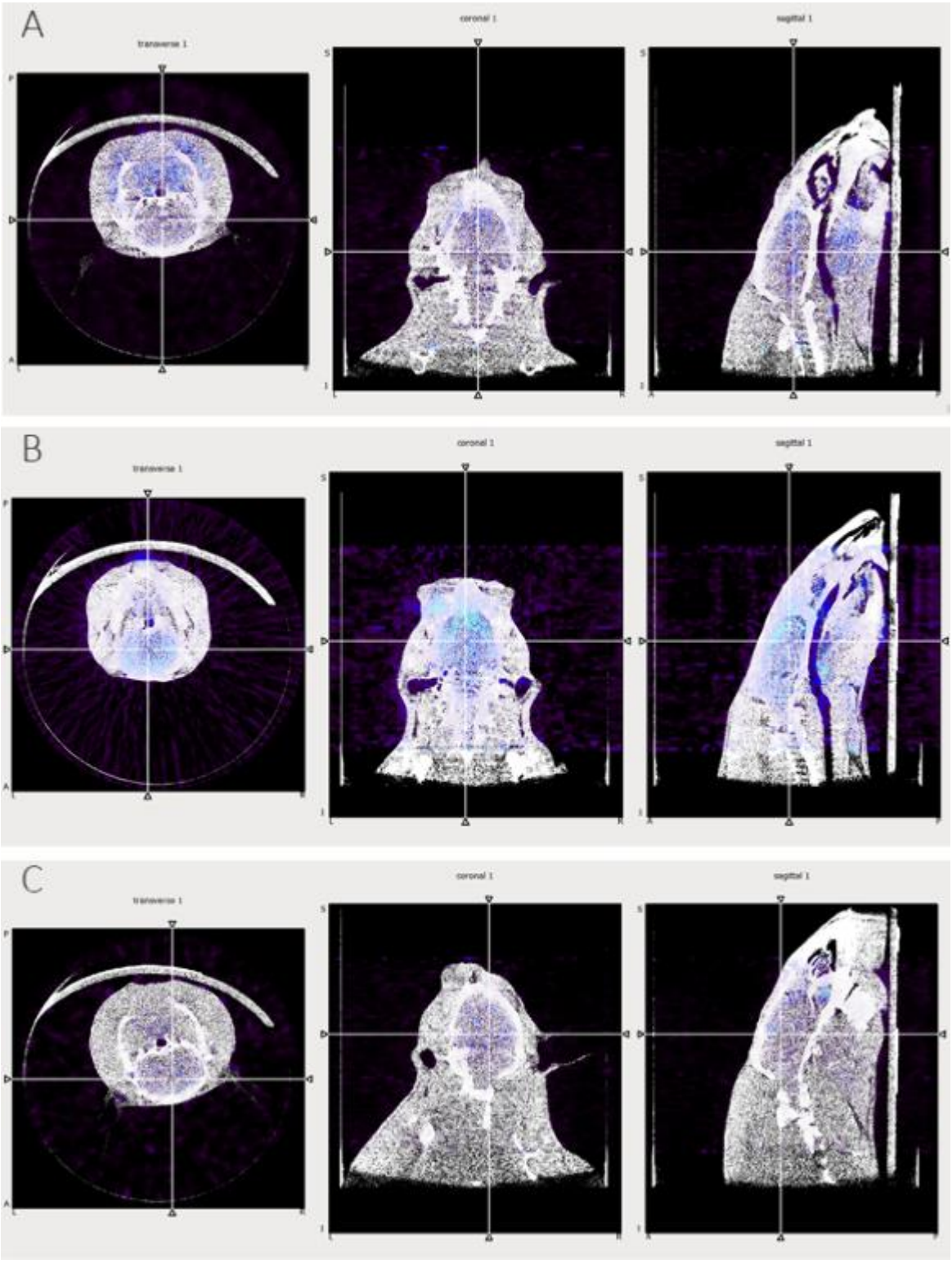
SHIFT 02-289

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
4-5 April 2025

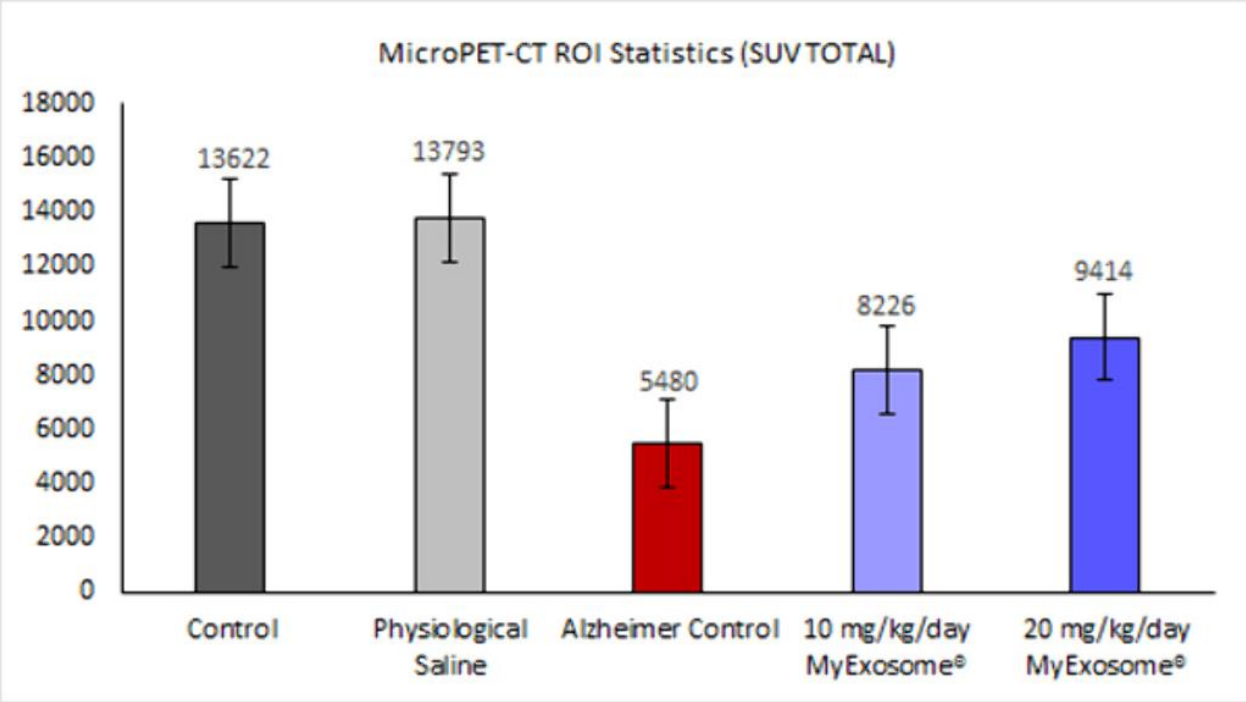
MYEXOSOME® AN INNOVATIVE SUPPLEMENT HAS PREVENTIVE AND THERAPEUTIC EFFECTS IN RATS WITH ALZHEIMER'S DISEASE MODEL

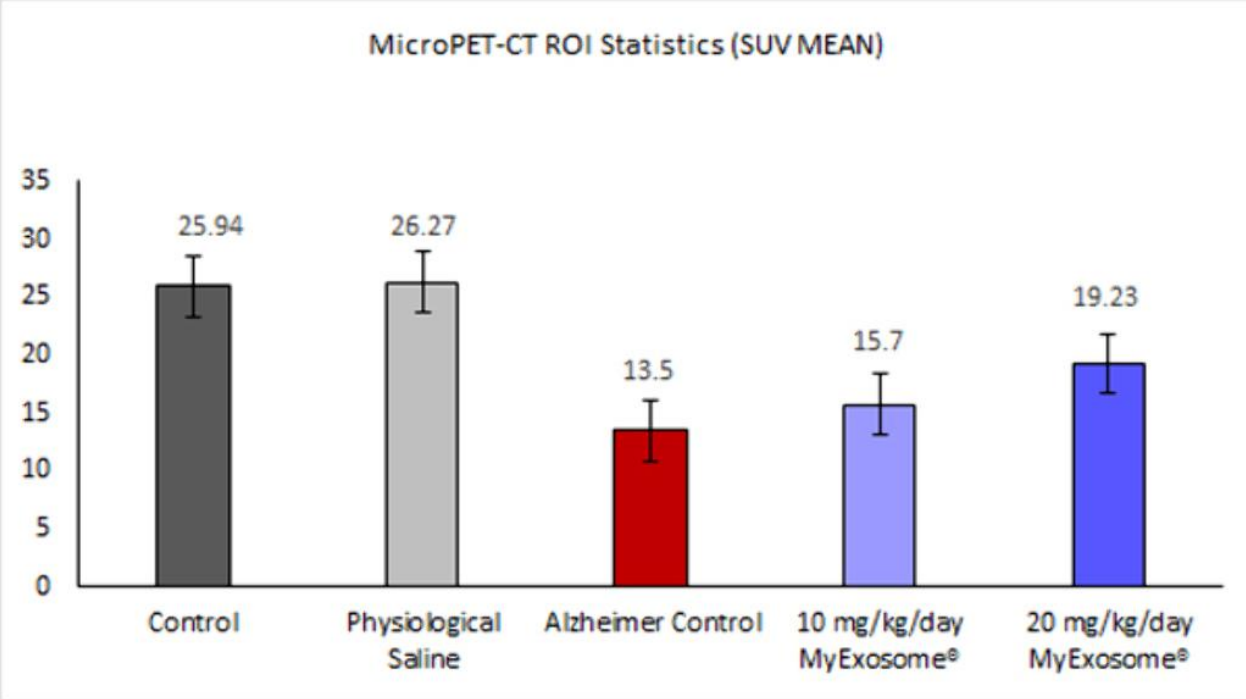
Eren Kahyaoğlu[1], Cenan Öztürk[2], Yusuf Küçükbağrıaçık[3], Cüneyt Göksoy[3], Alper Karaçalıoğlu[4], Gülistan Sarıbaş[5], Sezen Kışlal[6], Cemile Akgül[6], Mehmet Zülküf Önal[7], Murat Kantarcıoğlu[8]
[1]Ondokuz Mayıs University, Graduate School of Education, Department Of Biology, Samsun, Turkey, [2]Ankara University, Graduate School of Natural and Applied Sciences, Department Of Biology, Ankara, Turkey, [3]University of Health Sciences, Gülhane Medical Faculty, Department Of Biophysics, Ankara, Turkey, [4]University of Health Sciences, Gülhane Medical Faculty, Department Of Nuclear Medicine, Ankara, Turkey, [5]University of Health Sciences, Gülhane Medical Faculty, Department Of Histology And Embryology, Ankara, Turkey, [6]Middle East Technical University, Faculty of Arts and Sciences, Department Of Psychology, Ankara, Turkey, [7]Atılım University, Faculty of Medicine, Department Of Neurology, Ankara, Turkey, [8]Güven Çayyolu Surgical Medical Center, Department Of Gastroenterology, Ankara, Turkey

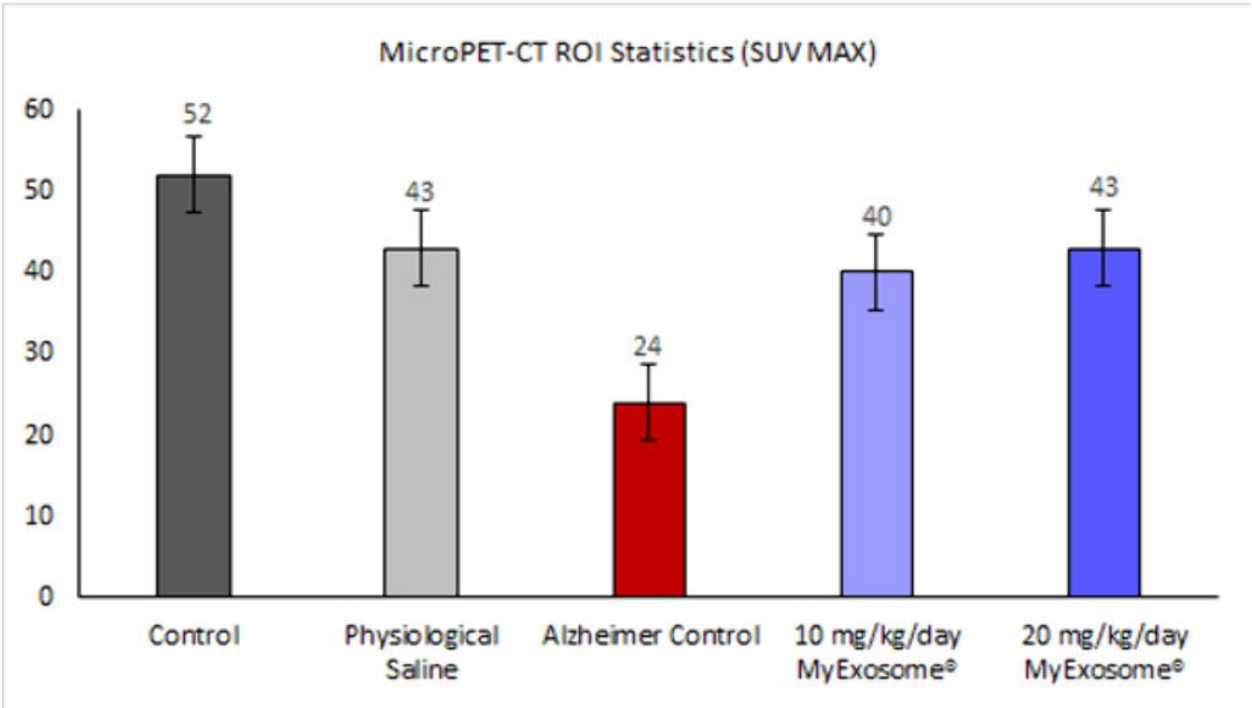
Aims: Alzheimer's disease (AD) is the main cause of dementia. To date, there is no effective treatment. Many studies have shown that edible plant derived exosome like nanoparticles (EPDENs) are responsible for beneficial effects on the human body. MyExosome® is composed of purified EPDENs derived from coffee, ginseng panax, and gingko biloba. In the literature, the beneficial effects of all three plants on brain health are emphasized. In this study, the aim was to evaluate the efficacy of MyExosome® in an Alzheimer's disease animal model using MicroPET-CT imaging.
Methods: The study, approved by the local animal ethics committee, involved 32 rats and was conducted with Kobay Lab. Inc., Gulhane and Ankara Universities, and AYE Exocure Inc. Thirty rats received amyloid beta 1-42 injections; one healthy rat served as the control, and one received saline injection. Treatment groups received MyExosome® 24 hours post-operation: Group 1 (10 mg/kg/daily, n=10) and Group 2 (20 mg/kg/daily, n=10). The Alzheimer's model group (n=10) received no treatment. Fourteen days post-surgery, MicroPET/CT scans were performed, and data were analyzed using IBM SPSS Ver. 25.0, Kruskal Wallis, and Bonferroni tests, with $p<0.05$ considered significant.
Results: Images of sham and control rats showed physiological FDG uptake, aligning with literature values. MyExosome®-treated rats demonstrated significantly higher FDG uptake than the Alzheimer's model group (Figure 1). MicroPET-CT analyses indicated significant differences in SUV total ($KW=30.077$, $p<0.001$) (Figure 2), SUV mean ($KW=28.610$, $p<0.001$) (Figure 3), and SUV max ($KW=24.133$, $p<0.001$) (Figure 4). No significant difference was observed between MyExosome® treatment


A
transverse 1
coronal 1
sagittal 1
B
transverse 1
coronal 1
sagittal 1
C
transverse 1
coronal 1
sagittal 1

groups.


MicroPET-CT ROI Statistics (SUV TOTAL)
18000
16000
14000
12000
10000
8000
6000
4000
2000
0
13622
13793
5480
8226
9414
Control
Physiological Saline
Alzheimer Control
10 mg/kg/day MyExosome®
20 mg/kg/day MyExosome®


MicroPET-CT ROI Statistics (SUV MEAN)
35
30
25
20
15
10
5
0
25.94
26.27
13.5
15.7
19.23
Control
Physiological Saline
Alzheimer Control
10 mg/kg/day MyExosome®
20 mg/kg/day MyExosome®



Conclusions: In an experimental Alzheimer's model, PET-CT scans suggest MyExosome® protects brain tissue activity against amyloid beta exposure, indicating potential as a therapeutic candidate for early-stage Alzheimer's disease.

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SHIFT 02-290

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
4-5 April 2025

MODULATING DEFAULT MODE NETWORK CONNECTIVITY WITH RTMS IN PERSONS AT HIGHER RISK OF ALZHEIMER'S DISEASE

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Aims: A large body of literature shows that the default mode network (DMN) is disrupted in Alzheimer's disease (AD) since preclinical stages. Repetitive transcranial magnetic stimulation (rTMS) can modulate neural signals, however whether it can modulate DMN connectivity in individuals at-risk of AD is unclear. We conducted a randomized, double-blind, sham-controlled trial of real rTMS targeting the DMN in Apolipoprotein ε4 carriers (APOEε4+).
Methods: Thirty-eight APOEε4+ and 36 non-carriers (APOEε4-) underwent real or sham rTMS targeting the DMN over four consecutive days. Resting-state fMRI (rs-fMRI) and cognitive measures were collected before and after the intervention. Rs-fMRI data were processed with group-based ICA to extract the DMN. A template-matching procedure identified 2 dorsal and 1 ventral DMN components. The effect of time, intervention, and time x intervention were tested using voxel-wise t-tests adjusted for mean baseline connectivity and framewise displacement (imaging outcomes), and generalized linear mixed models adjusted for cognitive reserve (cognitive outcomes).
Results: At baseline, APOEε4+ showed lower MMSE score than APOEε4- (29±1 vs. 30±1; p=.043), while the groups were comparable on other cognitive tests. In the whole sample, ventral DMN connectivity increased after real (p for time<.050; right angular gyrus) but not after sham (p>.050) rTMS, with no significant time x intervention effect (p>.050). When the analysis was stratified for genotype, the time effect was confirmed in APOEε4+ (p<.050) but not in APOEε4- (p>.050). In the whole sample, a time x intervention effect was

observed for delayed memory (p=.002, real>sham), confirmed only for APOEε4+ subgroup (p=.005). **Conclusions:** These results support the feasibility of rTMS-based DMN modulation in cognitively unimpaired older adults at increased risk of AD. Future studies in larger samples are needed to assess the potential of non-invasive stimulation for AD prevention.

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SHIFT 02-291

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / NON-PHARMACOLOGICAL INTERVENTIONS
4-5 April 2025

AN INTEGRATED ACTION PLAN FOR DEMENTIA PREVENTION IN GENEVA: THE COGNITIVE PILLAR OF THE SWISS BRAIN HEALTH PLAN

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Aims: Dementia prevention represents a critical public health challenge, impacting individuals' quality of life, family well-being, and societal costs.The World Health Organization has designated dementia prevention as a public health priority. Individuals with no cognitive impairment are seeking consultations at memory clinics, driven by concerns about dementia.However, standardized procedures to adequately address their needs simply do not exist.At the Geneva Memory Center, we have developed an integrated action plan to promote cognitive health and prevent cognitive decline.This plan consists of community education, involvement of general practitioners, and the delivery of targeted initiatives.
Methods: Our pipeline consists of 3 components:(1)memory workshop (so called "*Atelier mémoire*"-AM), (2)*"Cours Lémanique sur les Démences et les Troubles Cognitifs"* (CL);(3)Brain Health Services for the prevention of dementia (dBHS).
Results: The AM includes structured activities aimed at educating laypersons about brain function during aging, identifying risk factors, and offering actionable recommendations to prevent dementia. By enhancing cognitive functions and fostering social engagement, the program promotes brain health. The significant engagement and positive feedback from the community highlight its potential as a scalable model for dementia prevention. The CL has been actively involving general practitioners as key contributors in discussions on best practices for dementia prevention in the French-speaking Switzerland. The dBHS offers a comprehensive approach to dementia prevention, providing risk assessments, communication, and personalized risk-reduction strategies. Utilizing advanced diagnostic tools, it identifies individuals at-risk of dementia and designs personalized intervention plans, integrating both lifestyle modifications and biological interventions.
Conclusions: This work aims to document the development and outcomes of these initiatives, emphasizing the importance of comprehensive dementia prevention strategies.We aim to provide valuable insights and practical models that can be implemented in diverse settings, addressing the growing global challenge of dementia prevention.

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SHIFT 02-294

Poster on Board - Shift 02
β-AMYLOID DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS / REGULATORY ASPECTS, OTHER
4-5 April 2025

ADAS-COG IN FOCUS: UNDERSTANDING ADMINISTRATION AND SCORING ERRORS IN ALZHEIMER'S DISEASE CLINICAL RESEARCH

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Aims: The Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) is the most commonly used cognitive efficacy measure in Alzheimer's disease clinical trials. Our research aimed to identfy the most frequent administration and scoring errors on the ADAS-Cog and to determine if an association exists between scoring and administration errors both within and across study visits.
Methods: Data were pooled from 14 global dementia clinical trials where the ADAS-Cog was used as an efficacy outcome. ADAS-Cog recordings and data were reviewed by Central Quality Reviewers who were trained and calibrated by Signant Health. We evaluated the most frequently occurring administration and scoring errors for each item on the ADAS-Cog scale. The association between administration and scoring errors within visits and across visits over time were analyzed using Chi-square test and regression analysis.
Results: The total of 47,238 ADAS-Cog assessments were reviewed. ADAS-Cog administration and/or scoring errors occurred in 9,288 (19.6%) visits. The proportion of administration and scoring errors varied notably across individual items. The items with the largest number of errors were the following: Number Cancellation (23.38%), Constructional Praxis (20.48%), Orientation (12.25%), Word Recognition (11.9%) Naming Objects and Fingers (10.84%). The presence of administration and scoring errors were not statistically significantly associated within visits. There was a mean change in the number of flags per visit of -0.0287, representing a reduction of 8.38% relative to the baseline number of flags per visit.
Conclusions: Our study identified a high prevalence of scoring and administration errors on the ADAS-Cog, which tend to occur independently of one another. The findings support the importance of data quality monitoring, the effectiveness of remediations at reducing errors and the need to focus additional training on items with the largest prevalence of errors.

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SHIFT 02-296

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / AGING
4-5 April 2025

A COMPARATIVE ANALYSIS OF POLYGENIC RISK SCORES FOR PREDICTING ALZHEIMER'S DISEASE AND RELATED DEMENTIAS IN THE UK BIOBANK

Shayan Mostafaei, Daniel Shemer, Jonathan Mak, Ida Karlsson, Sara Hägg
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Aims: This study aims to improve the predictive accuracy of polygenic risk scores (PRS) for Alzheimer's disease and related dementias (ADRD).
Methods: PRS and polygenic hazard scores (PHS) were computed as weighted sums of risk alleles associated with ADRD based on summary statistics from recent genome-wide association studies (GWAS). Three different computational approaches—Bayesian variational autoencoder as a data-driven machine learning (DDML) approach, SBayesR, and the clumping and thresholding (C_T)—were applied to calculate PRS and PHS. The primary outcomes measured were all-cause dementia and time to dementia diagnosis (i.e., time from baseline assessment to dementia diagnosis, death, or end of follow-up on April 1, 2018). We evaluated predictive performance using time-dependent Area Under the Receiver Operating Characteristic curve (AUC) and the C-index, which serves as an overall measure of model fit in survival analysis.
Results: A total of 487,000 participants free of dementia at baseline from the UKB were included (mean age: 56.5 [SD=8.09] years, 45.77% men). The median follow-up time was 9.1 (interquartile range=1.41) years. Among them, 2,379 individuals (0.49%) were diagnosed with all-cause dementia. The predictive accuracy of the PRS models based on the testing set, with and without the APOE region, demonstrated strong performance across all models. The AUC values ranged from 0.71 to 0.83, with DDML_PRS showing the highest accuracy. The HR for DDML_PRS (Q1 vs. Q4 as a ref.) was significantly lower than others (HR: 0.39, 95% CI: 0.07-0.89, C-index: 0.739). The DDML_PRS approach, as the best-performing model, achieved the highest accuracy in predicting ADRD in the 60-70 years age-group at baseline (AUC = 0.847).
Conclusions: The findings suggest that the PRS based on a DDML approach offers superior predictive performance, particularly for individuals in the 60-70 age range at baseline.

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SHIFT 02-297

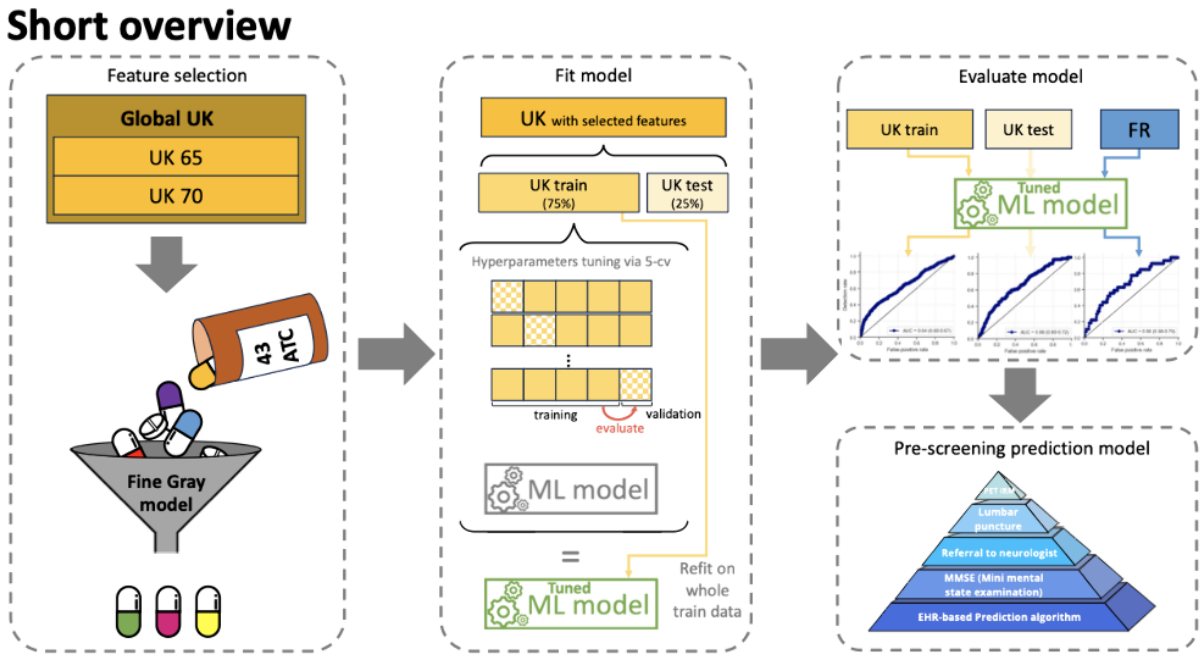
Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / AGING
4-5 April 2025

MACHINE LEARNING PREDICTION ALGORITHMS FOR 2- , 5- AND 10-YEAR RISK OF ALZHEIMER'S, PARKINSON'S AND DEMENTIA USING MEDICAL RECORDS FROM FRANCE AND THE UK

Charlotte Montaud, Karim Zaidi, Octave Guinebretiere, Thomas Nedelec, On Behalf Of The Lemerend Jpnd Consortium
Paris Brain Institute, Icm, Paris, France

Aims: Leveraging machine learning on electronic health records presents a promising approach for the early identification of individuals at risk of developing dementia or neurodegenerative diseases. Age is the primary predictor in current dementia risk algorithms, underscoring the need to develop alternative models with significant discriminatory power at specific ages, such as 65, when it is crucial to identify patients eligible for closer screening and early prevention
Methods: This prospective study of 76,427 adults (age 65, 52.1% women) utilized the THIN database, comprising electronic medical records from general practitioners in France and the UK, to develop and validate a general risk algorithm of Alzheimer's disease, Parkinson's disease, and all-cause dementia, that could be applied in primary care, hence simple and interpretable.
Results: Specific medication categories, such as laxatives , urological drugs , and antidepressant drugs, in addition to sex, BMI, and Charlson Comorbidity Index, were included in the prediction algorithm for the three outcomes. In predicting future dementia at age 65 and when calibrated to achieve a 5% false-positive rate, the algorithm detected 42.8%, 22.5%, and 17.8% of incident cases in the 2-, 5-, and 10-year follow-ups, respectively. The 2-year AUC in an independent validation cohort was 0.78 (0.65-0.90) for Alzheimer's disease, 0.55 (0.38-0.72) for Parkinson's disease, and 0.78 (95% CI 0.70-0.86) for dementia.
Conclusions: The new validated prediction algorithms, which can be derived without laboratory measurements, can identify 65-year-old patients at high near-term risk of Alzheimer's disease and all-cause dementia. Utilizing routinely collected electronic medication records, these algorithms are cost-effective, straightforward to implement, and can be fully automated in primary health care settings. Figure : Overview

of the modeling



strategy

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SHIFT 02-298

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / AGING
4-5 April 2025

THE NATIONAL INSTITUTE ON AGING ALZHEIMER'S DISEASE FAMILY BASED STUDY, AN ENRICHED RESOURCE FOR THE SCIENTIFIC COMMUNITY.

Kelley Faber[1], Abigail Erickson[1], Pamela Del Rosario[2], Amber O'Reilly[3], Joanne Norton[4], Jen Gentsch[5], Olga Valdez[5], Cory Weinfeld[2], Kelly Horner[1], Krystal Encarnacion[2], Victoria Orr[6], Sarah Payne[6], Alexis Navarro[7], Elise Weamer[8], Katy Figueroa[9], Karen Elrayes[10], Madison Potocki[11], Celina Pavon[12], Malia Rumbaugh[1], Amanda Chan[13], Dolly Reyes-Dumeyer[2,13]
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Aims: The National Institute on Aging Late-Onset Alzheimer's Disease Family Based Study (NIA-LOAD FBS) is multi-site, longitudinal study aimed to be a data and bio sample resource for investigators worldwide.
Methods: The focus of the Family Based Study (FBS) has been the recruitment of families with at least two affected individuals and a third first degree relative with or without dementia and willing to participate. Participants are from different ethnic backgrounds including Caucasian, African American and Hispanics. The FBS study is actively recruiting both late onset (LOAD) and early onset Alzheimer's Disease (EOAD) families. Uniform assessments are completed across all sites and include DNA, Plasma, PaXgene and PBMC samples collection as well as Neuropathology whenever possible. We conduct both in person and remote evaluations and use the services of a mobile phlebotomy company to collect bio samples. In addition, we've created a protocol for genetic testing on the proband for EOAD families where an additional sample is sent to a CLIA approved lab and after genetic counseling, the presence or not of AD related mutations is disclosed to the families.
Results: To date, this cohort has recruited 1,756 families and acquired data from 9,682 family members. Families are from Caucasian, African Americans and Hispanics ethnic groups. The cohort has longitudinal

clinical data, cognitive assessment, family history and bio samples available for sharing. Genotype data includes APOE, GWAS, WES, WGS, brain methylation, RNA sequencing and biomarkers data.
Conclusions: The NIA-LOAD FBS study is the largest collection of familial Alzheimer's Disease worldwide. Over 140 publications have used data and/or samples from FBS to address the genetics of Alzheimer's Disease. The enriched resources provided by this cohort are unvaluable to the scientific community.

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SHIFT 02-299

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / DISEASE-CAUSING MUTATIONS
4-5 April 2025

NEUROPATHOLOGICALLY CHARACTERISING AMYLOID LOAD AND PLAQUE PATHOLOGY IN AN ABCA7 RISK VARIANT FOR LATE ONSET ALZHEIMER'S DISEASE

Marianna Papageorgopoulou[1], Emily Adair[1], Samuel Boulger[2], Mara Wuelfing[1], Vicky Chau[1], To Ka Dorcas Cheung[1], Johanna Jackson[3], Paul Matthews[4]
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Aims: ABCA7 loss of function variants are associated with increased risk for Late Onset Alzheimer's Disease (LOAD). The rs3752231 SNP mutation is commonly found in the population (AAF= 0.239) and linked to an increased LOAD occurrence (OR=1.09 95% CI = 1.07-1.1). Neuropathological and molecular changes in human disease, linked to the variant have not been elucidated. Here, we characterise the neuropathology by examining amyloid load and Aβ plaque pathology in postmortem human brain tissue of 47 individuals carrying the rs3752231 SNP and 28 non-carrier controls.
Methods: Mid-temporal gyrus FFPE tissue slides were immunohistochemically stained for the neurotoxic Aβ40 and Aβ42 isoforms of Aβ. The % positivity of a region of interest from the grey matter of each sample was determined. Aβ deposits (diameter>16μm) were characterised into 4 groups (diffuse, dense core, compact, and cerebral amyloid angiopathy) using a deep learning model, trained by in-house 2x2mm slide tiles. Two rounds of manual corrections followed and the same region of interest was used for plaque characterisation.
Results: Preliminary results indicate that this cohort shows no significant differences between carriers and non-carriers across stages of disease (Early: Braak 0-2, Mid: Braak 3-4, Late: Braak 5-6). However, there is a trend (Wilcoxon rank sum p=0.08, moderate effect size) for ABCA7 carriers to show more diffuse plaque coverage and density in late-stage disease and higher amyloid load (t-test p=0.07, moderate effect size).
Conclusions: Further explorations are needed to validate potential trends, as well as consolidation with transcriptomics and proteomics of the cohort.

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SHIFT 02-301

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
4-5 April 2025

ASSOCIATION OF PRENATAL PESTICIDE EXPOSURE WITH PLASMA AMYLOID-BETA 42/40 RATIO IN MIDLIFE: EVIDENCE FROM THE CHILD HEALTH AND DEVELOPMENT STUDIES

Isha Mhatre-Winters[1], Jason Richardson[1], Piera Cirillo[2], Pam Factor-Litvak[3], Nickilou Krigbaum[2], Yoonhee Han[1], Young-Mi Go[4], Dean Jones[4], Barbara Cohn[2]
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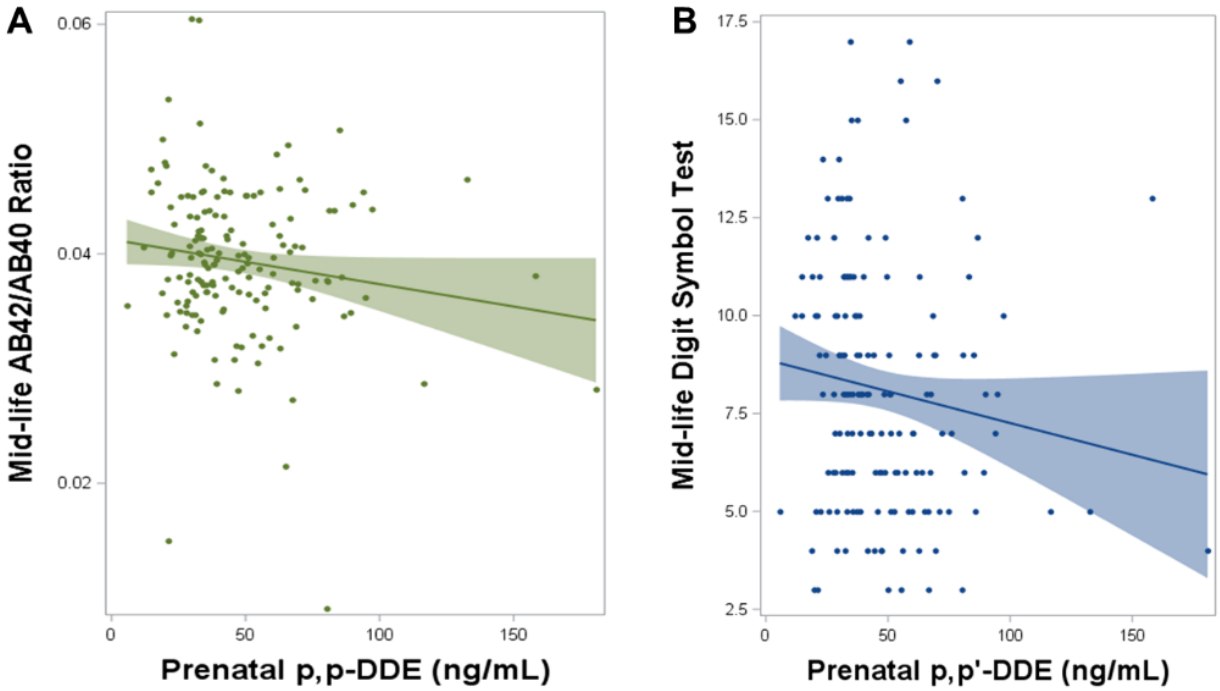
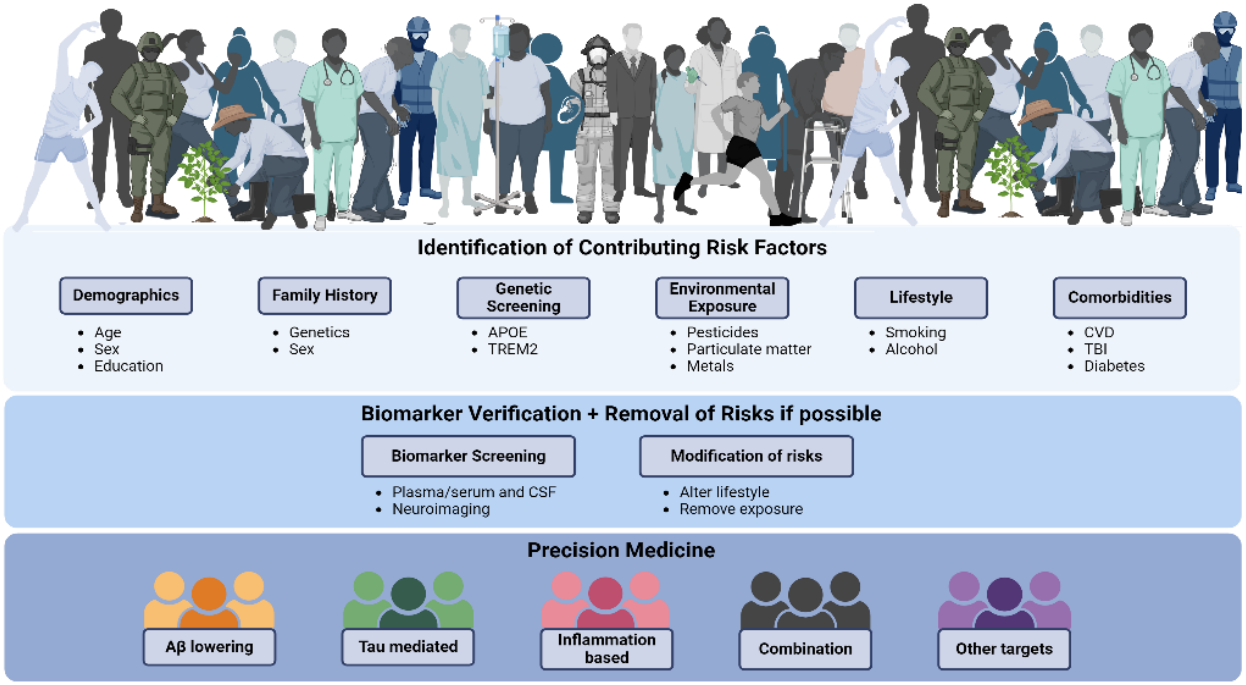
Aims: Environmental factors are increasingly recognized as significant contributors to Alzheimer's and Related Dementias (ADRD). We previously reported that higher serum DDE, a persistent DDT metabolite, is associated with increased Alzheimer's risk. Additionally, we showed that DDT and DDE increase amyloid pathology and impair memory in cell and animal models. However, little is known about the effects of prenatal DDT and DDE exposure on amyloid and cognition in humans.
Methods: In 2010, offspring from the Child Health and Development Studies (CHDS) pregnancy cohort (1960–1963) in Oakland, California, were recruited for a follow-up study on health disparities. Participants (average age 50) completed cognitive function assessments and provided interview data and blood samples. We used the Quanterix Neurology 3-Plex-A kit to measure plasma Aβ-42/40 in mid-life and analyzed prenatal *p,p'*-DDE in archived maternal pregnancy serum (n=160). Associations were estimated in logistic regression models, adjusted for race and sex.
Results: Higher prenatal *p,p'*-DDE was associated with lower mid-life Aβ-42/40. The Odds Ratio (OR) for estimating lower Aβ-42/40 = 2.6 (95% CI=1.0-6.9) and 3.2 (95% CI=1.1-9.8) for *p,p'*-DDE tertiles 2 and 3, respectively. The test for trend across *p,p'*-DDE tertiles was significant (P-value=0.04). Higher prenatal *p,p'*-DDE was also associated with lower mid-life Wechsler Digit Symbol Substitution (DSS) score (β = −0.0221, 95% CI = −0.041 to −0.004; P-value=0.02). Adjusting for mid-life education did not alter



Scatter plot of (A) Aβ-42/40 ratio and (B) DSS score measured in mid-life by level of prenatal p,p'-DDE in the CHDS pilot samples, n=160; adjusted for race and biological sex.

results.

Conclusions: Higher prenatal DDE exposure is correlated with lower midlife plasma Aβ-42/40, a potential early marker for ADRD, and lower DSS scores, indicating that prenatal pesticide exposure may have long-lasting effects on cognitive function. Our findings in this unique prospective cohort provide evidence that prenatal and early-life environmental exposures increase ADRD risk, advancing opportunities for early mid-life interventions to prevent disease progression.



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SHIFT 02-302

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
4-5 April 2025

MIDDLE AGED CONCUSSION IN MICE EXHIBITS ALZHEIMER'S DISEASE AND RELATED DEMENTIA SYMPTOMOLOGY

Amandine Jullienne[1], Jiamin Yan[1], Margaret Bright[2], Scott Persohn[2], Rojina Pad[1], Brenda Noarbe[1], William Horspool[1], Oluwadara Ogundare[1], Anh Vu[1], Denes Agoston[3], Paul Territo[4], Andre Obenaus[5]
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Aims: Traumatic brain injuries increase the risk of Alzheimer's disease (AD) and related dementias (ADRD). Previous studies have shown that a closed head injury (CHI) results in progressive AD-like symptoms, including cognitive decline, brain atrophy, blood-brain barrier alteration and neuronal loss. The goal of our study was to characterize a new middle aged mouse concussion model of ADRD.
Methods: Eight month-old C57BL/6J male and female mice were subjected to CHI and then surveyed for 60 days using neuroimaging with T2, perfusion, T1, susceptibility-weighted imaging, and 18F-FDG PET. Behavioral testing was performed for cognitive performance. At 60 days post-injury (dpi), mice underwent plasma collection and vessel painting. Ex vivo diffusion MRI was performed to assess brain tissue alterations. These experiments were performed across two sites to assess reproducibility and rigor.
Results: No parenchymal bleeding nor edema was detected in CHI mice between 1 and 60 dpi. Cortical cerebral blood flow was not affected by CHI at 30 and 60 dpi. Brain glucose metabolism did not exhibit overt changes. However, neurovascular coupling (NVC) was perturbed at 30 and 60 dpi, particularly in female CHI mice. NVC was region-specific with ipsilateral cortex and hippocampus exhibiting vulnerability. Brain volumes were not changed by CHI but ipsilateral corpus callosum showed significant increases in volume at 60 dpi.
Conclusions: We demonstrate CHI model reproducibility between two sites. Moreover, we found significant dynamic and progressive alterations in NVC that exhibit similarities in vascular dysfunction as observed in other AD or AD risk models. A single CHI at mid-life can alter vascular function in the lifespan of the mouse, similar to those observed in human patients progressing to ADRD. Funding: NIH NINDS R01 NS119605 (AO/JB), RO1NS135556 (AO/VS/DA), 1RF1NS138032 (AO/PT)

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SHIFT 02-303

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
4-5 April 2025

CO-CARRIERSHIP OF HERPES SIMPLEXVIRUS AND AGGREGATIBACTER ACTINOMYCETEMCOMITANS LEUKOTOXIN ASSOCIATED WITH DECLINING HIPPOCAMPAL VOLUMES IN HEALTHY ELDERLY ADULTS

Bodil Weidung[1], Maria Josefsson[2], Vilma Velickaite[3], Jan Olsson[4], Fredrik Elgh[4], Lars Lind[5], Håkan Ahlström[6], Anders Johansson[7], Eric Westman[8], Hugo Lövheim[9]
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Aims: Hippocampal atrophy typically is an early defining characteristic of AD and may be useful to model associations with very early neurostructural changes in AD. Microbial agents such as Herpes simplex-virus (HSV)-1 and *Aggregatibacter actinomycetemcomitans* may be involved in the pathology of AD as potential triggers of Aβ deposition and inflammation. This study aims to assess potential cross-sectional and longitudinal associations between HSV-1 and the leukotoxin (LtxA) produced by *A. actinomycetemcomitans* with hippocampal atrophy.
Methods: The study included 408 75-year-olds in the population-based Prospective Investigation of the Vasculature in Uppsala Seniors study. Magnetic resonance imaging was performed at the ages of 75 (*n* = 408) and 80 years (*n* = 201) to assess hippocampal volumes. Antibody seropositivity was assessed using enzyme-linked immunosorbent assays.
Results: Mean hippocampal volume was 3.45 ± 0.38 ml at 75 years and declined with on average 0.16 ± 0.16 ml over 5 years. The prevalence of anti-HSV-1 IgG carriers was 79% and of anti-Ltxa IgG carriers was 46%. *C*arriership of anti-HSV-1 IgG and Ltxa antibodies were not separately associated with hippocampal volume at 75 years, but the interaction was associated with a decrease over 5 years (β for interaction = -135.11 µl, 95% CI = -244.98–-25.23 µl, *p* = .016) in mixed models.
Conclusions: Concurrent carriership of HSV-1 and the *A. actinomycetemcomitans* Ltxa may be associated with 5-year hippocampal atrophy among 75-year-olds.

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SHIFT 02-304

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / ENVIRONMENTAL RISK FACTORS
4-5 April 2025

HORMONAL IMBALANCES AND ALZHEIMER'S DISEASE RISK IN WOMEN: A LIFECOURSE APPROACH

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Aims: This study investigates the relationship between hormonal imbalances at various life stages in women and their impact on Alzheimer's disease (AD) risk. We aim to assess whether hormonal imbalances, caused by conditions such as pregnancy, polycystic ovary syndrome (PCOS), thyroid dysfunction, or the use of hormonal medications (e.g., birth control or hormone replacement therapy [HRT]), influence the likelihood of developing AD.
Methods: Using data from the UK Biobank (UKB), we will investigate medical records to identify women exposed to various hormone-altering conditions and treatments. Alzheimer's cases will be identified using ICD codes, and the relationship between hormonal imbalances and AD risk will be examined using Cox proportional hazard models adjusted for confounding factors such as age, genetic risk, and lifestyle variables.
Results: We hypothesize that different hormonal exposures across the lifespan will be linked to an increased risk of Alzheimer's disease. For instance, prolonged use of birth control, hormonal fluctuations during pregnancy, and untreated thyroid dysfunction may differentially impact cognitive health and AD risk. The effects of these hormonal exposures will be analyzed to determine their respective impacts on neurodegenerative risk.
Conclusions: This study aims to clarify how hormonal imbalances—whether due to natural processes or medical interventions—serve as potential modifiable risk factors for Alzheimer's disease. By examining a wide range of hormonal influences, this work seeks to inform more personalized preventive strategies for women at risk of AD, based on their hormonal and reproductive health history.

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SHIFT 02-310

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4-5 April 2025

NEW REAL-TIME PCR TEST FOR APOE GENOTYPING IN PATIENTS WITH ALZHEIMER'S DISEASE BEFORE ANTI-AMYLOID THERAPY

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Aims: Anti-amyloid drug trials demonstrated an elevated risk for amyloid-related imaging abnormalities with cerebral edema (ARIA-E) in carriers of the Alzheimer's disease (AD) risk allele apolipoprotein E epsilon 4 (APOE-ε4), especially in ε4/ε4 homozygous individuals. This study evaluates a new real-time PCR test for APOE genotyping.
Methods: The EURORealTime APOE test (EUROIMMUN), which enables testing for all six APOE genotypes (ε2/ε2, ε2/ε3, ε2/ε4, ε3/ε3, ε3/ε4, ε4/ε4), was performed using genomic DNA (gDNA). Samples from healthy blood donors (HBD) were used to assess intra-assay/ inter-assay/ between-lot precision (n=6) and analytical sensitivity (n=21), with each APOE genotype represented by ≥1 sample. Assay accuracy was analyzed by comparing genotype assignments to the CE-IVD-marked EUROArray APOE test (EUROIMMUN) and bidirectional Sanger sequencing using 110 samples (100 AD, 10 HBD). APOE genotype frequencies were compared between patients (100 AD) and controls (250 HBD).
Results: Precision testing of the EURORealTime APOE system resulted in 100% correct genotype calls. Assessment of the analytical sensitivity revealed valid and correct genotype assignment in all 21 samples, confirming 1 ng/µl as the recommended minimum gDNA concentration. The analytical accuracy amounted to 100%. Comparison of the APOE genotype distribution showed a higher proportion of ε4 allele carriers (ε2/ε4, ε3/ε4, ε4/ε4) in AD patients than in HBD (50.0% vs. 25.2%). The prevalence of the ε4/ε4 genotype in these cohorts was 25.0% for AD patients compared with 2.8% for HBD.
Conclusions: The well-established high APOE-ε4/ε4 prevalence in AD patients and the increased risk of ARIA-E in these homozygous carriers substantiate the relevance of APOE genotyping prior to anti-amyloid treatment. The EURORealTime APOE test provides sensitive and reliable determination of APOE alleles, thus presenting a suitable tool to improve risk stratification for potential recipients of anti-amyloid drugs.

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SHIFT 02-311

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4-5 April 2025

APOLIPOPROTEIN (APOE) 4 CARRIERSHIP IS ASSOCIATED WITH SUPERIOR EXECUTIVE FUNCTION IN MICE AND HUMANS

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Aims: Our objectives are threefold: (1) Use a novel touchscreen continuous performance task (CPT) to determine if the ApoE4 genotype (ApoE4 carrier versus noncarrier) influences executive function in cognitively normal adults at risk for Alzheimer's disease; (2) use a virtually identical touchscreen CPT to assess executive function in novel humanized ApoE4 and ApoE3 knock-in mouse models of AD risk; (3) Examine sensitivity of the touchscreen CPT to longitudinal changes in executive function in both species.
Methods: Human participants were recruited from the PREVENT-AD cohort (McGill University). Human touchscreen CPT testing was conducted using a Microsoft Surface Pro. Mice were tested with a virtually identical touchscreen CPT task using an operant chamber platform. In the full mouse sample, and in a subset of the PREVENT-AD participants, we have collected longitudinal CPT data (3-month intervals in mice spanning 6-18 months of age; 1–2-year intervals in humans spanning 55 to 85 years of age).
Results: Our behavioral results indicate that ApoE4 carriers exhibit better executive functions—specifically in attentional demand—than non-carriers in both our mouse and human cohorts, with this effect being more robust in females of both species. The magnitude of longitudinal decline on CPT performance also differentiated ApoE4 carriers from noncarriers in both species, again suggesting a protective effect of ApoE4 carriership.
Conclusions: Taken together, these results support the antagonistic pleiotropy hypothesis, whereby *ApoE4* carriership confers greater attentional performance in middle age in both humans and mice compared to non-carriership. Moreover, we provide validation for a fully translatable touchscreen CPT in mouse and human which is sensitive to the interaction between *ApoE4* and age on executive function in both cross-sectional and longitudinal datasets.

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SHIFT 02-312

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4-5 April 2025

FUNCTIONAL EVALUATION OF GENETIC VARIANTS RELATED TO POLYGENIC RISK FOR ALZHEIMER'S DISEASE USING A MASSIVELY PARALLEL REPORTER ASSAY

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Aims: Synapse degeneration is a primary neuropathological factor associated with cognitive decline in Alzheimer's disease (AD). We recently reported a Polygenic Risk Score (PRS) restricted to variants in synaptic genes with a diagnostic accuracy of 72% in an AD cohort. The aim of this study was to determine whether variants within linkage disequilibrium (LD) blocks represented by the PRS have regulatory activity *in vitro*.
Methods: We cloned an oligonucleotide library of 137 putative regulatory variants each represented by 5 barcodes per allele into pMPRA1 vector. We transfected the plasmids into HEK293 cells (n=5) and extracted DNA and RNA for posterior sequencing on an Illumina MiSeq. Using the *mpra* package in R, we normalized the tag counts to 10 million reads and computed paired log ratios of RNA/DNA counts for each barcode. Weighted linear models were used to test for differential activity of the minor versus the major allele of each SNP using the *mpralm* function, adjusting for multiple testing using the Benjamini-Hochberg method.
Results: We acquired approximately 15 million reads of DNA and RNA from 5 independent experiments. 35 out of 137 SNPs tested had differential activity between alleles (adj. $p < 0.05$). Three of the SNPs that showed regulatory activity were included in the PRS (*BIN1*: rs17014923 and rs35114168; *DLG2*: rs286043); the remaining 32 were captured on LD blocks within the synaptic PRS.
Conclusions: All LD blocks captured by the synaptic PRS contain SNPs with regulatory activity *in vitro*, supporting a potential mechanism where altered expression of these specific loci could lead to a modified cumulative risk for AD. Further studies to determine the precise mechanism involved in this regulatory activity at the synapse could guide future therapeutic strategies for AD.

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4-5 April 2025

TITLE: THE INFLUENCE OF ALZHEIMER'S DISEASE-RELATED GENETIC PATHWAYS ON AGING-RELATED COGNITIVE DECLINE

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Aims: Previous studies on late onset Alzheimer's disease (AD) have demonstrated its complex polygenic pathophysiology, and risk genes are overrepresented among tau-, amyloid-, protein-lipid-, and immune system pathways. This study aimed to investigate the role of these pathways on both AD risk and normative aging-related cognitive decline.
Methods: Analyses were performed in the longitudinal Betula study, in which individuals were assessed in 5-year intervals up to 25 years (N=1737, 44% men and 56% women). We calculated polygenic risk scores (PRS) based on genetic risk variants for AD across the genome and in five *a priori* selected AD-related pathways, while excluding the *APOE* genomic region. Linear mixed-effect models and survival analyses were used to assess the influence of AD pathway PRS for associations with (i) cognitive level and decline in normative cognitive aging, and (ii) risk for AD.
Results: One standard deviation (SD) higher overall AD PRS was associated with lower cognitive level (β = -1.22,p=0.02**)** and more cognitive decline (β= -0.05**,** p**=**0.01), and higher tau (β= -0.04,p=0.02) and immune system (β = -0.07, p=0.00) pathway PRS with cognitive decline. Additionally, one SD higher overall AD PRS (HR = 1.14, p = 0.00) and the amyloid- (HR = 1.09, p = 0.01), protein-lipid-(HR = 1.11, p < 0.01), and immune system (HR = 1.08, p = 0.01) pathway PRS were associated with elevated dementia risk.
Conclusions: The findings highlight a significant role of polygenic risk factors, particularly tau, amyloid, protein-lipid, and immune system pathways in both cognitive decline in normative aging and AD risk. These pathways may therefore play an importance role in early detection and AD intervention strategies.

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SHIFT 02-314

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / GWAS, GENETIC ASSOCIATIONS, SUSCEPTIBILITY & PROTECTIVE GENES
4-5 April 2025

GENETICS, ATROPHY, LIQUID BIOMARKERS AND COGNITIVE TESTS IN ALZHEIMER'S DISEASE: AN INTEGRATED AND MULTIMODAL ANALYSIS PIPELINE TO UNDERSTAND THE NEURODEGENERATIVE MECHANISMS

Margherita Squillario[1], Francesco Reggiani[1], Matteo Pardini[1,2], Michele Piana[1,3]
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Aims: Alzheimer's disease (AD) is the most common neurodegenerative disease among the elderly (50–75%) and the causes of the sporadic form are not yet clear. The genetic predisposition is relevant (60–80%), but alone is not sufficient to trigger those initial processes that lead to neurodegeneration and to the slowly atrophy of the brain. Several public datasets containing multimodal data centered on AD have emerged since the beginning of 2004 when ADNI come out. An appropriate integration of various data types (e.g., biomedical images, GWAS/WES, cognitive tests, liquor protein expression) is pivotal to understand this phenomenon.
Methods: Objective 1: we will develop a merged multimodal AD-centered dataset from a careful selection of public database. Objective 2: we will develop a user-friendly analysis tool starting from the multikernel/deep learning pipeline devised to properly address the analysis of multimodal data. Objective 3: in the merged multimodal AD-centered dataset we will evaluate the predictive performance of gene-SNPs panels, retrieved from the literature, using the developed tool. We will identify clusters of genes-SNPs (of the panel) and of specific neurodegenerative markers correlating with the atrophy (measure by FDG-PET) of the most affected brain regions through a weighted correlation network analysis (WCNA). Objective 4: we will validate those clusters in silico, in an independent partition of the merged multimodal dataset and/or in independent AD public dataset.
Results: The analysis of the merged multimodal AD dataset with the proper multimodal-oriented tool, will identify genes-SNPs signatures that correlate with atrophy starting from (i) promising genes-SNPs panels identified in the literature and (ii) neurodegenerative biomarkers (identified in cognitive tests, abundance protein dataset, imaging data) that correlate more strongly with atrophy.
Conclusions: We believe that multimodal data integration pipelines will be fundamental to understand AD.

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SHIFT 02-317

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / METABOLIC AND CARDIOVASCULAR
4-5 April 2025

MENDELIAN RANDOMIZATION STUDY IDENTIFIED POTENTIAL PATHWAY FROM CIRCULATING ACE LEVELS TO ALZHEIMER'S DISEASE VIA DIASTOLIC BLOOD PRESSURE

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Aims: Exploring the proteins that link potential risk factors and related traits to Alzheimer's disease (AD) can enhance our understanding of underlying pathways and help uncover new drug targets.
Methods: We conducted a proteome-wide two-sample Mendelian Randomization (MR) analysis on AD and its 14 modifiable risk factors using data from the UK Biobank Pharma Protein Project (UKB-PPP), which involved 54,219 participants and 2,923 proteins. Using univariable Wald ratio and inverse-variance weighted MR models, proteins identified associated with AD and its risk factors were further analysed using Multi-response MR and Multivariable MR to highlight underlying associations adjusted for their mutual influences. Mediation analyses were conducted when intermediary relationships between risk factors and the protein-AD associations were observed. Reverse MR from risk factors to protein levels, and three separate sensitivity analyses were performed to substantiate the robustness of our findings.
Results: The proteome-wide MR scan identified 25 circulating proteins associated with AD (false discovery rate (FDR) < 0.05), 14 of which were also associated with at least one risk factor (FDR < 0.05). Five proteins (ACE, CD2AP, LILRB5, PILRA, and SERPINF2) with strong instrumental variable strength (conditional F > 10) were included in the joint MR analyses. ACE levels were negatively associated with AD (OR = 0.85, 95% CI: 0.81, 0.89), potentially mediated by diastolic blood pressure (DBP). CD2AP and LILRB5 may contribute to AD via unclear mechanisms, while PILRA and SERPINF2 associations with AD might be confounded by unknown risk factors.
Conclusions: Identifying ACE in the AD pathway highlighted the interplay between cardiovascular factors and AD. Therapeutic targets involving ACE may potentially benefit both BP and AD management. Further investigation into other proteins associations may uncover additional mechanisms.

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SHIFT 02-320

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
4-5 April 2025

IS THE RESIDUAL APPROACH RELIABLE TO ESTIMATE RESILIENCE TO ALZHEIMER'S DISEASE PATHOLOGY?

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Aims: Cognitive and brain resilience (CR/BR) refer to the ability to maintain normal cognition or brain integrity despite neuropathological burden. Resilience is often quantified using the residual approach, where residuals are calculated from a linear regression with brain volume or cognition as the dependent variable and neuropathology as the independent variable. Residuals can be corrected for independence from the dependent variable, but comparative analyses of correction methods are lacking. This study compares non-corrected and corrected residual approaches in a memory clinic population.
Methods: 121 MCI patients from the Geneva Memory Center underwent amyloid-PET (A), tau-PET (T), MRI (N), and clinical / neuropsychological assessments. Standardized residuals were extracted from linear regression models between hippocampal volume and AT (BR) or MMSE scores and ATN (CR). We compared non-corrected residuals ($BR_{non\text{-}cor}$ and $CR_{non\text{-}cor}$), residuals corrected by regressing them on the original dependent variable ($BR_{res\text{-}cor}$ and $CR_{res\text{-}cor}$), and residuals corrected by adding the original dependent variable as a covariate to subsequent models ($BR_{cov\text{-}cor}$ and $CR_{cov\text{-}cor}$). Bivariate and multivariable linear regression models examined associations between resilience measures and various biomarkers, demographic, and clinical factors. Linear mixed-effects models assessed the impact of resilience on longitudinal changes in MMSE scores.
Results: Corrected residuals showed similar associations. However, corrected vs. non-corrected BR yielded distinct, sometimes opposing, associations. For example, GFAP plasma levels were negatively associated

with $BR_{non\text{-}cor}$ ($\beta = -0.33$; $p < 0.01$) but positively with $BR_{res\text{-}cor}$ ($\beta = 0.5$, $p < 0.001$) and $BR_{cov\text{-}cor}$ ($\beta = 0.13$, $p < 0.001$). For CR, only corrected measures yielded significant associations. Only $BR_{res\text{-}cor}$ and $CR_{res\text{-}cor}$ predicted cognitive decline, with lower scores associated with better performance.

Conclusions: The observed discrepancies raise concerns about the ability of the residual approach to accurately capture resilience.

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SHIFT 02-321

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
4-5 April 2025

PHYSICAL ACTIVITY AND THE RISK OF NEURODEGENERATIVE DISORDERS AND DEMENTIA SUBTYPES – A LARGE POPULATION COHORT

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Aims: Physical activity may reduce dementia risk and improve prognosis in Parkinson's Disease (PD). However, it remains unclear if the protective effects vary by dementia subtype or how physical activity influences key pathological markers such as A-beta, tau, or brain atrophy. Additionally, the impact on cognitive and motor reserves, and disease progression rates, is still uncertain. This cohort aims to examine the associations between a physically active lifestyle and the risk of developing different neurodegenerative diseases or dementia subtypes. It also explores whether exercise influences pathological hallmarks and progression in diagnosed individuals.
Methods: Our unique study design follows around 800,000 Swedes over up to 36 years to investigate how physical activity affects disease risk, using diagnoses from the National Patient Registry (Figure 1). Half of the cohort are participants in sport events such as Vasaloppet (skiing), Vätternrundan (biking), Vansbrosimningen (swimming), or Göteborgsvarvet (running). They are compared with a less active group of matched (age, sex, and residency) non-participants from the Swedish population. By excluding individuals who develop disorders of interest within five years of inclusion, we aim to reduce bias from reverse causation. From the conscription registry, objective measures of fitness and cognition in youth serve to analyze changes in capabilities over time. Quality registries, including SveDem (dementia) and the PD registry, are used to assess biomarker levels and disease progression in diagnosed participants. Cognition (MMSE) and brain atrophy data help explore the effects of physical activity on brain pathology. This study design allows us to follow the associations between fitness/physical activity and the development of neurodegenerative disorders in an adult life-time perspective.
Results: To be added later. Not available yet.
Conclusions: To be added later. Not available yet.

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SHIFT 02-322

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
4-5 April 2025

REDUCED CANCER RISK IN PATIENTS WITH DEMENTIA EVEN AFTER ACCOUNTING FOR SURVEILLANCE BIAS - RESULTS OF A POPULATION-BASED COHORT STUDY

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Aims: Several epidemiological studies have reported an inverse association between dementia and cancer risk. Whether this is due to an underlying biological mechanism or methodological bias is unclear. Surveillance bias is an example of the latter, describing reduced cancer screening in dementia patients as a cause of the lower cancer incidence. This study aims to assess the cancer incidence in a dementia cohort compared to a non-dementia cohort while accounting for surveillance bias.
Methods: For this nationwide population-based cohort study, the dataset of the Austrian National Health Insurance Association was used, including dementia patients and age- and sex-matched non-demented individuals. Hazard ratios (HR) for cancer diagnosis were calculated using univariate and multivariate Cox regression models. To mitigate surveillance bias, a sub-analysis was performed, including only individuals who underwent diagnostic/imaging tests used for cancer screening (colonoscopy, gastroscopy, imaging of head, chest, and abdomen).
Results: Overall, 340466 individuals were included in the study (170233/study cohort; mean age: 82.6 (68.9-91.6); female: 225180/340466 (66.1%)). A total of 33513/340466 (9.8%) individuals developed cancer during the follow-up. Dementia patients were significantly less often diagnosed with cancer, HR: 0.57 (95%-CI: 0.55-0.58, p<0.001). When including only individuals with diagnostic/imaging tests this result remained significant for all analysed cancer types with the HR ranging from 0.29 (95%-CI: 0.23-0.36, p<0.001) for brain and meningeal malignancies to 0.71 (95%-CI: 0.62-0.81, p<0.001) for colon, rectal and anal carcinomas.
Conclusions: This study shows that dementia patients have a lower cancer risk, a finding supported by consistent data from other studies. The inverse association is not attributable to surveillance bias, as it persists even when only patients with sufficient cancer screening are analysed. To our knowledge, this is the first study that accounts for this bias.

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SHIFT 02-323

Poster on Board - Shift 02
β-AMYLOID DISEASES / GENETICS, EPIDEMIOLOGY / OTHER
4-5 April 2025

ESTIMATING THE TREATABLE POPULATION FOR ANTI-AMYLOID THERAPY IN FRANCE

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Aims: Anti-amyloid therapies for early Alzheimer's Disease (AD) are now approved in several countries, globally. However, several publications raise concerns as to their potential impact on healthcare systems, as some fear exorbitant costs driven by high demand from a substantial pool of patients. Here we present a counter perspective based on a comprehensive patient journey for those with early AD used to estimate distinct eligible and treatable populations for anti-amyloid therapy in France.
Methods: A patient journey based on the Clarity AD screening protocol was developed as a model for patient identification in real-world practice. The proportion of patients with MCI or mild dementia suspected due to AD as well as the proportions of patients to remain eligible following MRI and amyloid screening were taken directly from Clarity AD screening data. Literature searches were used to identify other relevant epidemiological and capacity-based inputs.
Results: The total pool of patients with MCI or dementia due to any cause was estimated at 4,129,833 patients. The eligible population for anti-amyloid therapy, i.e., patients with early AD, confirmed amyloid pathology, to pass MRI screening, was estimated as 198,918 patients (4.8% of patients with MCI or dementia due to any cause). Applying estimates for the capacity of the French healthcare system predicted the size of the treatable population for anti-amyloid therapy as 3978 patients (0.1% of patients with MCI or dementia due to any cause).
Conclusions: Compared with the pool of patients with MCI or dementia due to any cause, the number of patients eligible for anti-amyloid therapy will be relatively small. Considering the initial capacity of healthcare systems to adequately identify and treat eligible patients further reduces the size of the treatable population substantially.

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SHIFT 02-328

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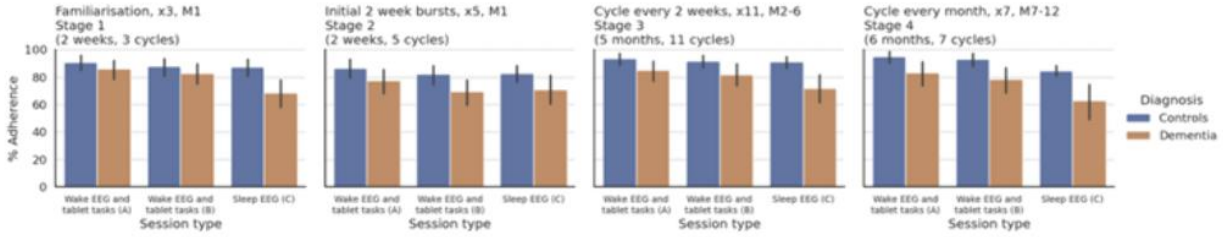
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
4-5 April 2025

NEUROPSYCHOLOGICAL PHENOTYPING OF ALZHEIMER'S DEMENTIA AT HOME, USING THE CUMULUS NEULOGIQ PLATFORM WITH PLASMA BIOMARKERS

John Dyer[1], Florentine Barbey[2], Alison Buick[1], Shannon Diggin[1], Hugh Nolan[2], James Rowe[3], Laura Rueda-Delgado[2], Brian Murphy[2]
[1]Cumulus Neuroscience, Belfast, United Kingdom, [2]Cumulus Neuroscience, Dublin, Ireland, [3]University of Cambridge, Department Of Clinical Neuroscience, Cambridge, United Kingdom

Aims: Current solutions for detecting and tracking impairment in Alzheimer's disease and other dementias are not fit for purpose, either being highly burdensome, costly, and/or requiring substantial clinical time and judgement. CNS101 was a year-long study designed with a consortium of 10 pharma companies, aiming to test the feasibility and evidential power of the NeuLogiq home-based platform to frequently and objectively sample cognitive function and neurophysiology.
Methods: Seven UK sites recruited Alzheimer's type mild dementia patients (n=59, ACE-III scores >60 and ≤88) and a matched cohort of controls (n=60). Participants completed a range of tablet-based functional tasks with wake EEG, and separately, sleep EEG. Initial burst sampling tapered to periodic sampling over the following year. Benchmark assessments (including ADAS-Cog, DSST, VPA) and self-reported usability (System Usability Scale – SUS) were collected at months 0, 6 and 12, and plasma was collected at months 6 and 12.
Results: Despite self-reported apprehension about using a perceived complex technology autonomously in the home, patient-judged usability was good (SUS: 62.2). Patient adherence was high at 69.8% during an intensive 2-week burst, and 77-79% during intermittent sampling to month 12 (Fig 1). Cross sectional analyses showed that neurophysiological endpoints aligned with the literature on dementia (e.g. resting EEG Alpha, Fig 2) and behavioural endpoints for executive function and memory correlated highly (rho=0.75-0.76, Fig 3) with benchmarks. Initial analysis of plasma results was able to partially differentiate dementia from control patients, with markers of AD-specific pathology (ptau217) and inflammation (GFAP) showing the strongest group-level effects.
Conclusions: Real-world frequent sampling of behaviour and neurophysiology in AD is feasible. Fuller results on association between markers of pathology and other endpoints will be ready for presentation in



April. Figure 1: Adherence across stages and per session type. Error bars depict bootstrapped 95% CI.

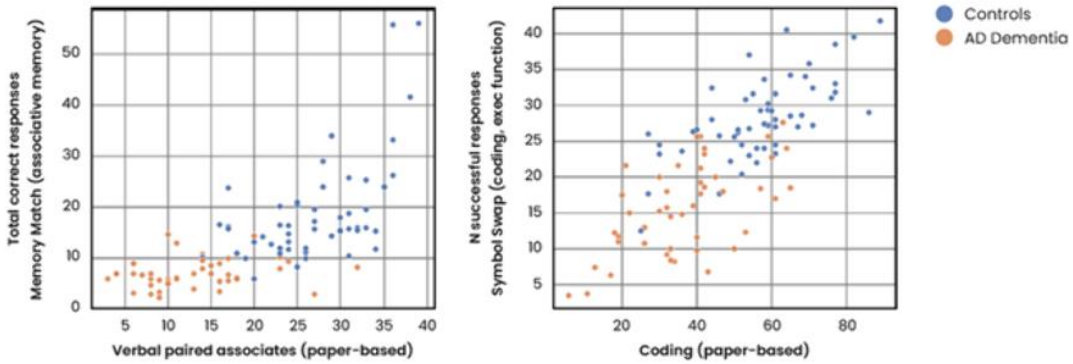


Figure 3: Scatterplots of Cumulus NeuLogiq variables against paper-based benchmarks. Left: The NeuLogiq associative memory task showed a correlation with Verbal Paired Associates I of 0.75 (p = 6.2e-19). Right: The NeuLogiq symbol coding task showed a correlation with the paper DSST of 0.76 (p = 5.0e-20).

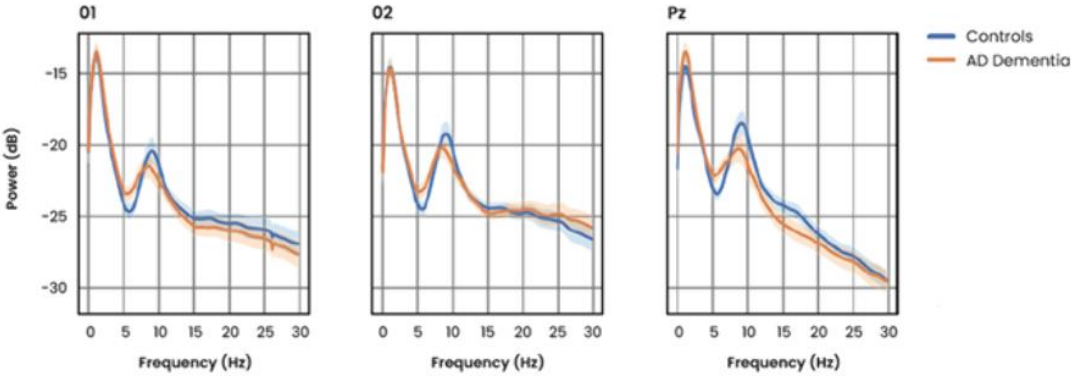


Figure 2: Group estimates from mixed models of the PSDs of channels O1, O2 and Pz during eyes closed. The alpha peak is reduced and slowed down, and the theta band is increased in the group with dementia when compared to the control group. 95% confidence intervals were obtained from the models' standard errors.

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EVALUATING THE UTILITY OF COGNITIVE CONSTRUCTS AND ASSESSMENTS IN CLINICAL TRIALS FOR ALZHEIMER'S DISEASE

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Aims: The failure of 98% of Phase II and III Alzheimer's disease (AD) clinical trials is often attributed to the use of inadequate cognitive scales. This poster evaluates the sensitivity and clinical utility of specific Clinical Outcome Assessments (COAs) for measuring cognitive constructs often associated with AD. The COAs assessed are the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) and the Delis-Kaplan Executive Function System (DKEFS) in AD patients. The goal is to identify which specific subtests effectively capture the essential cognitive and executive functioning constructs that best evaluate cognitive change over time and drug efficacy in clinical trials.
Methods: A comprehensive literature review and analysis of clinical trial data using the RBANS and DKEFS in AD patients was conducted. Construct validity was assessed to determine which cognitive domains and subtests most significantly contributed to the clinical profile of AD-related cognitive dysfunction. Group comparisons will be made to highlight distinct cognitive patterns in AD patients.
Results: Preliminary analyses indicates that the RBANS provides strong assessment of immediate memory and attention, while the DKEFS is effective in capturing executive function deficits, which are crucial for identifying cognitive decline. Specifically, subtests such as verbal fluency and delayed recall may be particularly sensitive in detecting early-stage cognitive changes in AD patients. We aim to identify distinct clinical profiles for patients with AD for each COA to determine the ideal cognitive constructs for patients with AD in clinical trials.
Conclusions: The selection of sensitive cognitive measures is critical for capturing cognitive changes over time and assessing treatment efficacy in AD clinical trials. Utilizing appropriate, well-validated COAs can enhance the reliability of trial outcomes, ensuring more accurate evaluation of drug efficacy.

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REMOTE DIGITAL SELF-TESTING FOR COGNITIVE IMPAIRMENT: RESULTS OF THE RE.COGNI.ZE STUDY ON FEASIBILITY AND ACCEPTANCE OF THE NEOTIVCARE APP

Emrah Düzel[1,2], Claudia Bartels[3], Dirk Czesnik[4], Thomas Duning[5], Andreas Lüschow[6], Gereon Nelles[7], Gerd Reifschneider[8], Michael Schöttler[9], Björn Schott[3,10], Martin Griebe[11]
[1]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany, [2]Institute of Cognitive Neurology and Dementia Research (IKND), Otto-von-Guericke University, Magdeburg, Germany, [3]University Medical Center Göttingen, Dept. Of Psychiatry And Psychotherapy, Göttingen, Germany, [4]Gemeinschaftspraxis für Neurologie, Göttingen, Germany, [5]Klinikum Bremen-Ost, Department Of Neurology, Bremen, Germany, [6]Charité Universitätsmedizin Berlin, Mvz Campus Benjamin Franklin, Berlin, Germany, [7]NeuroMed Campus, Köln, Germany, [8]NeuroCentrum Odenwald, Erbach, Germany, [9]Roche Pharma, Grenzach-Wyhlen, Germany, [10]German Center for Neurodegenerative Diseases (DZNE), Göttingen, Germany, [11]Medical Faculty Mannheim, University of Heidelberg, Department Of Neurology, Mannheim, Germany

Aims: Cognitive tests are critical for diagnostic workup in mild cognitive impairment (MCI) and Alzheimer's disease. Their limitations include the requirement of trained personnel and their limited ability to provide longitudinal information. Digital remote self-assessment tool may help to address these challenges. Here we evaluated the feasibility, added value and satisfaction of a digital remote digital self-assessment app certified as a medical device (neotivCare).
Methods: The multicentric healthcare study "re.cogni.ze" evaluated the usability, adherence and acceptance of remote digital self-assessment with the neotivCare app. 27 office-based board-certified neurologists and psychiatrists (specialists), 3 memory clinics, and 13 general practitioners (GPs) in Germany participated in the study. The app included three different previously validated memory tests. Each test was performed four times over a 12-week assessment period. A composite score and an automatically generated summary were provided for discussion by the patients and their physicians.
Results: 765 patients were offered to participate, and 574 (75%) agreed (mean age 67 +/- 10 years; 50.2% female). 496 (93%) completed the full assessment and discussed the app-generated results with their physicians. 368 participants completed a survey assessing usability, concerns, and experienced added value. 40% of paticipants with a composite score fell below the prevalidated cut-off for MCI. 71% of physicians and 71.5 % of participants found the app easy to use. 80% of physicians and 67.6% of participants reported an added value. Participants rated the assessment time and self-testing favourably (both 8.5 on a 10-point Likert scale).
Conclusions: In a multi-centric evaluation of a remote digital self-assessment app in persons with

subjective cognitive decline, the app found to be helpful and easy to use by clinicians and patients. Digital self-assessment may thus facilitate early diagnosis of cognitive impairment.

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A BLUEPRINT FOR EARLY DETECTION OF COGNITIVE IMPAIRMENT: A ROADMAP FOR GLOBAL HEALTHCARE SYSTEM READINESS

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Davos Alzheimer's Collaborative, Wayne, United States of America

Aims: Global healthcare systems are unprepared to care for the 55 million people affected by Alzheimer's disease and related dementias. Only 50% of clinical innovations are adopted into practice, with a 17 to 20-year lag. The Davos Alzheimer's Collaborative Healthcare System Preparedness (DAC-SP) program aims to catalyze healthcare system transformation, providing Alzheimer's patients quicker access to innovations and therapies. DAC-SP uses implementation science to evaluate programs that drive system change and sustainable solutions. Learnings from DAC-SP programs are synthesized into a practical, digital blueprint microsite (www.dacblueprint.org), a resource for healthcare systems seeking to adopt best practices for Alzheimer's care.
Methods: DAC-SP Early Detection Program began in 2021 across seven healthcare systems in six countries with the goal to improve early detection of cognitive impairment by implementing digital cognitive assessments in primary care settings. Over two years, site leaders regularly collaborated on operational and clinical challenges, potential solutions, and co-designed the blueprint.
Results: The blueprint distills insights across sites, offers field-tested, practical implementation strategies, essential tasks, resources, and solutions in an accessible format. The blueprint was developed through a thorough cross-site implementation evaluation and designed using human-centered best practices to ensure it is user-friendly and provides actionable content for a wide audience. Although every system is different, the blueprint allows users to leverage real-world experiences so new innovations and therapies can be applied more efficiently in clinical practice.
Conclusions: The blueprint is an open-source operational roadmap, enabling other healthcare systems to expedite changes in Alzheimer's care, so patients and families have access to breakthrough innovations sooner. The blueprint will continue to evolve with new program learnings, including best practice for implementing blood biomarkers into clinical pathways and addressing specific regional challenges.

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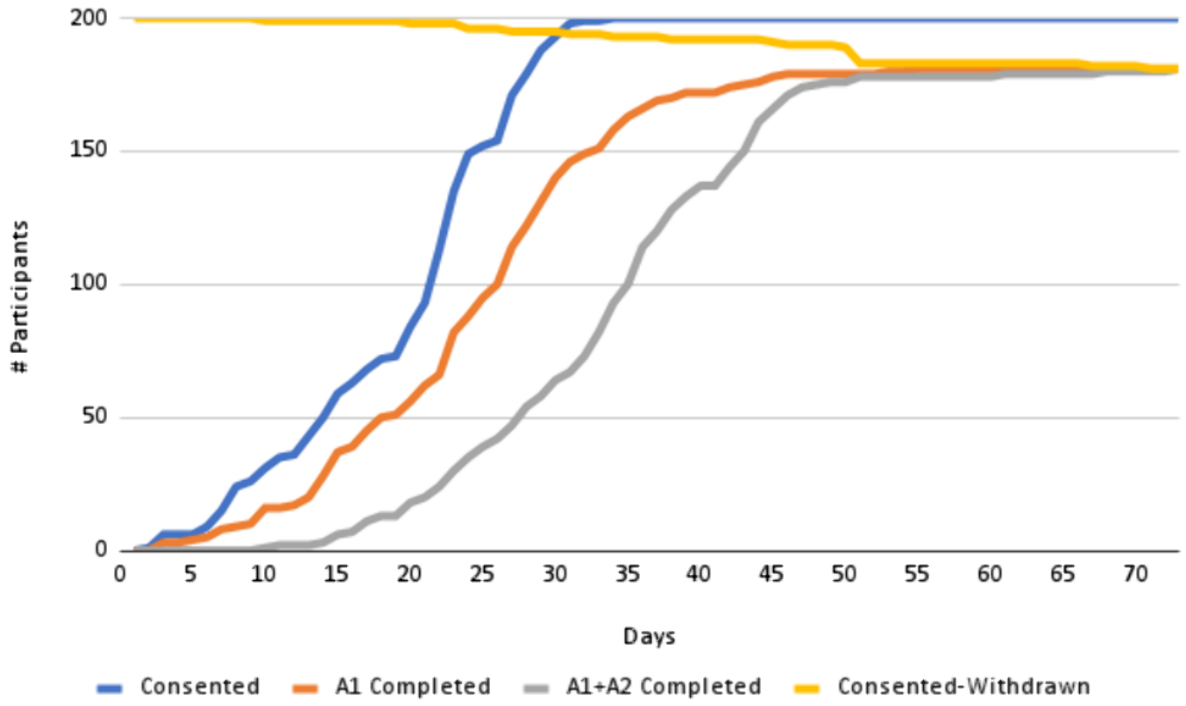
METHODS FOR RAPID RECRUITMENT IN DECENTRALIZED DIGITAL TRIALS: A CASE STUDY OF THE MODALITY REMOTE ASSESSMENT PLATFORM AND THE DEPARTMENT OF VETERANS AFFAIRS HOSPITAL SYSTEM

Oliver Roesler[1], Jackson Liscombe[1,2], Andrew Mcgarry[3], Michael Neumann[1], Hardik Kothare[1,2], Abhishek Hosamath[1], Lakshmi Arbatti[1], Anusha Badathala[2,4], Stephen Ruhmel[5], Bryan Hansen[5], Madeline Quall[5], Sandrine Istas[6], David Henley[5], Arthur Wallace[2,4], Karl Kieburtz[7], David Suendermann-Oeft[1], Vikram Ramanarayanan[1,2,4]
[1]Modality.AI, Inc., San Francisco, United States of America, [2]San Francisco Veterans Affairs Health Care System, San Francisco, United States of America, [3]Cooper University Healthcare at Rowan University, Department Of Neurology, Camden, United States of America, [4]University of California, San Francisco, San Francisco, United States of America, [5]Janssen Research & Development, LLC, a Johnson & Johnson company, New Brunswick, United States of America, [6]ICON Strategic Solutions, ICON plc., Mechelen, Belgium, [7]University of Rochester, Rochester, United States of America

Aims: To demonstrate the feasibility of rapid recruitment and high retention using a remote assessment platform.
Methods: Participant recruitment and retention are major bottlenecks in clinical trials. Multimodal digital health technologies (DHTs) that can recruit and assess patients remotely offer an excellent solution to this problem. Here, we investigate the efficacy of one such DHT to aid in rapid recruitment of 200 participants with Mild Cognitive Impairment (MCI) from the Department of Veterans Affairs (VA) hospital system, using a 5 step process. First, the number of eligible MCI patients and healthy controls was obtained by querying the VA data warehouse. Second, recruitment emails were sent to all 7,231 potential MCI participants (up to four times). Once an MCI participant replied with interest, they were sent a DocuSign consent form link via email and were offered a phone call to go over the form together, if required. Fourth, after they consented, they were sent the link for their remote MCI assessment. Finally, they were sent reminders before their second assessments. As MCI participants were consenting, emails were also sent out to 22,210 (out of 1,377,509) age and sex matched healthy controls.
Results: We demonstrated rapid recruitment of 100 MCI patients and 100 healthy controls within 5 weeks, with a retention rate of over 90% over the



study.

Conclusions: The use of remote DHTs such as Modality in partnership with large hospital systems allow for rapid participant recruitment and high participant retention.

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FACTOR ANALYSIS OF REACTION TIME MEASURES DURING PERFORMANCE OF THE PAIRED ASSOCIATES LEARNING TASK IN PEOPLE WITH MCI

Nicholas Taptiklis[1], Alexander Kaula[1], Francesca Cormack[1], Nora Stang[2], Ana Perez[2], Soraya Alfonsín[3], Timo Saarinen[4], Fernando Maestú[3], Hanna Renvall[5], Camillo Marra[6], Paolo Rossini[7], Christoffer Hatlestad-Hall[2], Ira Haraldsen[2]
[1]Cambridge Cognition Ltd., Cambridge, United Kingdom, [2]Oslo University Hospital, Department Of Neurology, Oslo, Norway, [3]Universidad Complutense de Madrid, Centre For Cognitive And Computational Neuroscience, Madrid, Spain, [4]Helsinki University Hospital, Biomag Laboratory, Hus Medical Imaging Centre, Helsinki, Finland, [5]Helsinki University Hospital, Biomag Laboratory, Hus Medical Imaging Centre,, Helsinki, Finland, [6]Fondazione Policlinico Universitario "A. Gemelli" IRCCS, Rome, Italy, [7]IRCCS San Raffaele Roma, Department Of Neuroscience And Neurorehabilitation, Rome, Italy

Aims: The AI-Mind study has collected rich longitudinal data from people with MCI, comprising cognitive, clinical, biological, and electrophysiological measures, including the CANTAB paired associates learning task (PAL), a well-established measure of memory and learning. This work aims to explore whether novel timing measures derived from this memory task may have value in better characterising aspects of the cognitive profile of MCI and potential pre-clinical Alzheimer's Disease.
Methods: Participants from the AI-Mind study (N=724 MCI) completed a battery CANTAB of tasks, comprising PAL, motor screening (MOT), delayed match to sample (DMS), pattern recognition memory task (PRM), spatial working memory (SWM) and rapid visual processing (RVP); indexing attention, short-term and working memory, executive function and speed of processing, respectively. We conducted factor analysis on outcome measures from these tasks completed at baseline, using varimax rotation to aid interpretability and combined these with twenty-one novel timing measures derived from the PAL task of visual memory and learning.
Results: The novel PAL timing measures primarily loaded onto a factor that also included PRM timing measures, with a subset also loading onto a unique factor which did not include variables from other tasks. The other factors included measures from more than one task. Most factors were either timing related, or accuracy related, with only one factor loading on both timing and accuracy measures.
Conclusions: Factor analysis suggests that novel timing measures from an episodic memory task provide complementary information to existing measures of performance on the CANTAB battery employed in the AI-Mind study. Further work will explore novel features from other CANTAB tasks where these are not routinely captured and will evaluate them with respect to clinical and biomarker data.

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DEFINING MINIMUM STANDARDS FOR DIGITAL COGNITIVE ASSESSMENTS: RECOMMENDATIONS FROM THE GLOBAL CEO INITIATIVE ON ALZHEIMER'S DISEASE

Louisa Thompson[1], Dustin Hammers[2], A.M. Barrett[3], Sol Fittipaldi[4], Emily Scholler[5], Chris Butler[6]
[1]Brown University Alpert Medical School, Department Of Psychiatry & Human Behavior, Providence, Rhode Island, United States of America, [2]Indiana University School of Medicine, Department Of Neurology, Indianapolis, United States of America, [3]University of Massachusetts Chan Medical School, Worcester, United States of America, [4]Global Brain Health Institute (GBHI), University Of California San Francisco, San Francisco, San Francisco, United States of America, [5]The Global CEO Initiative on Alzheimer's Disease, Wayne, United States of America, [6]Imperial College London, London, United Kingdom

Aims: New Alzheimer's diagnostic criteria and biomarker guidelines highlight the need for efficient, early screening for cognitive impairment, yet traditional paper-based tools often lack sensitivity, take time, and introduce biases. Digital cognitive assessments (DCAs) offer a promising alternative, potentially addressing these gaps with more sensitive, efficient tools. The Global CEO Initiative on Alzheimer's Disease (CEOi) convened a multidisciplinary workgroup to define minimum standards for DCAs to support their adoption in clinical practice.
Methods: The workgroup is led by clinicians and researchers with expertise in neuropsychology, neurology, and early detection of Alzheimer's disease and related dementias. Following literature review, weekly discussions, and progress meetings, the workgroup defined contexts of use and developed standards for DCAs in primary and specialty care.
Results: The workgroup defined three clinic-based contexts of use for DCAs: 1) detection of possible cognitive impairment in the absence of a recognized concern, 2) confirmation of a diagnosis of either mild cognitive impairment or a dementia syndrome in the presence of a cognitive concern, and 3) evaluation of etiology once cognitive impairment has been confirmed. Target product profiles were drafted for each context of use that include, but are not limited to, target population, test duration, intended use, and accuracy. Ideal test characteristics and validation recommendations related to psychometric integrity, linguistic and cultural applicability, and accessibility were also defined.
Conclusions: Given the limitations of traditional cognitive assessments, integrating high performing DCAs into clinical care may enable a more timely and accurate diagnosis. CEOi DCA Workgroup recommendations will help to establish a framework for standardization and optimize performance in DCA development, as well as facilitate the establishment of standard clinical protocols for their use across a variety of settings.

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CONSISTENT PERFORMANCE IN SUSTAINED ATTENTION ACROSS ONLINE AND IN-PERSON ADMINISTRATION

Emily Thorp[1], Mengdan Xu[2], Laura Keylock[1], Patrick Lown[3,4], Natasha Brooks[5], Fiona Cree[1], Elizabeth Wragg[1], Francesca Cormack[1,6]
[1]Cambridge Cognition Ltd., Cambridge, United Kingdom, [2]Cambridge Cognition Ltd., Toronto, Canada, [3]University of Essex, Department Of Government, Colchester, United Kingdom, [4]University of Essex, Centre For Behavioural Science, Colchester, United Kingdom, [5]University of Essex, Department Of Economics, Colchester, United Kingdom, [6]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom

Aims: Knowledge of the general populations' performance of cognitive test scores assists the interpretation of performances across disease cohorts and in clinical trials. We have previously collected normative data using online platforms, however some cognitive tasks require in-person rater administration, for example for scoring of participant word recall. It is important to evaluate the equivalence of these two methods of data collection. This study aimed to compare data collected from the same task using online versus in-person methods.
Methods: Participants completed CANTAB, online using Cambridge Cognition's secure web-based testing application with participants recruited via Prolific (https://www.prolific.co/) or via in-person rater administration at the ESSEXLab (https://www.essex.ac.uk/centres-and-institutes/behavioural-science/laboratory). Participants provided demographic information (age, sex and highest level of education) and then completed multiple cognitive assessments. This poster focuses on CANTAB® Rapid Visual Information Processing (RVP), a measure of sustained attention, for which scores were available from both normative sample collections. Performance across studies was assessed in key outcome measures for the task using an ANCOVA analysis, adjusting for age.
Results: In the online data collection, 697 participants were recruited (mean age 38.8±12.9, 51% male) and 198 participants were recruited for the in-person data collection (mean age 48.5±17.3, 52% male). Even age distribution was achieved for the in-person data collection due to the targeted participant recruitment across age ranges. RVP Median Latency (RVPMDL) and RVP A' (RVPA) showed no differences in performance between online and in person studies (RVPMDL: $F=1.38$, $p=0.241$, RVPA: $F=0.019$, $p=0.889$).
Conclusions: The method of normative data collection did not impact cognitive test performance and data from both collection methods can be reliably used to assist with the interpretation of performance in the CANTAB® tasks.

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TEST-RETEST RELIABILITY OF CANTAB® SMARTPHONE BATTERY IN HEALTHY ADULT VOLUNTEERS

Emily Thorp[1], Alexander Kaula[1], Nicholas Taptiklis[1], Elizabeth Wragg[1], Francesca Cormack[1,2]
[1]Cambridge Cognition Ltd., Cambridge, United Kingdom, [2]University of Cambridge, Department Of Psychiatry, Cambridge, United Kingdom

Aims: This study investigated a battery of CANTAB® tasks delivered remotely on a smartphone with the aims of estimating psychometric properties, compliance, and acceptability over one week.
Methods: A sample of 150 healthy volunteers aged 18-80 were recruited using the Prolific online platform for short longitudinal study comprising three visits: Familiarisation (Day 0), Baseline (Day 1), and retest at Day 8. The 125 participants (64F, 61M) who completed all three visits were included in this analysis. Each visit, participants carried out a four-task battery consisting of Paired Associates Learning (PAL), Spatial Working Memory (SWM), Match-to-Sample Visual Search (MTS), and Digit-Symbol Substitution (DSST[EW1]). On the final day, a questionnaire was also administered to collect feedback on user experience and acceptability. Visit durations were recorded and assessed. A correlation analysis tested reliability between baseline and retest for key outcome measures in each task, and questionnaire responses were analysed and explored to assess the acceptability of the battery.
Results: Pearson correlations of performance from baseline to retest showed reliability generally in the range of good to excellent, with mean correlations in outcome measures for each task of: PAL, r_p = .64, SWM, r_p = .82, MTS, r_p = .74, and DST, r_p = .83. Visit duration was consistent (M=25.8, SE=0.22 min), as expected. Usability questionnaire responses showed favourable impressions of the battery, with an 'excellent' net promoter score of 54 showing users were overall positively disposed towards the battery, and many participants freely reporting very positive sentiments.
Conclusions: The reliability of the tasks within the battery is very similar to that seen in-clinic. Combined with positive user feedback this supports the remote use of CANTAB® smartphone-based assessments, including in older adults.

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AUGMENTED REALITY AND MACHINE LEARNING-DRIVEN DIGITAL COGNITIVE ASSESSMENT FOR EARLY DETECTION OF MILD COGNITIVE IMPAIRMENT AND NEURODEGENERATIVE DISEASES

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Aims: Traditional cognitive assessments fall short in scalability and in detecting early signs of Alzheimer's disease (AD). Novel machine-learning (ML)-based digital cognitive assessments use objective tasks to generate biomarkers that could enable earlier, precise, and accessible diagnoses. Investigating these tools offers valuable opportunities to advance early detection in neurodegenerative diseases.
Methods: The Altoida NeuroMarker Platform is a tablet-based assessment (iOS) that enables the evaluation of cognitive functional abilities. It involves a 10-minute series of motoric, speech, and augmented reality (AR) tasks, consisting of placing and retrieving virtual objects. It evaluates diverse metrics (accuracy/speed/reaction times/navigation), generating hundreds of digital biomarkers. We tested the Altoida Platform on 70 participants from the SPIN cohort (51.4% female) who received a neurological and neuropsychological evaluation. Amyloid and tau status (Aβ42/40 and p-Tau181) were determined in CSF (Fujirebio). We compared AR average object retrieval times (in seconds) (ARAORT-s), across clinical groups and using biomarker-based classification.
Results: Participants were classified as Cognitively Normal (CN;n=19;66.9 (8.7) years;MMSE: 29.1 (1.1) points;Global Deterioration Scale (GDS)=1) or as having Mild Cognitive Impairment (MCI;n=51;73.5 (5.6) years;MMSE:27.4 (1.8);GDS=3). Participants with MCI took longer time to retrieve the objects compared with CN ($p<0.001$). Within the MCI group, Altoida's digital biomarkers differentiated MCI with AD pathology from MCI due to Lewy Body Disease (LBD) ($p<0.05$), Frontotemporal Lobar Degeneration (FTLD) ($p<0.05$), and non-degenerative causes ($p<0.001$), as well as between A+T+ and A-T- participants ($p<0.01$). **Figure 1.** ARAORT-s in participants classified as CN and with

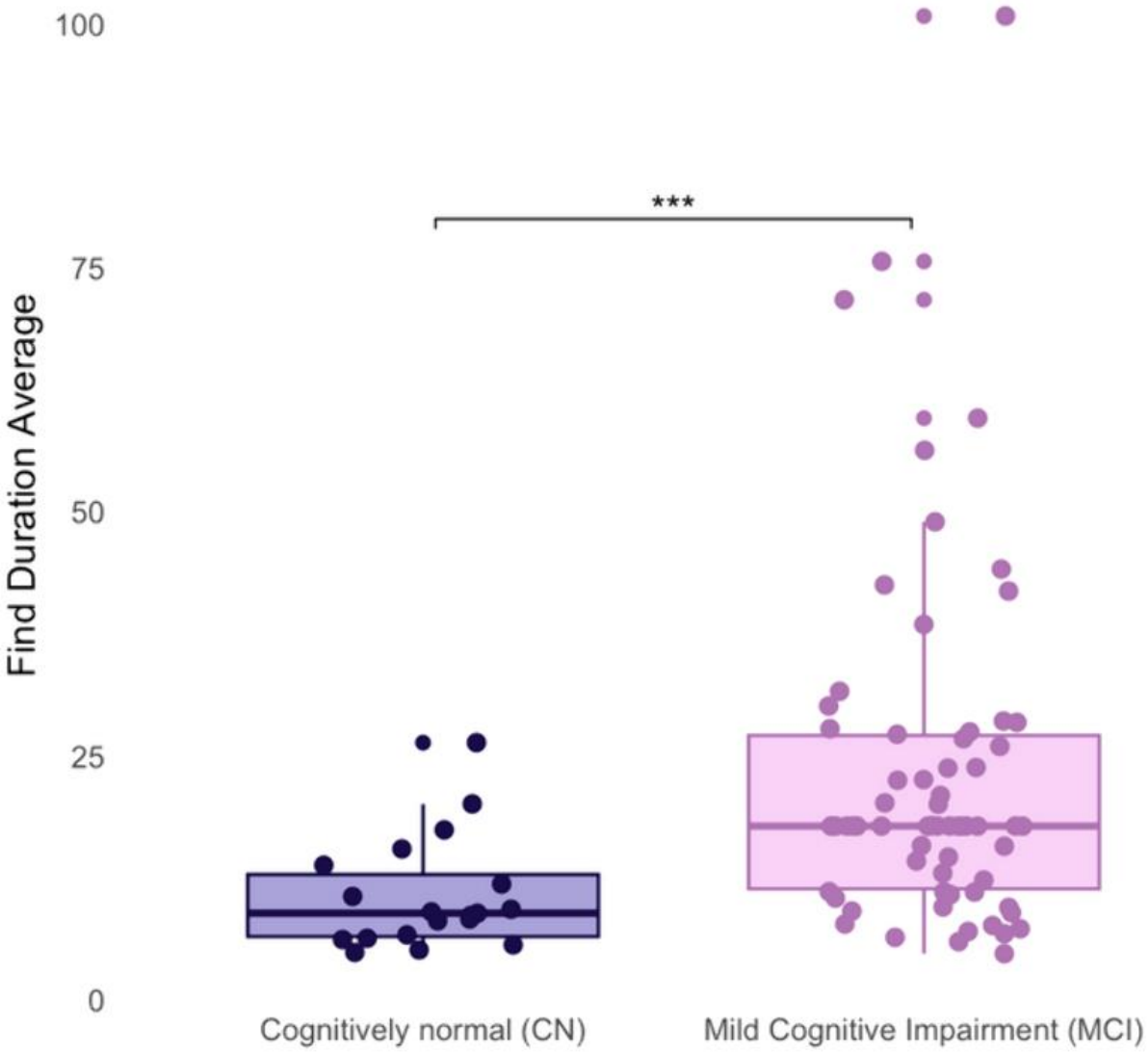


Figure 2. ARAORT-s in participants classified by underlying neurodegenerative condition.

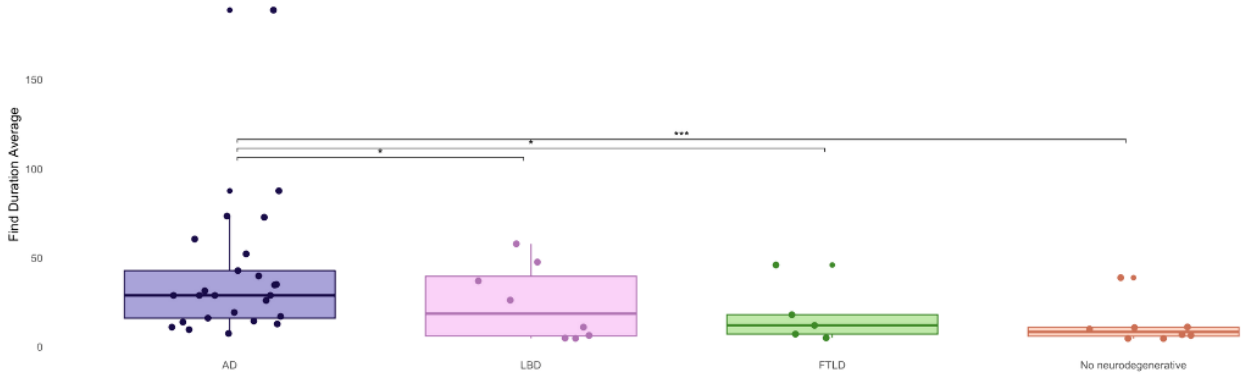
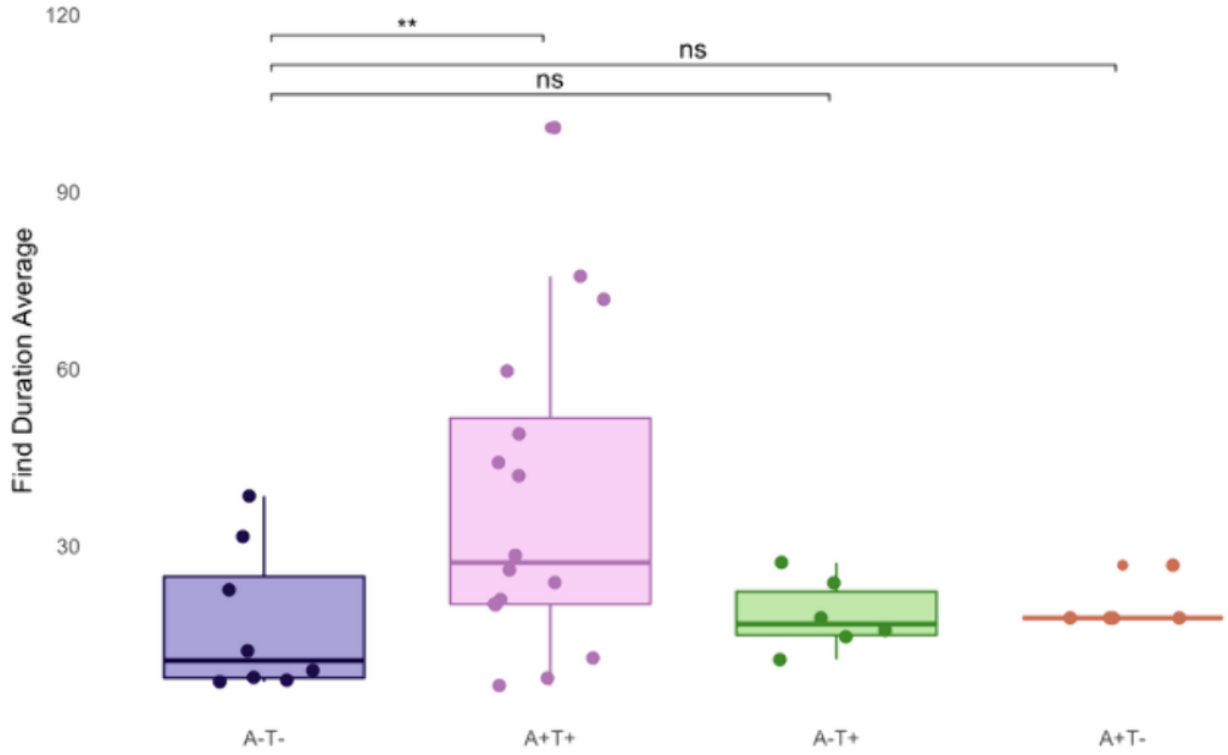


Figure 3. ARAORT-s in participants with MCI classified by CSF A(T) status (A=Aβ42/40;T=p-



Tau181)

Conclusions: Altoida's platform offers a promising solution for the large-scale evaluation of MCI due to different neurodegenerative causes.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
4-5 April 2025

A COMPREHENSIVE EXPLORATION OF THE ASSOCIATION BETWEEN HEARING AND COGNITIVE FUNCTION IN A DANISH COHORT OF OLDER ADULTS

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Aims: Hearing loss is the most prominent sensory impairment in older age. Previous studies have linked hearing loss to an increased risk of cognitive decline in otherwise healthy older adults. This study aims to better characterize this association by more thoroughly examining hearing and cognition in a cohort of older adults.
Methods: This cohort study included 60 adults above the age of 55 years recruited from public outreach. All had Clinical Dementia Rating Score of 0 and Mini Mental State Examination score of 26 or above. Objective measures of both hearing and cognition were included. The measures of hearing included both pure-tone audiometry and speech-in-noise test, including aided speech-in-noise for hearing aid users. Cognition was assessed with a comprehensive battery of tests examining memory functions, processing speed, executive functions, attention, and language.
Results: Significant differences were found between participants with normal hearing and participants with moderate-to-severe hearing loss on several cognitive tests, with participants with moderate-to-severe hearing loss performing significantly worse. Association analyses revealed significant associations between both pure-tone average and speech-in-noise score and tests of attention, working memory, processing speed, and verbal episodic memory, even when correcting for the effect of age. This relationship persisted even when accounting for aided speech-in-noise improvements for the hearing aid users.
Conclusions: This study demonstrates that both central and peripheral hearing processes are associated with cognitive performance in persons without cognitive impairment. The results show that hearing impairment are significantly associated with specific cognitive functions also some which do not depend on audiological processing. In future longitudinal studies, hearing loss and cognitive function should be examined to investigate the development of symptoms across time.

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4-5 April 2025

LANGUAGE CHARACTERISTICS CAN CONTRIBUTE TO THE CLASSIFICATION OF NEURODEGENERATIVE DISORDERS

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Aims: Aphasia impairs language production and comprehension. Evaluating aphasia is challenging owing to varied presentations. We developed the Japanese Language Screen (JLS) to assess 11 language aspects including agrammatism, apraxia of speech (AOS), word recall, syntactic comprehension, meaning of proverbs, and writing, considering the unique features of the Japanese language.
Methods: Using the JLS, we assessed language function in patients with Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), progressive supranuclear palsy (PSP), and healthy controls (HC) to identify language symptoms for each condition and determine whether JLS could differentiate between diseases and HC.
Results: The study included 168 participants. The total JLS score, calculated by adding up the scores of the 11 items, categorized participants' language status as normal or language impairment. According to the total score, PSP had more severe language deficits than AD despite comparable cognitive scores. Substantial language differences in 11 items were found for each disease. AD and PSP showed decreased performance in more than half of the items compared to HC, with the PSP group more impaired. ALS showed decreases in AOS and writing, notably in meaning of proverbs, whereas PD was almost comparable to HC.
Conclusions: A larger sample size is needed, especially for automated analysis and evaluation. This study indicated that the JLS is useful for understanding and classifying neurodegenerative disorders.

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4-5 April 2025

A NON-INVASIVE MASS SPECTROMETRY-BASED PANEL FOR INNOVATIVE ALZHEIMER'S DISEASE STRATIFICATION AND DIAGNOSIS

Florine Leipp[1,2], Jérôme Vialaret[3], Ann-Christin Niehoff[4], Sylvain Lehmann[3], Christophe Hirtz[3]
[1]Shimadzu France, Montpellier, France, [2]CHU Montpellier, PPC Clinical Proteomics Plateform, Montpellier, France, [3]Plateforme de Protéomique Clinique, Irmb - Chu De Montpellier - Hôpital Saint Eloi, Montpellier, France, [4]Shimadzu Europa, Duisburg, Germany

Aims: Current diagnostic methods for Alzheimer's disease (AD) involve invasive cerebrospinal fluid (CSF) collection or costly PET imaging, limiting accessibility. AD and related dementias are complex, with multifaced and intricate symptoms. A plasma-based biomarker panel, including neuroinflammatory and neuronal damage markers, could enable large-scale, non-invasive screening for early diagnosis and disease monitoring. This approach would also aid in characterizing AD subtypes, supporting targeted therapies. By aligning with the ATN(X) classification, this strategy advances personalized medicine and enhances patient care. The study aims to establish a novel diagnostic tool for optimized pathology assessment.
Methods: We developed a multiplex method using 10 µL of plasma, buffered in Tris 300 mM with 9 M Urea. The sample was reduced with 20 mM DTT, alkylated with 100 mM IAA, and heavy-labeled peptides were added for quantification. After overnight digestion with Trypsin/Lys-C, the reaction was stopped with 20% formic acid. Samples were purified using ASSAY-Map RP-S cartridges, dried, and reconstituted in 2% ACN + 0.1% FA. A 45 µL extract was injected in reversed-phase mode using a Shimadzu LCMS 8060NX triple quadrupole coupled with a Nexera Inert liquid chromatography system.
Results: The method was evaluated according to EMA and FDA guidelines for 24 biomarkers, successfully validating 18, including Chromogranin A, Osteopontin, APOE isoforms, Clusterin, Transthyretin, and PARK7. Key performance criteria—linearity, accuracy, precision, stability, sensitivity, and robustness—were met. Validation in a large cross-sectional cohort (n>400) covering various dementia types (AD, MCI, SCI, FTD, DLB) and controls is ongoing.
Conclusions: This study introduces a sensitive plasma-based biomarker panel for non-invasive AD diagnosis, validating 18 targets. It enables large-scale early detection and aligns with the ATN(X) classification for personalized care. Further validation in a larger cohort will confirm its clinical potential.

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Poster on Board - Shift 02
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4-5 April 2025

HIGH-THROUGHPUT PROTEOMIC PROFILING OF CSF TO IDENTIFY BIOMARKERS PREDICTIVE OF NEURODEGENERATIVE DISEASES

Anne-Li Lind[1], Muhammad Ali[2,3], Jigyasha Timsina[2,3], Menghan Liu[2,3], Rawan Tarawneh*[4], Carlos Cruchaga*[2,3,5,6,7], * Co-Last Authors, Contributed Equally[2,4]
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Aims: An understanding of the molecular underpinnings of neurodegenerative diseases (ND) would accelerate the path to precision medicine and drug discovery for patients with ND such as Alzheimer's disease (AD) and Parkinson's disease (PD). Cerebrospinal fluid (CSF), the most proximate biofluid to the brain, can be used to identify biomarkers for the diagnosis and treatment of ND. This study performed high-throughput CSF proteomics from multiple ND cohorts to identify biomarker models predictive of disease.
Methods: A total of 2,229 CSF samples including sporadic AD (n=693), autosomal dominant AD (ADAD, n=295), PD (n=165), Lewy body dementia (DLB; n=35), frontotemporal dementia (FTD; n=48) and cognitively normal (n=993) individuals were analyzed using Olink® Explore HT (5,420 proteins). Differential abundance analyses were performed to identify significantly altered (FDR<0.05) proteins unique to each ND. Significantly altered proteins were leveraged to disentangle differences between NDs, develop disease-specific prediction models, and perform pathway and cell type enrichment analyses.
Results: Differential abundance analyses identified novel common and disease-specific ND proteomic alterations, including 231 unique markers for AD and 20 for ADAD. The correlation in effect size for these proteins suggested high similarities between AD and PD (ρ=0.66) as well as PD and DLB/FTD (ρ=0.73). Iterative Lasso regression models of disease prediction were generated with 1 (FTD) to 20 (ADAD) disease-specific proteins, resulting in ROC values up to 0.95 and a strong ability to distinguish each disease from other NDs (ROC=0.52-0.82).
Conclusions: High-throughput CSF proteomic analysis of NDs facilitated the identification of novel common and disease-specific proteomic alterations that were combined into predictive disease-specific models that distinguished between unique disease states. Olink Explore HT is a powerful tool to reveal true biological insights in CSF and across different disease states.

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FULLY AUTOMATED ULTRA-SENSITIVE FOUR-PLEX SIMOA ASSAY FOR BD-TAU, NFL, GFAP, AND UCH-L1: ENHANCING CHARACTERIZATION OF ALZHEIMER'S PATHOLOGY IN BLOOD

Kishore Malyavantham, Jing Shi, Casey Sheehy, Raymond Fernalld, Danica Wuelfing, Briana Cooper, Julio Herrera
Quanterix, Billerica, United States of America

Aims: To develop an ultrasensitive Simoa four-plex assay that allows for the precise measurement in serum, plasma, and CSF of BD-Tau, NfL, GFAP, and UCH-L1. We further sought to use this assay to interrogate the BioHermes cohort and assess the clinical performance of this assay.
Methods: The two-step bead-based Simoa N4PD digital immunoassay enables simultaneous quantification of BD-Tau, NfL, GFAP, and UCH-L1. Clinical samples from the BioHermes Cohort were analyzed on the HD-X platform.
Results: The assay demonstrated high precision, with LoDs of 0.029 (BD-Tau), 0.094 (NfL), 0.121 (GFAP), and 0.577 pg/mL (UCH-L1) and %CVs <5% (intra-run) and <14% (inter-run). Average levels in plasma for BD-Tau, NfL, GFAP, and UCH-L1 were 7.2, 12.6, 65.4, and 46.2 pg/mL, respectively. The assay achieved >86% spike recovery and dilution linearity from 103% to 122%. Results from the BioHermes cohort showed excellent precision, effectively discriminating PET amyloid positivity with an AUC of 0.67, 0.653, and 0.774 respectively. Whereas, UCH-L1 (being TBI marker) levels did not show correlation to PET amyloid status.
Conclusions: The Simoa N4PD assay enables precise, non-invasive measurement of four key neurodegeneration markers, advancing our capacity to characterize AD, stroke, and other neurological conditions. These ultrasensitive Simoa assays will provide the tools necessary to better elucidate the role and utility of these phosphorylation sites in AD and other neuropathies.

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Poster on Board - Shift 02
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4-5 April 2025

FULLY AUTOMATED ULTRA-SENSITIVE SIMOA ASSAY FOR HIGHLY PRECISE QUANTIFICATION OF STREM-2 IN HUMAN PLASMA AND CSF

Kishore Malyavantham, Shubhankar Nath, Hana Na, Nikita Kulkarni, Molly Weik, Jalpa Patel, Hong Ni
Quanterix, Billerica, United States of America

Aims: Soluble Triggering Receptor Expressed on Myeloid Cells 2 (sTREM-2) is a ~25 kDa soluble form of the transmembrane protein TREM-2, primarily found on myeloid cells and generated via a proteolytic cleavage. TREM-2 plays a key role in activating and sustaining myeloid cells, including macrophages across tissues. sTREM-2 is increasingly recognized as a biomarker for neuroinflammatory and neurodegenerative diseases, indicating microglial activation. Elevated sTREM-2 levels are associated with early Alzheimer's Disease (AD), Parkinson's, Frontotemporal dementia, ALS, multiple sclerosis, cancer, and atherosclerosis, linking it to disease progression and severity.
Methods: The Simoa sTREM-2 assays are a three-step digital sandwich immunoassay employing paramagnetic beads with capture antibodies and biotinylated detector antibodies. Digital detection is mediated by Streptavidin-ß-galactosidase (SβG) and Resorufin-β-D-Galactopyranoside (RGP), amplifying specific sTREM-2 immune complexes immobilized on the bead surface.
Results: sTREM-2 was quantifiable in EDTA-plasma and CSF, with an LLOQ of 4.12 pg/mL and a detection limit of 0.905 pg/mL. Normal sTREM-2 levels were ~2045 pg/mL in plasma and ~1771 pg/mL in CSF. The assay showed a 4-log dynamic range with dilution linearity within 80-120%. Spike recovery was ~85% for plasma and ~105% for CSF. The assay is compatible with HD-X and SR-X platforms.
Conclusions: The Simoa sTREM-2 Advantage PLUS assay offers exceptional analytical sensitivity (LLOQ of 4.12 pg/mL) and a 4-log dynamic range, ensuring precise quantification in plasma and CSF. Its ultrasensitive detection from minimally invasive blood samples reduces the need for CSF collection, facilitating easier biomarker profiling. The assay's high specificity, reproducibility, and compatibility with HD-X and SR-X platforms make it an ideal tool for rigorous preclinical research. It enables researchers to explore the role of sTREM-2 in neuroinflammation and neurodegeneration, providing valuable insights into disease mechanisms and biomarker discovery.

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4-5 April 2025

PERFORMANCE OF ALZPATH PTAU217 IN A CLINICAL LABORATORY

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Aims: Blood-based biomarkers will be essential for providing clinicians an accessible and cost-effective Alzheimer's disease (AD) screening tool. Elevated levels of phosphorylated Tau at 217 (p-Tau217) correlates with amyloid and tau-PET consistent with AD diagnosis. We aimed to evaluated the analytical and clinical performance using a high-sensitivity methodology (Simoa®) in a clinical (CLIA-certified) laboratory.
Methods: Plasma pTau217 levels were measure using the ALZpath pTau217 assay on the Quanterix HD-X Simoa® platform. Analytical performance including sensitivity, linearity, precision, accuracy, cross-reactivity, interference, and sample stability was determined at Neurocode's CLIA laboratory using CLIA guidelines. Clinical testing was performed using CSF and neuropathology confirmed samples collected from the University of British Columbia (UBC) at the time of initial diagnosis (N = 119).
Results: The precision of ALZpath p-Tau217 using SIMOA is < 10% intra-laboratory coefficient of variation within and below reagent lots. No interference was observed for bilirubin, hemoglobin, intralipid, biotin, or heterophilic antibodies. The normal reference range based on an amyloid PET negative healthy aging cohort was determined to be ≤ 0.46 ng/L. The sample stability was determined to be ≤ 7 days at 2-8^{0}C or room temperature, allowing for ambient shipping and reduced pre-analytical error due to stability. The intermediate zone was established as between 0.34 – 0.63 ng/L based on an amyloid PET confirm cohort and constitutes around 20% of patients tested.
Conclusions: In conclusion, ALZpath pTau217 advocates shows robust performance in the clinical laboratory for patient testing. Plasma pTau217 is a reliable biomarker that can be used by clinician for accurate and reliable Alzheimer's disease diagnosis.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
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IDENTIFICATION OF DIFFERENTIALLY ABUNDANT PROTEINS IN ALZHEIMER'S, SYNUCLEIN, AND VASCULAR PATHOLOGIES USING THE NULISA PROTEOMICS PLATFORM

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Aims: The NIA-AA guidelines now emphasize the role of co-pathologies, such as synucleinopathy and vascular pathology, in the diagnosis and staging of Alzheimer's Disease (AD). However, distinguishing these pathologies, along with amyloid pathology, remains challenging. This study aims to identify proteins within the NULISA Panel that can differentiate amyloid, synuclein, and vascular pathology in cerebrospinal fluid (CSF) and plasma samples.
Methods: Proteins from the NULISA CNS-panel were measured in CSF and plasma samples from 749 participants in the Swedish BioFINDER-1 and BioFINDER-2 cohorts covering the whole AD continuum. Differentially abundant proteins in AD pathology (as presence of amyloid and tau pathology), synuclein pathology (defined by the synuclein seed amplification assay [SAA]), and vascular pathology (defined as white matter lesion [WML] volume >0.59% of intracranial volume) were assessed using linear models including presence/absence of all three pathologies as independent variables in a single model, adjusting for age, sex, and average protein levels.
Results: The study included 161 participants with AD pathology, 241had synuclein pathology and 241 showed signs of WML pathology (Table 1). P-tau217, p-tau181, and p-tau231 were strongly correlated with AD-pathology in both CSF and plasma $3.831<\beta std<5.637$, $p<0.0001$). Synuclein pathology was highly associated with CSF DDC ($\beta std =7.01$, $p<0.001$), and moderately associated with plasma NPY and VCAM1 ($\beta std=-3.11$ and 2.64, $p<0.05$). In CSF, NPTX2, NPTX1, and NPTXR were negatively associated with WML ($-2.09>\beta std>-2.41$, $p<0.0001$), whereas NEFL, PGF, and POSTN were positively associated with WML

(2.45<βstd<2.30, p<0.0001). In plasma, only NEFL showed a positive association with WML (βstd = 0.17, p<0.005; Figure 1].

	TOTAL	ALZHEIMER'S DISEASE PATHOLOGY		SYNUCLEIN PATHOLOGY		WHITE MATTER LESIONS	
		NEGATIVE	POSITIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE
	No. 749	No. 588	No. 161	No. 508	No. 241	No. 508	No. 241
Age at baseline (years)	74.24 (67.95 - 77.97)	74.42 (67.74 - 77.95)	74.11 (69.26 - 78.18)	74.01 (67.16 - 77.98)	74.61 (69.89 - 77.84)	73.00 (66.05 - 77.43)	76.45 (72.92 - 79.31)
Sex- Male [N(%)]	398 (53.14%)	324 (55.10%)	74 (45.96%)	250 (49.21%)	148 (61.41%)	243 (47.83%)	155 (64.32%)
APOE ε4 positivity [N (%)]	360 (48.06%)	306 (52.04%)	54 (33.54%)	241 (47.44%)	119 (49.38%)	224 (44.09%)	136 (56.43%)
MMSE	28.00 (26.00 - 29.00)	28.00 (27.00 - 29.00)	25.00 (20.00 - 27.00)	28.00 (26.00 - 29.00)	27.00 (24.00 - 29.00)	28.00 (26.00 - 30.00)	27.00 (24.00 - 29.00)
mPACC	-0.93 (-1.97 - -0.13)	-0.67 (-1.59 - 0.04)	-2.29 (-3.60 - -1.32)	-0.66 (-1.68 - 0.02)	-1.57 (-2.72 - -0.56)	-0.63 (-1.65 - 0.08)	-1.54 (-2.44 - -0.60)
Missing	85 (11.35%)	51 (8.67%)	34 (21.12%)	46 (9.06%)	39 (16.18%)	53 (10.43%)	32 (13.28%)

Table 1: Data shown as mean (95%CI) unless specified otherwise. Abbreviations: APOE, apolipoprotein E; MMSE, Mini-Mental State Examination; MPACC, Memory and Processing Accuracy Cognitive Composite; SUVR, standardized uptake value ratio. a. Amyloid positivity determined by F Amyloid positivity determined by [^{18}F]flutemetamol SUVR >1.033 (BF2) or >1.138 (BF1), or CSF Ab42/40 < 0.072 (Lumipulse G) b. Tau positivity defined by [^{18}F]RO948 tau-PET Braak I-IV SUVR > 1.362 c. WML positivity set at >0.59% of ICV d. Data missing for 25 participants on CSF measures

Figure 1: Volcano plots show proteins associated with Alzheimer's Disease, synuclein, and vascular pathology in a) CSF and b) Plasma. The x-axis represents the βstd values, indicating the strength and direction of the association, while the y-axis shows the -log10 p-values, highlighting statistical significance. The models are adjusted for age, sex, and average protein level. The dashed lines represent significance threshold at α=0.05 after FDR correction. Proteins below the p[FDR]<0.05 threshold were considered significant. Positive βstd values, colored in red, indicate higher protein abundance in the presence of the pathology, while negative values, colored in blue, indicate lower abundance.

Conclusions: Plasma and CSF biomarkers from the NULISA CNS-Panel provide insights into neurodegenerative disease processes. Further validation is needed for clinical application.

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SHIFT 02-359

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4-5 April 2025

PLASMA PTAU DISCRIMINATORY CAPACITY: EFFECT OF APOE, SEX, AGE AND COGNITIVE STATUS.

Carmen Peña Bautista[1], Lourdes Álvarez-Sánchez[2], Laura Ferré González[1], Mar Peretó[1], Lorena García[1], Miquel Baquero[3], Consuelo Cháfer Pericas[1]
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Aims: The main objectives of this work were to: i) evaluate and compare the capacity of plasma pTau biomarkers to discriminate AD, controls and other dementias; ii) establish the optimum cut-off points for each plasma pTau and the effect of risk factors (ApoE, sex, age) on the discriminatory capacity; iii) evaluate the association of plasma pTau biomarkers with AD pathology state and stage.
Methods: pTau181 levels were determined by Simoa and pTau217 by Fujirebio in 259 patients from a clinical cohort. There were included classified in AD (n=127) (including preclinical (n=9), MCI (n=98), dementia (n=20)), controls (n=57) and other dementias (n=75) (including DFT (n=15), vascular (n=8), DLB (n=2), and MCI due to other causes (n=50)). The discriminatory capacity was evaluated by ROC Curve and the optimum cut-offs were stablished as the maximum sum sensitivity and specificity.
Results: Plasma pTau181 and pTau217 showed an AUC of 0.86 and 0.93, respectively, discriminating AD from non-AD patients. This discriminatory capacity increased between AD and controls (AUC 0.89 and 0.95) and decreased between AD and other dementias (AUC 0.83 and 0.92). The evaluated risk factors (ApoE genotype, sex and age) modify the optimum cut-offs. Both pTau217 and pTau181 showed a high correlation with CSF biomarkers and cognitive status. However, pTau181 showed a stronger dependence on disease stage, while pTau217 more adequately determined amyloid status.
Conclusions: Plasma levels of pTau181 and pTau217 showed a high discriminatory capacity between AD and non-AD. Although ApoE, sex and age had an effect on the cut-offs, the discriminatory capacity did not change substantially when taking them into account. In addition, pTau181 and pTau217 could be indicative of pathology stage and amyloid status, respectively. However, further studies are required to confirm these preliminary results.

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SHIFT 02-360

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

CSF SERPINE1 LEVELS CORRELATE WITH ALZHEIMER'S DISEASE NEUROPATHOLOGY AND SLEEP DISTURBANCES IN PRESYMPTOMATIC INDIVIDUALS

Cynthia Picard[1], Andrée-Ann Baril[2], Béry Mohammediyan[1], Anne Labonté[1], Henrik Zetterberg[3], Kaj Blennow[3], Sylvia Villeneuve[1], Judes Poirier[1]
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Aims: The plasminogen activator system is pivotal in various physiological and pathological processes, encompassing coagulation, fibrinolysis, inflammation, wound healing and malignancy. SERPINE1, also known as plasminogen activator inhibitor (PAI), was shown to increase gradually in blood samples from controls, MCI and AD patients. Higher blood SERPINE1 levels were also correlated with sleep disturbances, which are increasingly associated with AD pathology. To validate that SERPINE1 could be used as an early AD biomarker with links to sleep perturbations, we turned to the PREVENT-AD cohort, where asymptomatic participants are at-risk of developing AD due to one or more relatives being affected by the late-onset sporadic form of the disease. We measured SERPINE1 protein levels in the CSF and compared it to AD biomarkers and sleep patterns.
Methods: CSF SERPINE1 protein levels were measured with the PEA technology from OLINK (Sweden). CSF AD biomarkers Aβ42, pTau181 and total Tau were measured by ELISA (Fujirebio, Sweden). Synaptic proteins GAP43, SNAP25 and SYT1 were immunoprecipitated and their concentrations measured by mass spectrometry. Hippocampal volumes were acquired using standardised MRI procedures whereas sleep patterns were assessed by actigraphy and with the concomitant use of a sleep diary.
Results: At the pre-clinical stage, CSF SERPINE1 levels correlate with early signs of neurodegeneration, namely with elevated levels of CSF pTau ($p<0.005$), total Tau ($p<0.001$) and with the synaptic markers GAP43 ($p<0.005$), SNAP25 ($p<0.005$) and SYT1 ($p<0.01$). Furthermore, CSF SERPINE1 levels show an inverse correlation with hippocampal volume ($p<0.0005$). The following sleep patterns were also associated with CSF SERPINE1 levels: sleep onset latency ($p<0.05$), fragmentation ($p<0.01$) and sleep efficiency ($p<0.01$).
Conclusions: Alterations in sleep patterns, hippocampal volume and CSF AD proteins can be detected before the emergence of AD symptoms.

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SHIFT 02-361

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

THE RELATIONSHIP BETWEEN DEMENTIA AND INSULIN-LIKE GROWTH FACTOR-1 OF THE ENGLISH LONGITUDINAL STUDY OF AGEING

Jermaine Ross, Mohamedi Kagalwala, Yoonjeong Cha
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Aims: Insulin-like Growth Factor-1 (IGF-1) plays a significant role in the regulation of aging. However, due to inconsistencies between studies, the relationship between IGF-1 and memory remains elusive. This study aims to determine whether IGF-1 levels affect the risk of dementia in participants of the English Longitudinal Study of Ageing (ELSA).
Methods: We accessed the ELSA data from the Dementias Platform UK (DPUK) Data Portal. We analyzed serum IGF-1 levels from 6,288 participants collected during Wave 4 of ELSA, the baseline timepoint for IGF-1 measurement. Baseline differences were characterized across sex-specific quintiles of IGF-1. We employed linear regression models to estimate trends in IGF-1 and cognitive performance over time. Cognitive domain changes were explored both individually (orientation, delayed recall, and executive cognitive function) and as a composite measure.
Results: In cognitively normal participants, we observed an age-related decline in IGF-1 ($p < 0.0001$) and cognitive ability (composite score, $p < 0.0001$). As expected, subjects diagnosed with dementia had significantly lower cognitive performance (composite score, $p < 0.0001$) compared to healthy controls. These significant functional differences extended to individual cognitive domains. Age-matched groups revealed lower levels of IGF-1 in subjects diagnosed with dementia compared to healthy controls ($p < 0.01$). In contrast, subjects with a cognitive score below 10 (range 0–23) had significantly lower IGF-1 levels ($p < 0.001$). We also observed similar trends with poor cognitive scores at the individual domain level, further suggesting that clinical diagnosis may not fully capture the neural correlates associated with IGF-1.
Conclusions: Our analyses revealed a relationship between functional cognitive scores and IGF-1. Given the current emphasis on developing dementia biomarkers, these results suggest that IGF-1 could serve as a potential surrogate blood-based marker for cognitive decline.

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SHIFT 02-362

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

ULTRASENSITIVE DETECTION OF BLOOD-BASED PTAU 217 USING SINGLE-MOLECULE COUNTING TECHNOLOGY: ADVANCING SAMPLE ACCESS IN ALZHEIMER'S DISEASE RESEARCH

Gipshu Dave[1], Mariya Soban[1], Kumiko Hamano[2], Yukina Kawada[2], Ko Kobayashi[1], Masayasu Imaizumi[2], Kazushige Moriyama[2], Katsumi Aoyagi[2], Frank Zaugg[1], Peter Wagner[1], Johanna Sandlund[1], Renee Tobias[1], Valerie Brachet[1]
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Aims: Blood-based detection methods may provide a less invasive and more accessible alternative to traditional imaging or cerebrospinal fluid assessments in Alzheimer's disease (AD). This approach holds promise as a scalable tool for clinical management and trials in AD research. Phosphorylated tau at threonine 217 (pTau217) is closely associated with key AD neuropathological hallmarks, including amyloid status. We have developed a novel ultrasensitive blood-based pTau217 immunoassay, utilizing single-molecule counting technology (Fluxus, Inc., Sunnyvale, CA, USA). Here, we report key performance characteristics of the pTau217 assay and compare quantified clinical sample values across different sample types and other commercially available technologies.
Methods: The pTau217 assay was developed using high-performing anti-pTau217 monoclonal antibodies (Fujirebio, Inc., Tokyo, Japan), with capture antibodies immobilized on magnetic beads and detection antibodies linked to a fluorescent reporter. After multiple incubation and wash steps, immune complexes were dissociated, and the fluorescent reporters were injected into an ultrasensitive optofluidic device for single-molecule counting. Key performance characteristics, including limits of detection (LoD), quantification (LoQ), dynamic range, linearity, and precision, were assessed. Clinical sample testing comparisons of sample types and technologies are ongoing.
Results: The pTau217 assay demonstrated excellent analytical sensitivity, achieving an LoD and LoQ of 0.005 and 0.02 pg/mL, respectively, with a working range spanning five logs (0.0156–1,024 pg/mL). The mean intraassay CV was 4.5% and the interassay CV was 10.9%.
Conclusions: The development of an ultrasensitive pTau217 assay in blood offers a less invasive, more accessible, and scalable method for sample collection, with potential utility in AD management and clinical trials.

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SHIFT 02-363

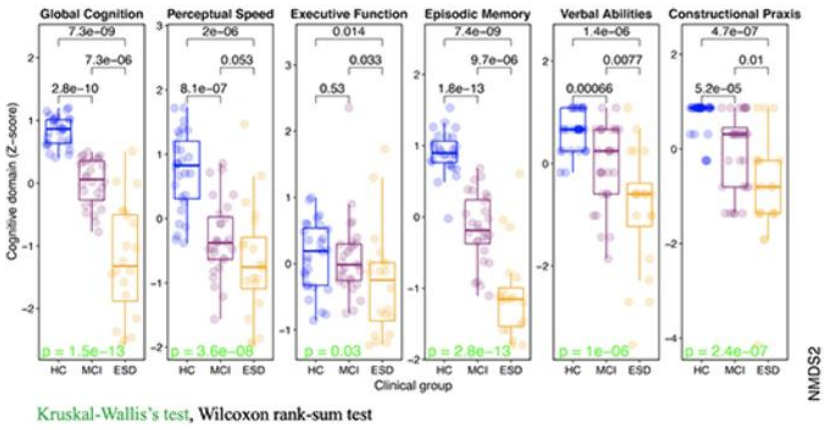
Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

COGNITIVE TEST PERFORMANCE AND ASSOCIATED BRAIN AND INFLAMMATORY BIOMARKERS IN NEUROCOGNITIVE DISORDERS

Kseniya Simbirtseva[1], Suzanne Timmons[2], Paul O'Toole[1], Junhui Li[1]
[1]University College Cork, Apc Microbiome Ireland, Cork, Ireland, [2]University College Cork, Centre For Gerontology And Rehabilitation, School Of Medicine, Cork, Ireland

Aims: This study investigates the relationships between cognitive test performance, brain and inflammatory biomarkers in individuals with neurocognitive disorders (NCDs), exploring their correlation with cognitive function across clinical groups: cognitively healthy (HC), mild cognitive impairment (MCI), and early-stage dementia (ESD).
Methods: A cohort of 77 participants (HC=29, MCI=28, ESD=20), aged over 60, underwent cognitive assessments using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery and five additional cognitive tests. Raw scores from the CERAD subtests (excluding the Mini-Mental State Examination (MMSE)) and single tests were standardized into Z-scores. Global cognition (MMSE and CERAD-total score) and individual cognitive domains were analysed. Plasma samples were measured for amyloid-beta42 (Aß42), amyloid-beta40 (Aß40), pTau181, pTau217, GFAP, NfL using ultrasensitive Simoa immunoassay technology. Inflammatory cytokines were analyzed using V-PLEX multiplay assay kits (Meso Scale Discovery).
Results: Cognitive domain scores (average Z-score) differed across clinical groups, explaining 29.3% of variance (p=0.001), with significant effects from age, gender, education, and Health Food Diversity index (Image1). Group differences were significant for GFAP, NfL, and both phospho-tau markers (p=0.002), but not Aß42 or amyloid ratios. The non-amyloid brain biomarkers correlated with raw scores from CERAD subtests and with cognitive domains: particularly global cognition, perceptual speed, and episodic memory ($p<0.05$). Elevated IL-10, IL-6, and TNF-α levels were observed in ESD and/or MCI vs HC ($p<0.05$). pTau181 correlated positively with IL-31 and IL-10, linking tau pathology to inflammatory responses ($p<0.05$; Image2). pTau217 had slightly more correlations with cognitive tests than pTau181, but both markers performed similarly.

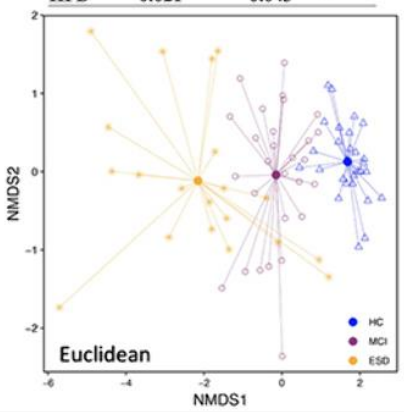
Cognitive domains (average Z-score) across clinical groups



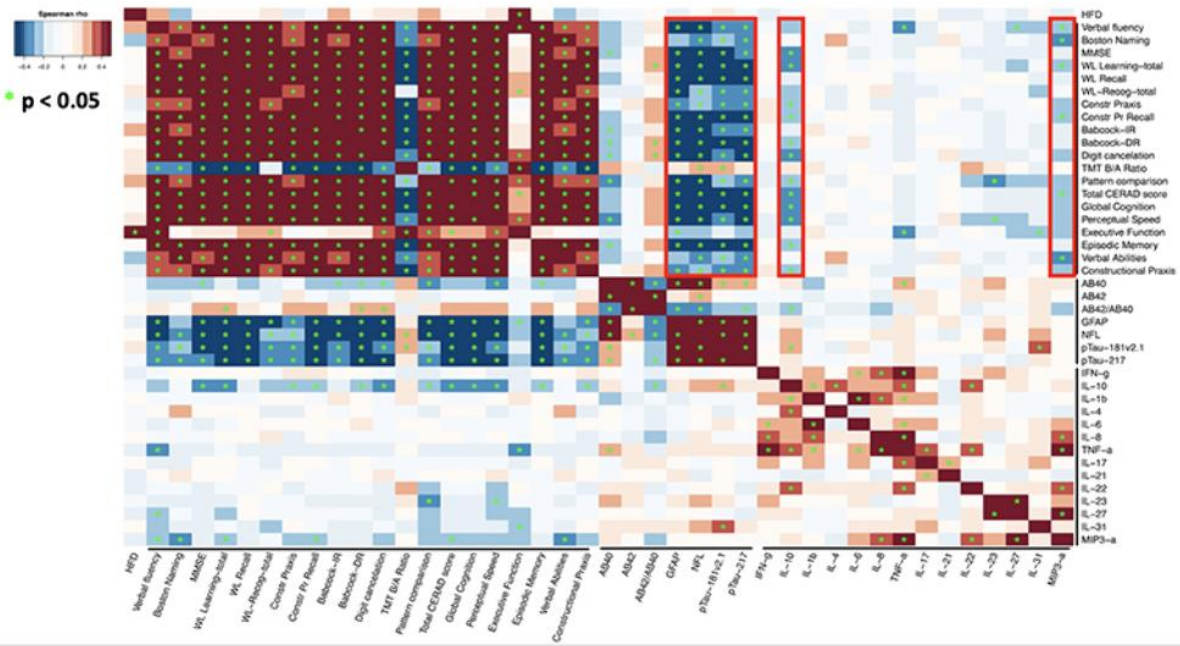
Kruskal-Wallis's test, Wilcoxon rank-sum test

PERMANOVA

	R^2	P-value	
Group	**0.293**	**0.001**	***
Gender	**0.019**	**0.040**	*
Age	**0.026**	**0.024**	*
BMI	0.009	0.226	
Education	**0.025**	**0.026**	*
HFD	**0.021**	**0.043**	*



Spearman associations between Cognitive tests, Brain markers, and Cytokines



Conclusions: Impaired cognitive performance is associated with elevated brain biomarkers and inflammatory cytokines, which emphasizes the role of inflammation and neurodegeneration in cognitive decline, suggesting the potential of these markers for tracking NCD progression.

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SHIFT 02-364

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

CHANGES IN THE CA2+ ACTIVITY OF PIEZO1 RECEPTORS IN RED BLOOD CELLS AS A NOVEL FUNCTIONAL HALLMARK FOR ALZHEIMER'S DISEASE

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Aims: Emerging evidence suggests that impaired microcirculation contributes to Alzheimer's disease (AD) pathology exaggerating neurodegeneration due to a limited supply of nutrients and oxygen to affected brain areas. This may require adaptation of RBC to squeeze through narrowed capillaries in the microcirculatory bed. Here, we hypothesized that, in AD patients, RBCs are undergoing modifications in the expression and function of calcium-permeable mechanosensitive Piezo1 channels which control the flexibility of these cells.
Methods: To assess the function of Piezo channels, we either measured using a flow cytometry assay, Yoda1-induced Piezo1-mediated calcium responses in RBCs of healthy individuals (HC), patients with mild cognitive impairment (MCI), and AD patients or tested the physical properties of the RBCs with a novel micropipette aspiration technique. We used a machine learning tool to evaluate whether the Ca^{2+} flux in RBCs outperforms the measurement of conventional AD-biomarker in plasma and provides additional benefit for clinicians in diagnosing patients with early AD-related dementia.
Results: RBCs obtained from patients with MCI and AD patients showed significantly higher calcium responses to the Piezo agonist Yoda1, compared to RBCs from age-matched HC suggesting enhanced function of Piezo1 channels in AD pathology. RBC membrane incubated with Aβ showed significantly higher activated pressure during aspiration and increase in deformability of the membrane. Interaction analysis performed based on the medical information of the patients demonstrated that Yoda1-induced Ca^{2+} flux provides significant benefit for detecting AD cases from healthy individuals.

Conclusions: Together, our data suggest a significantly altered function of Piezo1 channels in peripheral circulation which might be an adaptive reaction to the impaired microcirculation, and therefore, Yoda1 elicited activation of Piezo1 in RBCs may be used as a functional biomarker for early AD.

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SHIFT 02-365

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

EVALUATING PLASMA BIOMARKERS AS EARLY PREDICTORS OF AMYLOID AND TAU PET PATHOLOGY IN ALZHEIMER'S DISEASE

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[1]University of California San Francisco, Department Of Radiology And Biomedical Imaging, San Francisco, United States of America, [2]Department of Veterans Affairs Medical Center, Northern California Institute for Research and Education (NCIRE, San Francisco, United States of America

Aims: To investigate how plasma biomarkers from Roche (Aβ42/40 and p-tau181) and C2N (p-tau217 and %p-tau217) reflect PET-detectable amyloid and tau brain pathology. With increasing evidence that plasma biomarkers may change before PET-detectable pathology appears, we also assessed how early and to what extent plasma biomarker changes signal amyloid and tau PET accumulation.
Methods: Data from 220 ADNI subjects were analyzed with partial least squares regression (PLSR) to examine associations between plasma biomarkers and multimodal PET. A product space, defined by the convex combination of whole-brain amyloid and tau PET data, was constructed to evaluate the relationship with plasma biomarkers. Analysis was repeated at three PET scan time points: within 6 months of plasma collection, 18-30 months post-collection, and 42-54 months post-collection.
Results: Aβ42/40 levels were best explained (R^2=0.324) by a 60% amyloid and 40% tau PET weighting, peaking four years post-sample collection. Both p-tau181 and %p-tau217 levels showed highest explainability (R^2=0.418 and R^2=0.633, respectively) with a 40% amyloid and 60% tau PET weighting two years post-collection, while p-tau217 was maximally explained (R^2=0.587) at sampling with a 30% amyloid and 70% tau PET weighting. Figure 1 previews these relationships for Aβ42/40 and %p-tau217 across PET scan intervals.

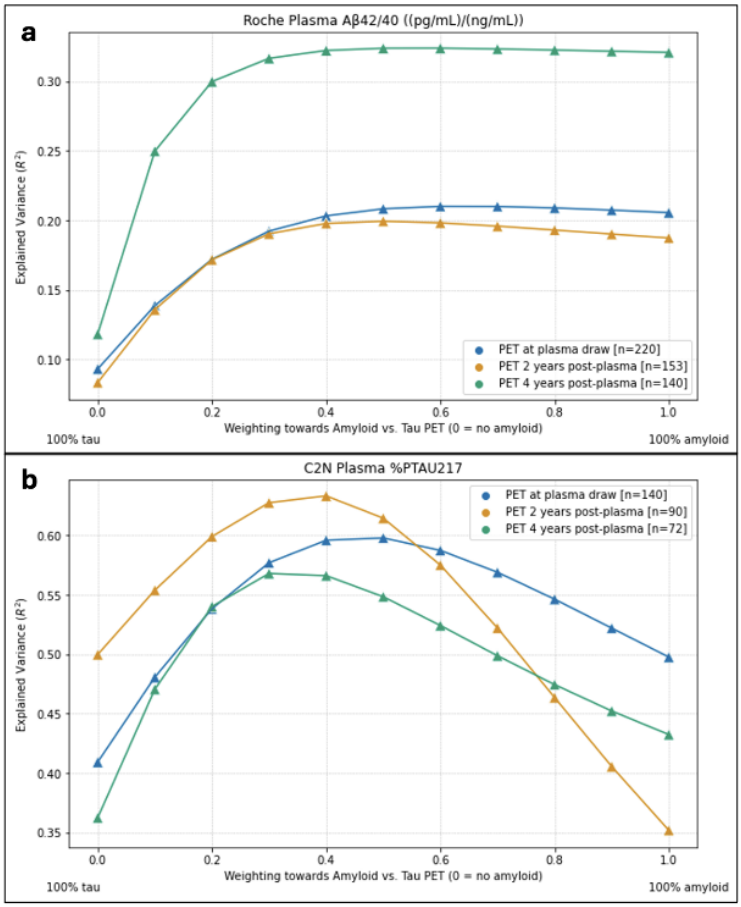

Figure 1: Variance explained (R^2) by amyloid and tau PET in plasma biomarkers Aβ42/40 (a) and %p-tau217 (b) across PET imaging time points relative to plasma sampling (at draw, 2 years post, and 4 years post). The x-axis represents the weighting between amyloid and tau PET (0 = no amyloid, 1 = all amyloid), illustrating how plasma biomarkers relate to concurrent and future PET-detectable pathology.

Conclusions: These findings indicate that PET-detectable amyloid and tau accumulation explain plasma biomarker levels, with optimal associations for Aβ42/40, p-tau181, and %p-tau217 occurring 2–4 years post-plasma collection, and for p-tau217 around collection time. The specific associations of Aβ42/40 and p-tau181 with amyloid, versus p-tau217 and %p-tau217 with tau, suggest plasma biomarkers reflect specific stages of PET-detectable pathological changes. The high explainability of %p-tau217, potentially detectable two years in advance, highlights the importance of timing when using plasma biomarkers as surrogates for PET imaging in Alzheimer's research.

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SHIFT 02-366

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

ULTRA-SENSITIVE DIFFERENTIATION OF PTAU 217 IN MCI AND DEMENTIA PATIENTS: COMPARING AMYLOID PET NEGATIVE AND POSITIVE RESULTS

Tsz Wing Fan, Corinne Thomas, Wonhee Kim, Feng Xuan
Spear Bio, Woburn, United States of America

Aims: Research on neurodegenerative blood-based biomarkers requires fg/mL sensitivity to overcome blood-brain barrier dilution. Current ultra-sensitive technologies need high sample volumes, high-affinity antibodies, immobilization of target binding reagents, stringent washing, and rely on proprietary instrumentation. This limits frequent longitudinal monitoring and population-scale screening, highlighting the need for a scalable ultra-sensitive solution.
Methods: SPEAR utilizes unique two-factor authentication mechanism for attomolar detectability from 1 µL of sample, employing a 3-step, wash-free workflow with readout on qPCR. SPEAR pTau 217 was evaluated for differentiation of PET negative and positive (samples from GAP), comparing sensitivity, specificity, and foldchange to a comparator pTau217 assay using a competitive immunoassay platform.
Results: SPEAR pTau 217 quantified all samples above the functional lower limit of quantitation (LLoQ), whereas the comparator assay quantified 88% of samples (2% above the upper limit of quantitation (ULoQ); 10% below the LLoQ). SPEAR demonstrated nearly double the fold increase of PET positive results over PET negative compared to comparator assay, with a 4.7-fold increase versus 2.5-fold. A single cutoff yielded 89.5% sensitivity, 95.5% specificity, 96.2% positive predictive value (PPV), and 87.5% negative predictive value (NPV). Optimizing for specificity and sensitivity to be 95% or higher for both comparator and SPEAR pTau 217 exhibited a reduction from 24.8% to 15.7% for the indeterminant range with the SPEAR assay.
Conclusions: SPEAR pTau 217 exhibited exceptional analytical sensitivity, quantifying all tested samples and providing clear clinical differentiation between PET positive and negative cases with 4.7x change. Clinical sensitivity and specificity optimized for 95% resulted in 1.6 fold reduction of indeterminant range compared with the comparator. Its features, including 25-100 times less sample volume, wash-free workflow, and compatibility with standard qPCR instruments, make SPEAR accessible and scalable for neurological studies.

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Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

DEVELOPMENT OF A BLOOD TEST FOR DEMENTIA PREVENTION: ASSOCIATIONS WITH LIFESTYLE-RELATED DISEASES AND MIDLIFE LIFESTYLE FACTORS

Kazuhiko Uchida, Kenji Tayama, Shan Liu, Toshie Shinagawa
MCBI, Inc, Research Division, Tokyo, Japan

Aims: Key risk factors for Alzheimer's disease (AD) are linked to lifestyle-related diseases and midlife lifestyle factors. In our previous study, we identified nine plasma proteins as potential biomarkers for cognitive impairment[1)]. This study aims to examine the relationships between these biomarkers and various risk and protective factors to develop methods for assessing and preventing dementia risk.
Methods: We analyzed the plasma protein levels of nine biomarkers in a cohort of 1,739 participants over the age of 55. Data from annual health examinations, clinical records, and lifestyle questionnaires were also examined to assess associations between these biomarker levels and various lifestyle or medical factors. Composite scores calculated from these biomarker levels were used to categorize participants and analyze risk.
Results: Participants were divided into two groups: a low-risk group with lower scores and a high-risk group with scores above the cut-off levels used to differentiate cognitive impairment from normal cognition. In the high-risk group, compared to the low-risk group, the odds ratio for dementia cases was 2.88 (CI: 1.34–5.85, P=0.005). Composite scores were significantly higher among participants with diabetes mellitus (P=0.00121; CI=-0.0993, -0.0245), hypertension (P=1.56E-07; CI=-0.131, -0.0599), and hyperlipidemia (P=0.03; CI=-0.0747, 3.58E-3) compared to those without these conditions. Notably, among participants with these medical histories, those with a history of medication use showed a significant decrease in composite scores for hypertension (P=0.02912; CI=0.00518, 0.0968), hypertension with systolic blood pressure under 150 mmHg (P=0.0112; CI=0.01428, 0.110), and hyperlipidemia (P=0.0492; CI=1.73E-4, 0.101).
Conclusions: Our findings suggest that proactive management of lifestyle-related diseases in middle age may contribute to dementia prevention. Additionally, the blood test used in this study presents a potential tool for developing individualized strategies for dementia prevention. *1) Int. J. Mol. Sci.* **2023**, doi:10.3390/ijms241713064

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4-5 April 2025

A NOVEL PLASMA PTAU231 PROTOTYPE ASSAY ON THE FULLY AUTOMATED LUMIPULSE® G PLATFORM

Jeroen Vanbrabant[1], Charlotte Lambrechts[1], Cindy François[1], Daniel Antwi-Berko[2], Wiesje M. Van Der Flier[3], Inge Verberk[2], Charlotte Teunissen[2], Erik Stoops[1]
[1]ADx NeuroSciences NV, Ghent, Belgium, [2]Amsterdam UMC, Neurochemistry Lab, Dept Of Laboratory Medicine, Amsterdam, Netherlands, [3]Alzheimer Center and Department of Neurology, Amsterdam Neuroscience, VU University Medical Center, Amsterdam UMC, Amsterdam, Netherlands

Aims: Among the different phospho-Tau sites, phosphorylation at Threonine 231 (pTau231) in CSF, serum and plasma has been shown to be a promising early marker of Alzheimer's Disease (AD) pathology. As measured with research Quanterix Simoa assays, pTau231 is able to identify vulnerable populations below the PET threshold for amyloid-β positivity (Ashton *et al.* 2021). We aimed to develop a prototype Lumipulse G assay for quantification of pTau231 in EDTA plasma and serum.
Methods: A prototype assay was developed using a proprietary recombinantly expressed mAb RD-077 to capture pTau231 combined with an alkaline phosphatase-conjugated Fab fragment digested from ADx' N-terminal recombinant mAb RD-073. Among other analytical parameters, intra- and inter-run precision, accuracy and LLOQ were determined. The assay was tested in an age- and sex-matched EDTA plasma cohort of 20 AD patients (defined by CSF biomarker profile; Amsterdam Dementia Cohort) and 20 healthy controls (Dutch Brain Research Registry; Hersenonderzoek.nl).
Results: Precision was assessed with a three-plasma sample panel in 5 independent duplicate test runs. Mean intra- and inter-run CV% of sample concentrations were 4.2% and 9.2%, respectively. Analytical LLOQ was assessed at 0.34 pg/mL by precision profile of back-calculated calibrator values in 4 independent test runs. Accuracy was between 97-100% over the calibrator range. ROC-curve AUC of 20 AD vs 20 Controls was 0.835 [95% CI 0.71-0.96; p=0.0003], with pTau231 concentrations ranging between 0.62 & 3.43 pg/mL.
Conclusions: A prototype Lumipulse assay for pTau231 was developed using a pT231 specific capture mAb combined with an N-terminal pan-tau detector, demonstrating promising analytical performance and ability to discriminate between AD and healthy controls with high accuracy. Further exploration in larger cohorts using this fully automated platform is warranted.

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SHIFT 02-369

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

PERFORMANCE EVALUTION OF A LUMIPULSE® G PTAU217 CSF PROTOYPE ASSAY

Manu Vandijck, Yurina Hasumi, Jelle D'Hont, Roger Moonen, Filip Dekeyser, Caroline Dobbels, Ina Vandenbroucke
Fujirebio Europe NV, Ghent, Belgium

Aims: pTau217 has been shown to be a reliable biomarker for detecting amyloid pathology associated with Alzheimer's disease (AD). Fujirebio has developed a Lumipulse® *G* pTau217 Cerebrospinal fluid (CSF) prototype assay to complement the existing commercially available Lumipulse® *G* neuro portfolio. This study presents the preliminary analytical performance of the Lumipulse® *G* pTau217 CSF prototype assay.
Methods: The LUMIPULSE® *G* System is a fully automated chemiluminescent enzyme immunoassay platform using cartridges that processes samples within 30 minutes. The current assay format, using a proprietary monoclonal antibody targeting pTau217, was evaluated for key analytical performance parameters, including sensitivity, spike recovery, precision, dilutional linearity and lot-to-lot consistency, using multiple CSF samples.
Results: The Lumipulse® *G* pTau 217 CSF prototype assay met all pre-determined analytical acceptance criteria, including the lo-to-lot consistency. The analytical sensitivity was confirmed as all clinical samples exceeded the limit of quantification (LoQ), which was determined based on repeat testing of low pTau217 CSF samples. Total imprecision remained below 15% coefficient of variation (CV), spike recovery was within ±20%, and dilutional linearity was within ±20%, demonstrating high assay reliability.
Conclusions: These results highlight the potential of the Lumipulse® *G* pTau217 CSF prototype assay as a robust tool for AD research, offering high sensitivity, low variability, and reliable dilutional linearity. Further research in diverse, well-characterized cohorts will evaluate the potential clinical utility of this biomarker in CSF including the added value compared to the existing CSF biomarker panel.

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SHIFT 02-370

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

PERFORMANCE OF BLOOD BIOMARKERS FROM INTERNAL JUGULAR VEIN ON THE DIAGNOSIS OF ALZHEIMER'S DISEASE

Jun Wang, Yan-Jiang Wang
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Aims: Blood biomarkers exhibite excellent performance in the diagnosis of Alzheimer's disease (AD). Before widespread implementation, the effects of peripheral metabolism on blood biomarkers need to be overcome, which interfered the interpretation of the results. Compared to the median cubital vein (MCV) routinely used for blood sampling, the internal jugular vein (IJV) collects blood flowing out of the brain and are enriched with brain-derived molecules. This study investigated the performance of AD biomarkers in IJV on the diagnosis of AD.
Methods: We enrolled 351 participants with or without cognitive impairment from the Chongqing Ageing & Dementia Study (CADS) cohort. Fasting blood from the IJV and MCV were collected within 1 hour. Blood biomarkers were measured on two platforms: Fujirebio Lumipulse and Quanterix Simoa.
Results: The levels of all biomarkers in IJV blood were higher than in MCV. The difference of Aβ42 levels between IJV and MCV was smaller in Aβ-PET(+) than in Aβ-PET(+) subgroup, indicating less Aβ42 flowing out of the brain in AD patients. In contrast, the difference of p-tau between IJV and MCV were larger in Aβ-PET(+) subgroup. The correlation analysis showed that IJV Aβ42/40 had stronger correlation with brain Aβ-PET centiloid compared with MCV Aβ42/40. For p-tau, no significant differences on the correlation with brain Aβ burden were observed between IJV and MCV. In the classification of Aβ-PET status, the performance of IJV-Aβ42/40 was superior to MCV-Aβ42/40, but still inferior to MCV-p-tau217. The performance of p-tau217 and p-tau181 were similar in IJV and MCV.
Conclusions: The IJV-Aβ42/40 has a stronger correlation with brain Aβ burden and better diagnostic performance for AD compared to MCV-Aβ42/40. Detecting biomarkers in IJV is a promising strategy to reduce the impact of peripheral metabolism or comorbidities on blood tests.

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4-5 April 2025

BLOOD BIOMARKERS FOR IDENTIFYING ALZHEIMER'S DISEASE PATHOLOGY IN DEMENTIA PATIENTS

Tianyi Wang[1], Yuyue Qiu[1], Li Shang[1], Jialu Bao[1], Yuhan Jiang[1], Bo Li[1], Yixuan Huang[1], Wenjun Wang[1], Yuanheng Li[1], Yunfan You[1], Yutong Zou[1], Yifei Wang[1], Shanshan Chu[1], Wei Jin[1], Dan Lei[2], Meiqi Wu[1], Longze Sha[1], Ling Qiu[1], Li Huo[1], Qi Xu[1], Liling Dong[1], Charlotte Teunissen[3], Chenhui Mao[1], Jing Gao[1]
[1]Peking Union Medical College Hospital, Beijing, China, [2]Beijing Tsinghua Changgung Hospital, Beijing, China, [3]Amsterdam UMC, Amsterdam Neuroscience, Amsterdam, Netherlands

Aims: To evaluate the diagnostic efficacy of blood-based biomarkers (BBMs) in distinguishing Alzheimer's disease (AD) from a variety of other neurodegenerative dementias, using both SIMOA and Lumipulse as the detection methods for blood biomarker measurement.
Methods: This cross-sectional study used data collected from March 2017 to February 2024 from the Peking Union Medical College Hospital (PUMCH) dementia cohort. A total of 292 patients were recruited. The clinical diagnosis of these patients include AD, cerebral amyloid angiopathy (CAA), Creutzfeldt-Jakob disease (CJD), frontotemporal dementia (FTD), hereditary diffuse leukoencephalopathy with spheroids (HDLS), neuronal intranuclear inclusion disease (NIID), normal pressure hydrocephalus (NPH), vascular dementia (VAD) and dementia of undetermined etiology. The primary outcomes of this study were the levels of plasma biomarkers, measured using SIMOA and Lumipulse methods, across various clinical diagnostic groups, as well as their ability to predict cerebrospinal fluid (CSF) Aβ status, and the validation of these cutoff values through amyloid PET and tau PET imaging results.
Results: A total of 292 patients were included in this study, comprising 148 diagnosed with AD and 100 with other neurodegenerative conditions. Among the biomarkers assessed, plasma pTau217 demonstrated the most significant difference between AD and other neurodegenerative disease, although levels were comparable in specific groups such as CAA and CJD. For predicting CSF Aβ status, SIMOA plasma pTau217 exhibited 94.7% accuracy. Lumipulse plasma pTau217 showed comparable performance with 93.4% accuracy. When applied to predict Aβ PET status, SIMOA plasma pTau217 achieved 93.3% accuracy, while Lumipulse pTau217 achieved 91.3% accuracy. PTau217 achieved 97.7% accuracy with both SIMOA and Lumipulse methods for predicting Aβ and tau positivity on PET.
Conclusions: Plasma pTau217 levels can effectively differentiate AD pathology in dementia patients, with accuracy comparable to that of CSF and PET imaging.

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SHIFT 02-372

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

PREDICTION OF CEREBROSPINAL FLUID (CSF) AMYLOID-BETA(AB) 42 USING CLINICAL INFORMATION, BLOOD-BASED MARKERS AND GENETIC DATA

Shipeng Xiong, Fumie Costen
University of Manchester, Manchester, United Kingdom

Aims: This research project aims to produce a blood signature using machine learning methods to precisely predict the status and levels of CSF amyloid-beta 42. The study has effectively utilized the random forest method to create a predictive model. The model demonstrates a receiver operating characteristic area under the curve (ROC-AUC) of 0.92 and a prediction accuracy of 0.89.
Methods: Data Collection and Cleaning: Utilizing self-developed automated tools to collect datasets from ADNI, sort, and clean the data for the project. These tools are designed to handle large file sizes and unstable network conditions efficiently by using multithreading and coroutines, allowing for accelerated downloads and the ability to restart interrupted downloads. **Decision Tree Analysis**: Determining the output value of child nodes after samples are split in a decision tree. This involves finding the optimal cut point and calculating the mean of all sample values in each child node to determine the output value. **Random Forests and Ensembled Methods**: Implementing ensemble methods, specifically Random Forests, which involve multiple decision trees to improve the model's accuracy and robustness against overfitting. This method leverages the aggregation of multiple decision trees to ensure more reliable predictions and generalization over different datasets.
Results: The performance metrics indicate that the model using Mice imputation achieves the highest accuracy (0.886), AUC (0.920), and sensitivity (0.791), suggesting it correctly classifies the majority of instances and has superior discriminatory power. The R2 value of 0.515 indicates a significant amount of explained variance.
Conclusions: This research successfully collected and analyzed ADNI data, developing tools for efficient data acquisition and utilizing machine learning models for prediction. Future work will focus on improving model accuracy and exploring the application of these models in clinical settings.

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SHIFT 02-373

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

BLOOD ALZHEIMER BIOMARKERS AND BRAIN VOLUME CHANGES IN SCD WITH HEARING IMPAIRMENT –TWO-YEAR FOLLOW-UP RESULTS FROM THE COSCO STUDY

Dong Won Yang[1], Hyuk-Je Lee[2], Bora Yoon[2], Yun Jeong Hong[3], Jee Hyang Jeong[4], Kee Hyung Park[5], Sangyun Kim[6], Min Jeong Wang[7], Seong Hye Choi[8], Ji Sun Ryu[9], Sungmin Kang[9]
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Aims: Hearing loss is prevalent and represents a significant modifiable risk factor for AD in the elderly. This study investigated the association between hearing loss, AD blood biomarkers, and brain volume changes in individuals with SCD.
Methods: 104 SCD were divided into a normal hearing (NH) group (PTA ≤ 25 dB) and a hearing loss (HL) group (PTA > 25 dB). Baseline blood AD biomarkers, including Aβ40, Aβ42, GFAP, NFL, and pTau181, were quantified using the Simoa method. Baseline amyloid PET and brain volumetric analysis using baseline and two-year follow-up T1 3D and FLAIR MRI were performed.
Results: Of the 104 SCD subjects, 61 were classified as NH and 43 as HL. The HL group was older than the NH group (72.79 vs. 69.05 years). No significant differences were observed between the groups regarding education, MMSE, APOE4, or global SUVR of amyloid PET. NFL was higher in the HL group (27.72 ± 13.03) than in the NH group (22.15 ± 11.24, p = 0.02), and pTau181 was higher in the HL group (34.32 ± 16.86) compared to the NH group (26.03 ± 8.58, p = 0.001). After adjusting for age, pTau181 remained significantly elevated in the HL group (F = 6.13, p = 0.015). Over the two-year follow-up period, the HL group exhibited decreased volume in the left cuneus and inferior parietal cortex (p = 0.030, p = 0.033), along with increased periventricular WMH volume (p = 0.023).
Conclusions: SCD with HL was linked to elevated levels of phosphorylated blood pTau181 and neurodegenerative changes in specific brain regions, even in cognitively unimpaired individuals. Further studies are required to better understand the clinical significance of elevated pTau181 in the progression of hearing impairment and its relationship to brain atrophy.

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SHIFT 02-374

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

A LONGITUDINAL ANALYSIS OF THE INFLUENCE OF RENAL FUNCTION ON PLASMA BIOMARKER LEVELS IN DEMENTED PATIENTS WITH NEUROPATHOLOGICAL DIAGNOSIS.

Maria Ascensión Zea-Sevilla, Elisabeth Lucia Valeriano-Lorenzo, Maria Belen Frades Payo, Mario Ricciardi, Francisco Javier Lopez, Meritxell Valenti, Sonia Wagner, Alicia Ruiz, Ana Pastor, Nekane Moreno, Minerva Martinez-Castillo, Teodoro Del Ser, Maria Jose Lopez, Alberto Rábano, Pascual Sanchez-Juan
Reina Sofia Alzheimer Center. CIEN Foundation, ISCIII,, Madrid, Spain

Aims: Fluid biomarkers are an important tool for the detection of neurodegenerative disease, but their levels can be affected by age and other circumstances. The aim of this study is to investigate the longitudinal trajectory of 6 blood biomarkers of neurodegenerative disease in patients with AD, to analyse the influence of renal function on the biomarkers levels and their rate of change over time.
Methods: Clinical and plasma biomarker data were obtained from 137 dementia patients (mean age 83.6 ±6.4 years, 80.3% women, average follow-up of 4.3±3.1 years, 80% mainly with AD diagnosis), residents in Queen Sofia Foundation Alzheimer Center. A concentration of GFAP, NfL, AB40, AB42, total tau and p-tau181 were measured (SIMOA-Quanterix SR-X) at three time points. Linear mixed effects models were performed adjusting for age of onset, age at death, and sex.
Results: Cases with altered glomerular filtration (AGF) (serum creatinine >1.3mg/dl) presented lower survival ($\mu_{non\text{-}IR}$ =12.7, μ_{IR} =9.9 years; P=0.03). Also, baseline levels (β=0.52; P=0.005) and rate of change (β=0.53; P=0.008) of GFAP were significantly higher in patients with CE, in the total group and in AD+ and VaD+ cases. In the same pathological groups, baseline and premortem levels of p-tau181 ($\beta_{baseline}$=0.38; P=0.005, $W_{pre\text{-}mort}$= 221, P=0.002), and NfL (β=0.19; P=0.003, $W_{pre\text{-}mort}$= 240, P=0.003) were significantly higher in AGF cases.
Conclusions: Renal function altered was associated to rapid evolution and greater and persistent astrocyte activation (GFAP) in AD+ and VaD+ cases. In the same cases, we found in baseline and premortem analysis, concentrations of p-tau181 and NfL higher. Renal function should be considered in the clinical management of these markers.

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SHIFT 02-378

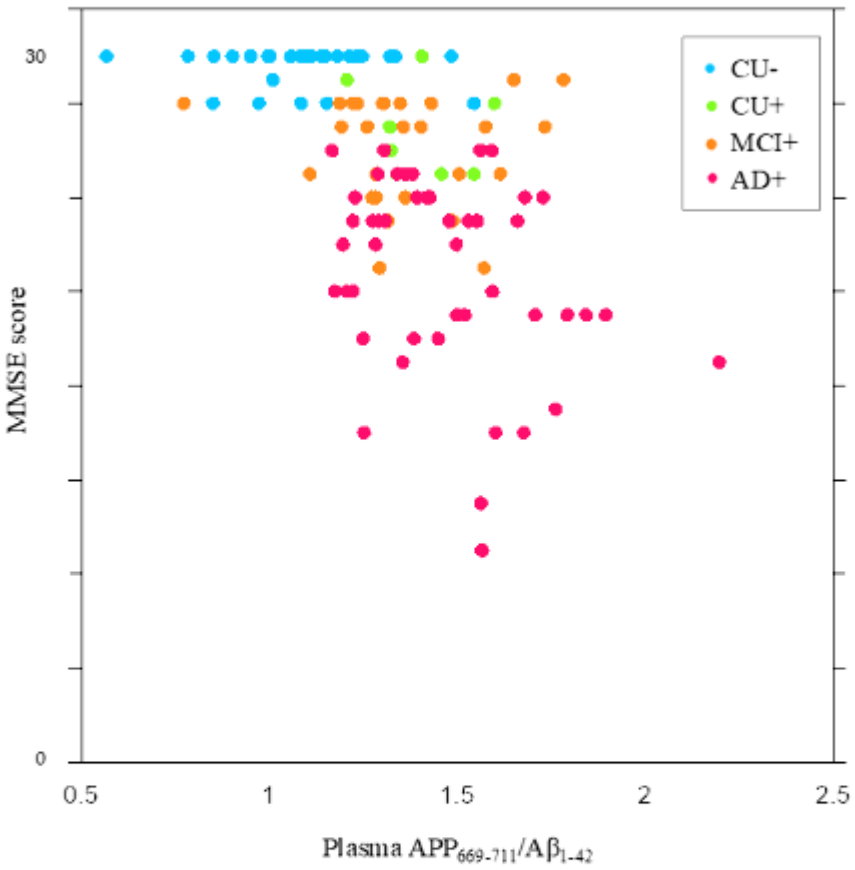
Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

THE ASSOCIATION BETWEEN PLASMA AMYLOID MARKERS AND COGNITION IN PATIENTS WITH ALZHEIMER'S DISEASE

Moeko Noguchi-Shinohara[1], Yasuhiro Sakashita[1], Hiroto Nakano[1], Daiki Muramatsu[1], Sadao Hikishima[1], Junji Komatsu[1], Hidetomo Murakami[2], Yukiko Mori[2], Kenjiro Ono[1]
[1]Kanazawa University, Department Of Neurology, Kanazawa, Japan, [2]Showa University, Department Of Neurology, Tokyo, Japan

Aims: Plasma amyloid markers predict amyloid-β (Aβ) pathology. However, their prognostic value for cognition in patients with Alzheimer's disease (AD) is unknown.
Methods: We compared plasma amyloid-β precursor protein $(APP)_{669\text{-}711}$ and $Aβ_{1\text{-}42}$ levels between patients with MCI due to AD, AD dementia, and the CU group which was divided into CU+ or CU- groups according to presence of Aβ pathology.
Results: The plasma $APP_{669\text{-}711}/Aβ_{1\text{-}42}$ ratio was significantly elevated in patients with Aβ+ group compared with those with Aβ- group. Furthermore, the plasma $APP_{669\text{-}711}/Aβ_{1\text{-}42}$ ratio was significantly associated with the MMSE score ($r_s = -0.544$, $p < 0.001$). Analysis of the Aβ+ group revealed that the significant association between MMSE score and plasma $APP_{669\text{-}711}/Aβ_{1\text{-}42}$ ratio remained unchanged ($r_s = -0.244$, $p =$

Figure. The associations between MMSE score and the levels of plasma amyloid markers



For all,
rs = -0.544
p < 0.001

For Aβ+ group,
rs = -0.244
p = 0.024

0.027).

Conclusions: We conclude that the plasma $APP_{669-711}/A\beta_{1-42}$ ratio is associated with cognition in patients with AD.

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SHIFT 02-379

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

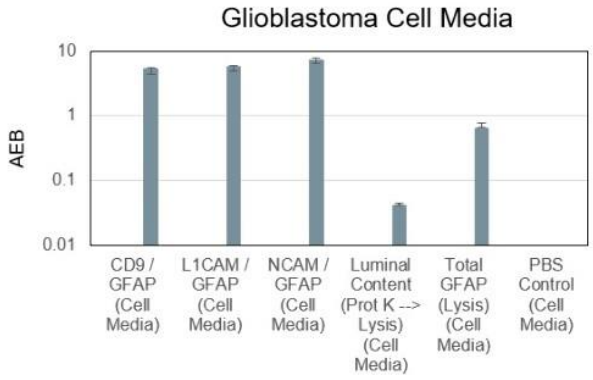
UNLOCKING THE DIAGNOSTIC AND THERAPEUTIC POTENTIAL OF ULTRASENSITIVE EXTRACELLULAR VESICLE AND BIOMARKER DETECTION USING SINGLE MOLECULE DETECTION ARRAY (SIMOA)

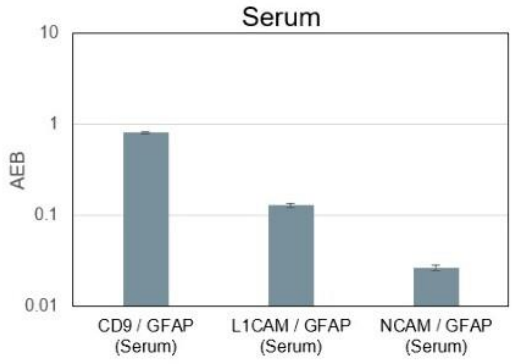
Anubhav Tripathi, Jennifer Pollock
Brown University, Engineering, Providence, United States of America

Aims: A methods review for isolating and characterizing EVs in order to address the challenges associated with the widespread heterogeneity in the size and composition of EVs. We will present a high-throughput single molecule detection array (SiMoA) for fast immune-phenotyping of extracellular vesicles from low-volume biofluids. The array has been used to observe changes in protein expression across different EV populations and identify key proteins associated with neurodegenerative diseases and disorders.

Methods: Neuronal derived EVs will be isolated from plasma using anti-NCAM and anti-L1CAM magnetic beads. A portion of the isolated nEVs will be lysed to analyze the total levels of Aβ, GFAP, and NFL loaded into the EVs. The remaining nEVs will be treated with protease K prior to lysis to remove surface proteins in order to determine where Aβ, GFAP, and NFL is located within the EV (i.e. surface of luminal). The lysates will then be measured using commercial Simoa kits obtained from Quanterix on the SR-X machine. The reported protein concentrations will then be normalized to the EV concentration reported from NTA analysis. This will provide useful information on the average loading capacity of nEVs. Changes in loading capacity between healthy and diseased cohorts will be evaluated.

Results: Preliminary results utilizing normal human plasma and a glioblastoma cell line as controls, suggest that the protein GFAP is presented primarily on the surface of EVs. EVs treated with protease-K prior to lysis were found to contain very little GFAP when analyzed using SiMoA. A custom homebrew assay developed by our team identified the colocalization of GFAP with the known nEV surface markers CD9, L1CAM, and NCAM.





Conclusions: These results suggest that the colocalization of proteins on the surface nEVs may provide the basis for a powerful diagnostic test.

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SHIFT 02-380

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

PREDICTION OF THE CONVERSION FROM SCD TO MCI USING CSF AND PLASMA BIOMARKERS

Yiping Qian, Fumie Costen
University of Manchester, Manchester, United Kingdom

Aims: The aim of this study is to use cerebrospinal fluid (CSF) biomarkers, plasma biomarkers, neuropsychological test scores, and demographic data to train and evaluate machine learning models on the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset to predict the ten-year conversion of SCD patients to MCI, and to find methods and data that can efficiently and accurately predict the conversion.
Methods: This experiment uses SCD patient data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) dataset, including biomarkers data, neuropsychological test scores, and demographic data. After a series of preprocessing work such as labeling and grouping (stable SCD or converted SCD) and using random forest to handle missing values, the biomarkers data (CSF and plasma) were input into the XGBoost for training and testing separately and simultaneously, and performance indicators such as sensitivity and specificity were used to test the performance of the model.
Results: showed that when random forests were used to fill in missing values, the model achieved the highest performance (93% accuracy and 0.99 AUC value) when considering a combination of cerebrospinal fluid biomarkers, demographic data, and neuropsychological test scores.
Conclusions: The model achieved high performance when using a combination of cerebrospinal fluid biomarkers, demographic data, and neuropsychological test scores, but the experiment lacked external validation to further confirm the model's generalization ability.

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SHIFT 02-381

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

CSF LEVELS OF PHOSPHORYLATED TDP-43 ARE INCREASED IN PATIENTS WITH VASCULAR DEMENTIA AND CORRELATE WITH MARKERS FOR VASCULOPATHY

Zeinab Rafiee, Jessica Santiago, Dovile Poceviciute, Shorena Janelidze, Oskar Hansson, Malin Wennström
Lund university, Dept Of Clinical Sciences, Malmö, Sweden

Aims: Accumulation of phosphorylated TDP-43 (pTDP-43) in hippocampal neurons and astrocytes is associated with a more aggressive progression of Alzheimer's disease (AD). We have recently shown that pTDP-43 inclusion can be found in astrocytic end-feet. The inclusions were more prominent in AD patients and were associated with a loss of CD146 and aquaporin 4. Since these molecules are implicated in blood brain barrier (BBB) integrity and glymphatic system (GS) function (systems crucial for amyloid-beta clearance) we hypothesiz that pTDP-43 plays a significant role in vasculopathy and AD progression. **Objectives:** To explore our hypothesis, we here investigate if cerebrospinal fluid (CSF) levels of pTDP-43 are altered in patients with AD and vascular dementia (VaD) and if the levels correlate with vasculopathy markers.
Methods: pTDP-43 levels in CSF samples from non-demented controls (NC), patients with stable MCI (sMCI), MCI-AD (those who later developed AD), AD, and VaD were measured using an in-house ELISA and correlated with previously measured biomarkers of vascular integrity (ICAM-1, VCAM-1, VEGF, PIGF) and BBB permeability (Q-albumin).
Results: VaD patients showed significantly higher CSF pTDP-43 levels compared to NC ($p=0.0004$), AD ($p=0.002$), and sMCI ($p=0.016$), but no difference was found between AD and NC. pTDP-43 levels positively correlated with Q-albumin ($r=0.384$, $p<0.001$) (marker for BBB dysfunction). Additional correlations were found between pTDP-43 and vascular markers ICAM-1, VEGF, and PIGF across different patient groups. These correlations persisted after adjusting for age, gender, and APOE4 status.
Conclusions: Our result supports our previous findings suggesting a link between vasculopathy and pTDP-43 accumulation and highlight the need to further explore the role for pTDP-43 in vascular changes in neurodegenerative diseases.

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SHIFT 02-382

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

PATIENTS WITH DISCORDANT CSF AMYLOID PET RESULTS: WHO ARE THEY?

Anja Simonsen, Malthe Hansen, Kristian Frederiksen, Steen Hasselbalch
Rigshospitalet Danish Dementia Research Centre, Copenhagen, Denmark

Aims: Amyloid in cerebrospinal fluid (CSF) and amyloid positron emission tomography (PET) are considered interchangeable when diagnosing Alzheimer's disease (AD), but discordance between the two modalities has been observed. This study aimed to evaluate discordance in a retrospective cohort, comparing differences against concordant groups.
Methods: We included 132 patients from the Copenhagen Memory Clinic Cohort in a consecutive retrospective study of patients with both CSF Aβ-42 and Pittsburgh compound B(PIB)-PET measurements within 1 year. The patients were categorized as concordant positive (*n = 81*), discordant with positive CSF and negative PET amyloid (CSF+/PET-) (*n = 38*) and concordant negative (*n = 13*). We compared the discordant group with both concordant groups on demographics, blood tests, CSF biomarkers, cognitive function, brain imaging, comorbidity, and multimorbidity.
Results: The discordant (*CSF+/PET-*) group had similar cognitive dysfunction to the concordant positive group but was more multimorbid ($p = 0.007$), had more psychiatric history ($p = 0.039$), higher alcohol consumption ($p = 0.019$), increased CSF glucose ($p = 0.028$), and lower levels of CSF p-tau and t-tau ($p < 0.0001$ and $p = 0.0001$, respectively). Compared to the concordant negative group, the discordant group had higher medial temporal atrophy scores ($p = 0.032$), lower p-tau ($p = 0.019$), more psychiatric history and concurrent affective disorders ($p = 0.0175$ and $p = 0.023$, respectively) and slightly more cases of hypercholesterolemia ($p = 0.042$).
Conclusions: Our study found 29% of patients had discordant results, mainly CSF+/PET-. This discordant group differed from both concordant groups on several relevant parameters, suggesting that discordance is not merely a step in the development of amyloid pathology. Furthermore, our findings question the interchangeability of amyloid measured by CSF and PET.

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SHIFT 02-383

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

EXPLORING THE LINK BETWEEN APOE GENOTYPE AND CEREBRAL MICROBLEEDS IN PATIENTS WITH ALZHEIMER'S BY MRI BASED SWI AND GRE SEQUENCES

Maryam Vejdani-Jahromi[1], Esteban Calle Cadavid[1], Odette Ganem Chagui[2], Hana Farzaneh[1], Harry Griffin[1], Benjamin Kozak[1], Jeremy Ford[3], Saurabh Rohatgi[1], Javier Romero[1]
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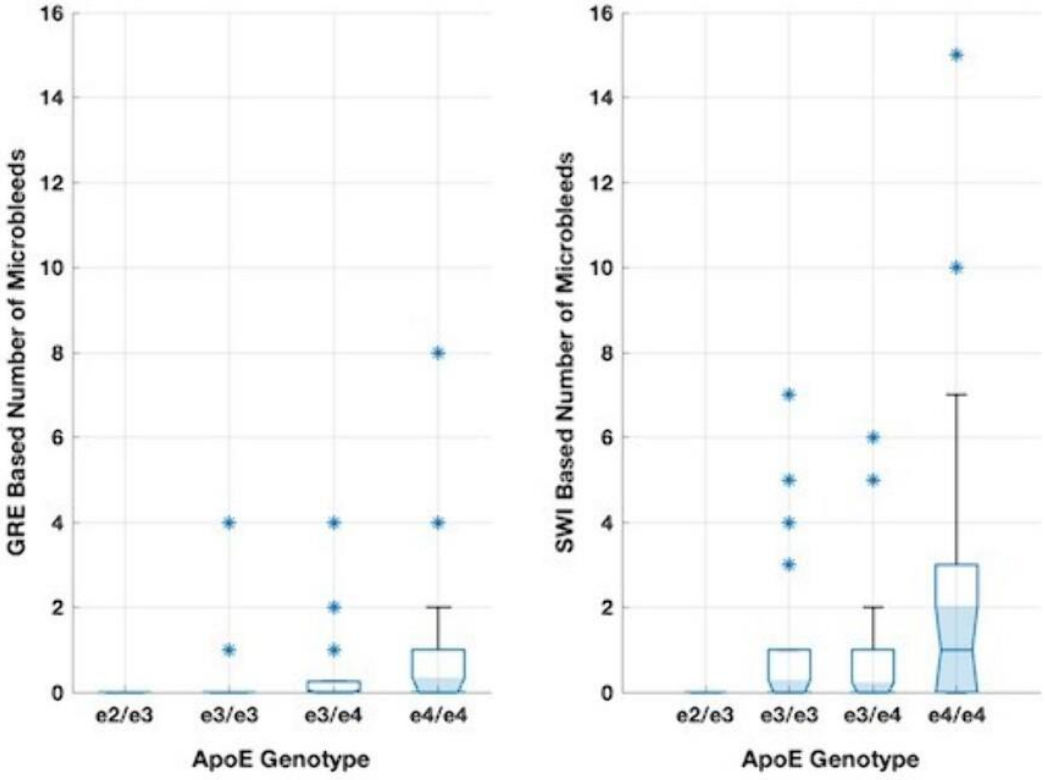
Aims: Alzheimer's disease is a neurodegenerative condition affecting the aging population worldwide. Recently approved anti-amyloid beta (anti-Aβ) therapies are designed to slow down or stop the progression of Alzheimer's disease. A major challenge remains in determining which patients are at risk for developing adverse effects, such as amyloid-related imaging abnormalities (ARIA) including cerebral microbleeds (CMB)s. CMBs are increasingly recognized for their clinical significance in the selection of patients considered for anti-Aβ therapies (e.g. Lecanemab). Strong association has been detected between ApoE-e4 genotype status and CMBs, but this relationship has not been well evaluated on different MRI sequences (i.e. GRE vs. SWI). Our objective is to compare the burden of CMBs in different APOE genotypes of patients with Alzheimer's being considered for Lecanemab treatment by GRE and SWI sequences.
Methods: Patients with Alzheimer's disease being considered for Lecanemab treatment were included in this retrospective study (99 patients, 48 male/51 female, average age=71 years). CMBs were defined as hypointense lesions within the brain parenchyma on GRE and SWI (size <10mm). The number of CMBs in the brain were determined by six readers/radiologists (blinded to ApoE status) on SWI and GRE sequences for each subject.
Results: Figure 1 shows the prevalence of CMBs with an increasing trend toward APOE-e4 homozygous status on SWI and GRE sequences. ANOVA test was performed to evaluate the association between ApoE genotype status and number of microbleeds demonstrating significant association based on SWI sequence ($p=0.02$). The association did not reach significance level on GRE sequence



(p=0.11).

Conclusions: This study demonstrates the trend of increased CMB's in patients with higher ApoE genotype and establishes the superior sensitivity of SWI sequence to detect CMBs compared to GRE.

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4-5 April 2025

MULTIOMICS APPROACH TO IDENTIFY NOVEL FECAL BIOMARKERS IN A MOUSE MODEL OF ALZHEIMER'S DISEASE

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Aims: Currently, there is no specific diagnostic test available for Alzheimer's disease (AD). Diagnosis requires the execution of various clinical and instrumental tests. Nowaday, the possibility of early diagnosis with prompt management of AD patients, remains highly challenging. Cerebrospinal fluid is considered the ideal sample for the evaluation of AD's biomarkers, but its collection is invasive, poorly tolerated and expensive. Accordingly, research is focused on identifying new biomarkers in easier-to-obtain biological samples such as blood and saliva. Previously, we demonstrated that feces can be used for biomarkers identification in inflammatory bowel disease (DOI:10.1093/ecco-jcc/jjac110). Since recent knowledge highlights a role of the intestinal microbiota in neurodegenerative diseases (microbiota-gut-brain axis). We hypothesized that microbiota alteration in AD could be mirrored in stool composition, therefore we proposed fecal samples for the screening of AD biomarkers. The aim of the study was to identify diagnostic biomarkers for AD using a multiomics approach (miRNome and proteome) on fecal samples.
Methods: The study was carried out in AD-transgenic mouse model (3×Tg-AD) with three mutations associated with familial AD (APP-Swedish, MAPT-P301L, and PSEN1-M146V) and age-matched controls. miRNome and Proteomic analyses were performed by Next Generation Sequencing (NGS) and high definition mass spectrometry techniques, respectively.
Results: Omics analyses identified 31 microRNAs and 81 proteins differentially modulated in AD-fecal samples compared to controls, suggesting these molecules as potential biomarkers. Their validation by Real-Time PCR, ELISA or immunoblotting is in progress.
Conclusions: This pioneering study on a mouse model of AD proposes fecal samples as suitable for identifying biomarkers in neurodegenerative diseases, suggesting their translational potential for AD patients. Importantly, fecal samples offer several advantages, as they represent an easily obtainable, non-invasive, cost-effective, and repeatable matrix for AD diagnosis and prognosis.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4-5 April 2025

COMBINING MASS SPECTROMETRY IMAGING AND IMMUNOHISTOCHEMISTRY TO ANALYZE AB PEPTIDE AND LIPID COMPOSITION IN ALZHEIMER'S DISEASE PATHOLOGY

Elisabeth Mueller[1,2], Corinna Klein[3], Knut Biber[3], Carsten Hopf[1,2,4]
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Aims: Alzheimer's disease (AD) is the leading cause of dementia and characterized by deposition of extracellular amyloid peptides called plaques and intracellular Tau tangles in neurons. Recent research suggests that components surrounding the amyloid plaque, such as microglia might drive the development of neurodegeneration and cognitive decline. Therefore, we developed an analytical multimodal approach to investigate the microenvironment of individual amyloid-β (Aβ) plaques, focusing specifically on lipid composition and inflammation markers in AD brain samples.
Methods: We developed a workflow combining classical mass spectrometry imaging of small molecules (i.e. lipids and Aβ peptides) with an adapted immunohistochemical staining. The main goal was to obtain both lipid information and spatial information by immunohistochemistry from the same tissue sample. The multiplex set up includes antibodies directed against Iba-1, amyloid precursor protein (APP), NeuN, NF-L and amyloid beta 42.
Results: Using APP/PS1 mouse samples, we developed a method to analyze various lipid classes and different Aβ peptides ($Aβ_{1-38}$, $Aβ_{1-40}$, $Aβ_{1-42}$ etc.). Based on peptide and lipid composition, we identified a single class of plaques in the mouse model. These plaques were decorated with Iba-1 immunereacitve microglia and lipids such as phosphatidylinositol, phosphatidylethanolamine, glycosphingolipids and sulfatides clearly co-localize with them. In human brain samples from AD patients we observed heterogeneous plaque populations based on peptide composition. When comparing the lipid composition to the mouse model samples, only the glycosphingolipids (GM1, GM2, and GM3) were found to accumulate at the Aβ plaque sites.
Conclusions: Our results suggest that there are plaques with different peptide compositions in the human brain tissue of Alzheimer's patients, which in turn are additionally characterized by a different lipid composition.

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TASK-BASED FUNCTIONAL MRI REFLECTS HIPPOCAMPAL VOLUME AND CSF T-TAU/ AB1-42 IN COGNITIVELY NORMAL OLDER ADULTS AT RISK FOR AD

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Aims: Numerous studies have demonstrated impairment in odor identification in AD, in MCI and in cognitively normal older adults with the APOE-ε4 allele, suggesting that it may serve as a biomarker (Murphy, Nature Reviews Neurology, 2019). Olfactory assessment has the potential to contribute to increased accuracy of detection of prodromal AD. Its contribution will be determined by how precisely we understand and assess olfactory function, its neural substrates, and relation to the disease process. Here we aimed to 1) investigate whether odor identification can signal hippocampal volume (HV) and CSF status for amyloid and tau in cognitively normal older adults who are at genetic risk for AD; and 2) investigate the underlying neural substrate for olfaction with the hypothesis that differences in structural MRI and olfactory task-based functional MRI will be captured while subjects at risk for AD perform tasks that require processing of olfactory information, and specifically, odor identification.
Methods: MRI was conducted at the UCSD Center for Functional MRI using a 3T GE MR750 Scanner. Subjects performed an odor identification test in the scanner.
Results: When subjects correctly identified odors, low hippocampal volume was associated with hyperactivation at the bilateral cuneus and precuneus. Two additional clusters of hyperactivation during correct identification responses were associated with low HV. These clusters were relatively large and located at important olfactory processing regions (i.e., piriform cortex, posterior OFC complex, hippocampus, amygdala), suggesting compensation. Participants with elevated CSF t-tau/$A\beta_{1-42}$ levels showed less activation in OFC and temporal pole, regions that are associated with functions necessary for odor identification, odor stimulus processing, and other task-critical cognitive functions.
Conclusions: Results suggest that poor odor identification reflects developing neuropathology in the prodromal period of AD. Support: NIH: R01AG062006 (CM)

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4-5 April 2025

A LARGE PUBLIC RELEASE OF CLINICAL AND IMAGING DATA FROM THE MAYO CLINIC STUDY OF AGING

Christopher Schwarz, Walter Kremers, Carl Prakaashana, Scott Przybelski, Luke Christenson, Josie Williams, Jeffrey Gunter, Matthew Senjem, Arvin Arani, Robert Reid, Mary Machulda, Julie Fields, Val Lowe, Kejal Kantarci, Jonathan Graff-Radford, Prashanti Vemuri, Ronald Petersen, David Knopman, Clifford Jack
Mayo Clinic, Rochester, United States of America

Aims: The Mayo Clinic Study of Aging (MCSA) is a longitudinal, population-based study of residents of Olmsted County, Minnesota, USA. MCSA is releasing de-identified clinical and imaging data on GAAIN.org to benefit the research community.
Methods: We included longitudinal clinical data from all MCSA participants 30-90 years of age (average 70.0y) through the first 15 years of the study. Clinical data includes age, sex, self-reported race/ethnicity, APoE4 allele status, cognitive impairment status (normal, MCI, dementia, or other), height, weight, blood pressure, multi-domain neuropsychological scores, neuroimaging summary measurements, medications, cardiovascular risk factors, social activity, sleep, mood/anxiety, functional measures, and more. For our initial release, we selected the first imaging visit with 3T GE MRI scanners and concurrent amyloid (PiB) PET from imaging participants 50-90 years of age (average 70.7y). We included 3D T1-weighted, T2-weighted FLAIR, diffusion MRI, and numeric SUVR and Centiloid values from PiB PET. PiB PET image volumes are being uploaded next, and follow-up scans are coming soon. All images are released in DICOM format after de-identification with CTP and de-facing with *mri_reface* to further protect participants' privacy, and all de-faced images were visually inspected by a trained data scientist for quality assurance.
Results: Our initial public data release includes clinical data from 5925 unique participants from the Mayo Clinic Study of Aging (MCSA), each ranging from 1-12 visits at roughly 15-month intervals. 1802 of these participants include MR and amyloid PET images. Demographic summaries are given in Table

Table 1. Characteristics table of clinical and imaging participants with the mean (SD) listed for the continuous variables and count (%) for the categorical variables. For the clinical dataset, these values are from the baseline visit.

	Clinical n = 5925	Imaging n = 1802
Age, years	70.0 (13.1)	70.7 (10.0)
Males, no. (%)	3014 (50.9%)	968 (53.7%)
Education, years	14.4 (2.8)	14.7 (2.6)
APOE-4 Carrier, no. (%)	1532 (27.4%)	516 (28.9%)
MMSE	27.8 (2.1)	28.1 (1.7)
Total Visits	3.8 (2.5)	1.0 (0.0)
Primary Diagnosis		
Cognitively Unimpaired, no. (%)	5135 (86.7%)	1573 (87.3%)
MCI, no. (%)	664 (11.2%)	202 (11.2%)
Dementia, no. (%)	87 (1.5%)	22 (1.2%)
Other, no. (%)	14 (0.2%)	2 (0.1%)
Missing/Protocol Deviation, no. (%)	25 (0.4%)	3 (0.2%)
Race		
White, no. (%)	5760 (97.2%)	1765 (97.9%)
Non-European Descent, no. (%)	101 (1.7%)	15 (0.8%)
More than one, no. (%)	38 (0.6%)	14 (0.8%)
Unknown/Not Reported, no. (%)	26 (0.4%)	8 (0.4%)
Ethnicity		
Hispanic/Latino, no. (%)	33 (0.6%)	5 (0.3%)
Non-Hispanic/Latino, no. (%)	5863 (99.0%)	1785 (99.1%)
Unknown/Not Reported, no. (%)	29 (0.5%)	12 (0.7%)

1.

Conclusions: This large, richly characterized, de-identified clinical and imaging dataset is available to the research community at https://www.gaaindata.org/partner/MCSA, and it is suitable for a wide range of research uses. Additional data will be released over time, including longitudinal follow-up imaging.

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Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4-5 April 2025

MULTIMODAL IMAGING OF WHITE MATTER HYPERINTENSITIES IN ALZHEIMER'S DISEASE: A PILOT STUDY

Yomna Takieldeen[1], Ho-Ching Yang[1], Salman Shahid[1], Tina Abraham[1], Khalid Al-Ali[1,2], Kalen Riley[1], Brian Graner[1], Yu-Chien Wu[1]
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Aims: White matter hyperintensities (WMHs) in Alzheimer's disease (AD) are commonly linked to vascular causes, but emerging evidence suggests AD-specific pathologies may also contribute. This pilot study used multimodal imaging to comprehensively analyze WMH volume, microstructural changes, perfusion abnormalities, and their associations with amyloid and tau pathologies, offering insights into the interaction between vascular and neurodegenerative factors.
Methods: Thirty cognitively normal (CN), 30 mild cognitive impairment (MCI), and 10 AD participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI3) underwent T1-weighted (T1w), fluid-attenuated inversion recovery (FLAIR), T2*-weighted, multi-shell diffusion MRI (dMRI), arterial spin labeling (ASL) perfusion, amyloid positron emission tomography (PET), tau PET, and vascular risk assessment. WMH volume was extracted using HyperMapp3r algorithm and Lesion Segmentation Tool (LST), and associated with amyloid and tau burden. Perfusion and diffusion metrics were also compared between WMHs and adjacent normal-appearing white matter (NAWM).
Results: The total WMH volume was higher in the AD cohort compared to MCI and CN, after adjusting for age, sex, and intracranial volume ($F(5, 60)=11.28$, $p<0.001$). Amyloid burden ($\beta=0.045$, $p<0.001$) was a predictor of WMH volume, independent of vascular risk factors, while tau was not. WMH volume was highest in amyloid-positive individuals with high vascular risk, followed by amyloid-positive individuals but with low vascular risk, and lowest in the amyloid-negative individuals with high vascular risk group. Across all groups, WMH showed more diffusion-related damage than normal-appearing white matter (NAWM).
Conclusions: Vascular and neurodegenerative factors influence WMH development in the setting of AD. This study and its data will help power future research aimed at differentiating the etiology of WMHs, which may provide a platform for targeted interventions and treatment strategies.

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β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
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THE ASSESSMENT OF AMYLOID B 42/40 LEVELS IN VARIOUS BODY FLUIDS IN POTENTIAL ALZHEIMER DISEASE PATIENTS.

Pawel Lisewski, Beata Lisewska, Martyna Wasilewska, Natalia Słomka
Centrum medyczne Neuromed, Bydgoszcz, Poland

Aims: We need to look for sensitive and non-invasive biomarkers of Alzheimer Disease that can be used in population screening. A small number of reports refer to studies assessing the range amyloid β 42/40 in various body fluids.
Methods: 80 patients with cognitive impairment in Neuromed Medical Centre, Bydgoszcz, Poland were included who have the memory test (MMSE, CDR, MoCA). Patients were enrolled and divided into two groups. The study group consisted of 90 patients diagnosed with cognitive impairment, aged 54-82 (mean of 66.8 years). The patients were treated in the Dr. Jan Biziel Memorial Clinical Neurological Outpatient Clinic, Department of Neurology and Stroke Treatment, University Hospital No. 2. in Bydgoszcz, and the Cognitive Center at the Neuromed Medical Center in Bydgoszcz. The control group consisted of 30 adult volunteers aged 55-80 years (mean of 67.8 years) without cognitive (normal results in the MMSE, Moca scales), including 15 women and 15 men, selected according to the study groups in terms of comorbidities. During the general and neurological examination, data of basic biometric measurements (height, weight, BMI, blood pressure, heart rate) were obtained. Based on the medical history, information was gathered concerning risk factors for the occurrence of Alzheimer Disease (smoking, use of other stimulants, the presence of comorbidities, treatment and use of anticoagulant prophylaxis).
Results: Using the ELISA method, the following parameters were determined in blood collected from the antecubital vein, in urine and saliva concentration of amyloid β 42/40. The concentrations can corelate with the cognitive test results.
Conclusions: Amyloid β 42 can be considered as potential biomarker for early Alzheimer Disease diagnosis not only in CSF.

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HOME-BASED BRAIN MONITORING WITH A SELF-MANAGED GARMENT EEG FOR EVALUATING COGNITIVE DECLINE: UPDATED RESULTS FROM THE HOGAR STUDY

Javier Minguez[1,2,3], Pablo Simón-Lobera[3], Esperanza Jubera-García[3,4], Mayelin Borrego[3], Javier Sutil-Jiménez[3], Jens Klinzing[3], Almudena Robledo-Menéndez[3], Olga Gelonch[5], Carmen Vicente-García[1,6], Jorge De Francisco Moure[6,7], José María Marín[6,7], Nora Molina-Torres[6,8], José María Perez-Trullén[6,8], Elena Muñoz-Farjas[6,9], Rosario Osta[1,6], Elena Lobo[1,6], Antonio Lobo[1,6], Pedro Modrego[6,7], Rosa Magallón-Botaya[1,6], Eduardo López-Larraz[3]
[1]University of Zaragoza, Zaragoza, Spain, [2]Aragon Institute for Engineering Research, Zaragoza, Spain, [3]Bitbrain, Zaragoza, Spain, [4]University of Cambridge, Cambridge, United Kingdom, [5]Hospital de Terrasa, Terrassa, Spain, [6]Instituto de Investigación Sanitaria de Aragón, Zaragoza, Spain, [7]Hospital Universitario Miguel Servet, Zaragoza, Spain, [8]Hospital Nuestra Señora de Gracia, Zaragoza, Spain, [9]Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

Aims: There is a growing need for accessible, automated tools to evaluate and detect cognitive decline. Wearable, self-managed electroencephalography (EEG) devices present a promising solution for home-based brain activity monitoring, enabling large-scale data collection. Paired with advanced AI techniques, these devices can potentially identify subtle EEG patterns missed by traditional methods. A home-based, user-friendly EEG tool could provide objective cognitive metrics, aiding primary care providers and specialists in early diagnosis, treatment monitoring, and in linking cognitive decline with EEG and sleep biomarkers.
Methods: The HOGAR study plans to collect data from 500 participants (>60 years) across four stages of cognitive decline: (1) cognitively healthy, (2) subjective cognitive decline, (3) mild cognitive impairment, and (4) mild dementia. All participants undergo comprehensive neuropsychological assessment in the lab and use a novel self-managed EEG device at home for two consecutive days, employing wearable EEG headbands to monitor the brain during wakefulness and sleep. We assess participants' ability to independently complete EEG sessions at home and analyze correlations between EEG patterns and cognitive/behavioral metrics. Additionally, we will evaluate the discriminatory potential of EEG data recorded at home in identifying stages of cognitive decline.
Results: As of November 2024, 130 participants have completed the study, including neuropsychological evaluations and home-based EEG use. Over 90% of the participants have successfully completed the EEG sessions at home, supporting the feasibility of the technology.
Conclusions: This is the first study to monitor EEG activity in elderly individuals at home using a fully self-administered approach. Participants along the cognitive decline continuum are effectively using the

technology, with family assistance but without requiring technical support. This study is expected to offer insights into the utility of home EEG in assessing and tracking cognitive decline.

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SHIFT 02-399

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

SPATIAL ANALYSIS OF IMMUNE CELLS IN ALZHEIMER'S DISEASE HUMAN BRAIN USING VALIDATED MABS AND MULTIPLEXED IMAGING

Yannick Nossin[1], Arindam Bose[2], Richard Cho[3], Supriya Singh[3], Gabriella Spang[3], Sophie Struble[2], Richard Heil-Chapdelaine[2], Natasha Fernandez Diaz Granados[2], Vasundhara Agrawal[2]
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Aims: Pathological hallmarks in Alzheimer's disease (AD) include the presence of plaques and neurofibrillary tangles composed of β-amyloid and hyperphosphorylated tau, respectively. The innate and adaptive immune response are likely to play roles in AD progression, but the extent of their roles is poorly understood. Proteomic characterization of immune cells that support an neuroimmune axis of AD may reveal the interplay of innate and adaptive immune systems that drive disease heterogeneity and disease pathogenesis.
Methods: The Cell DIVE Multiplexed Imaging Solution, in combination with IF/IHC-validated antibodies from Cell Signaling Technology (CST), can be used to computationally examine resident and infiltrating immune cells surrounding pathological hallmarks in AD. Segmentation and clustering analysis can identify spatially co-localized populations of cells, including subpopulations of microglia and, potentially T-cells, defined by specific disease-associated microglia markers and T-cell markers, respectively.
Results: CST's broad portfolio of Cell DIVE validated antibodies enables profiling of immune cell populations in the context of human AD tissue. Here, we demonstrate multiplexed Cell DIVE imaging using a novel CST panel and discuss the complexities of AD neuropathology highlighting immune cell identities and their interactions in the human AD brain.
Conclusions: Cell type specific markers, combined with multiplexed tissue imaging and spatial mapping, will provide a new approach to understand the existing challenges and accelerate immune-based therapies for treating and preventing AD.

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THE ROLE OF TDP-43 AS A CO-PROTEINOPATHY IN ALZHEIMER'S DISEASE: ASSOCIATIONS WITH TAU PATHOLOGY AND DISEASE PROGRESSION

Amrei Purwien[1], Nike Von Borcke[1], Jens Wiltfang[1,2,3], Yvonne Bouter[1,4]
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Aims: Transactive response DNA binding protein of 43 kDa (TDP-43) is an intranuclear protein commonly associated with neurodegenerative disorders. This study aims to investigate the role of TDP-43 as a co-proteinopathy in Alzheimer's disease (AD), examining the correlations between TDP-43 and known hallmarks of AD within the cortex and hippocampus of patients diagnosed with AD, focusing on its relationship with tau and amyloid-beta (Aβ) pathology. The goal is to better understand the regional distribution and impact of pathological TDP-43 in AD.
Methods: Samples from the Netherlands Brain Bank (NBB) of the cortex (n= 140) and hippocampus (n= 30) were analyzed using diaminobenzidine (DAB) to detect TDP-43, Aβ and tau pathology. The severity of proteinopathies was staged, using semi-quantitative assessments. The results were analyzed against known clinical and neuropathological parameters to determine correlations between the presence and severity of TDP-43 co-pathology and traditional AD markers. Fluorescence immunostaining will be employed to investigate the co-localization of the proteinopathies.
Results: In the cortex patients exhibited a significant higher amount of pathological cytosolic TDP-43 compared to controls. Additionally, TDP-43 pathology correlated with the severity of cognitive decline measured by the Reisberg score. In the hippocampus, TDP-43 correlated with neurofibrillary tangles and Aβ plaques. However, there was no significant difference in cytosolic TDP-43 levels between patients and controls in the hippocampus, likely due to the small hippocampal sample size. Further no correlations were found between TDP-43 and ApoE, age, or gender.
Conclusions: These findings suggest a possible role for TDP-43 in the progression of AD. The increased cytosolic TDP-43 in patients further reinforces its contribution to the disease and highlights the importance of TDP-43 as a potential therapeutic target in Alzheimer's pathology.

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SHIFT 02-401

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

(DEEP LEARNING-BASED) AUTOMATED CLASSIFICATION MODEL TO QUANTIFY CORTICAL IRON LEVELS ON HISTOLOGICAL SECTIONS IN ALZHEIMER'S DISEASE.

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Aims: Iron is crucial for many physiological processes like myelination and mitochondrial activity in the brain. However, in Alzheimer's disease (AD), we and others have shown that abnormal iron deposits occur in various brain regions, including the cortex, and higher iron levels correlate with cognitive decline. Despite many studies indicating altered iron homeostasis in AD, the pattern and temporal development of iron accumulation remain unclear. Therefore, our aim is twofold: 1. To study post-mortem cortical iron accumulation across different brain regions in a large cohort of individuals at various AD stages using the Leiden iron staining protocol, a modified DAB-enhanced Perl's staining method. 2. To develop an in-house automated iron scoring deep learning model to analyze large numbers of histological images, thereby increasing reliability and minimizing observer bias.
Methods: are described in

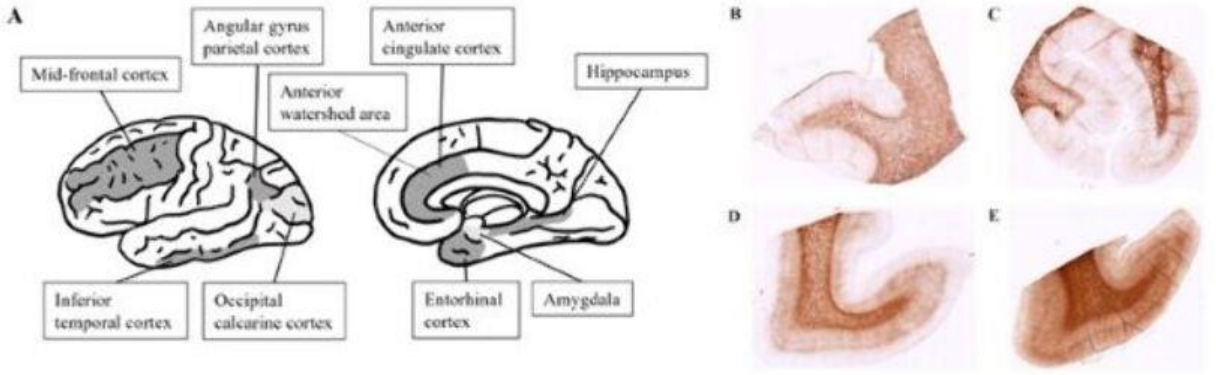

Figure 1: (A) Different brain regions were examined for iron accumulation across the brain. (B) Iron severity score 0: homogeneous gray matter (GM) with minimal iron present in GM. (C) Iron severity score 1: Iron rich band present in the mid-cortical layers, inhomogeneous GM. (D) Iron severity score 2: Diffuse iron band extending to the deep cortical layers, outer layers are still spared. (E) Iron severity score 3: heavy staining in all cortical layers with a wide diffuse mid-cortical band present (though not always).

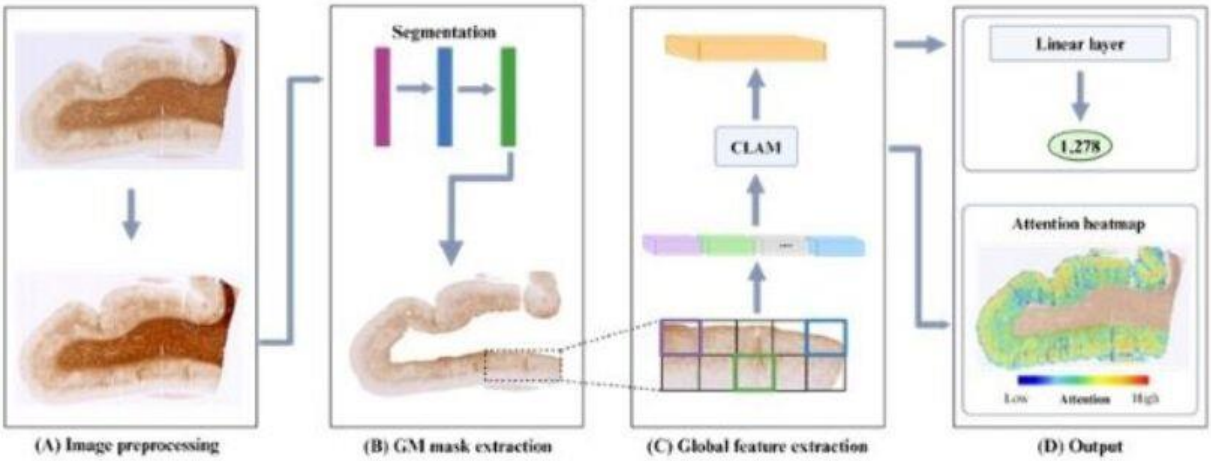

Figure 2: (A) Post-mortem brain regions were stained according to the Leiden Iron staining protocol. To correct for staining differences, the contrast of the images is adjusted. (B) Based on white matter (WM), segmentation is performed on the image to create and extract a gray matter (GM) mask further analysis. (C) The GM is divided into smaller patches to reduce computational power and for each patch, global features are extracted. For each patch, the attention score is obtained and used to construct an attention heatmap. Next, the features of all patches are then weighted according to their attention scores and summed to create a comprehensive feature representation. (D) The comprehensive feature representation goes into a fully connected layer to calculate the iron severity score. The output is the iron severity score between 0 and 3 for each image and an attention heatmap.
CLAM = Clustering -constrained Attention Multiple Instance Learning, GM = gray matter.

figures.

Results: We are currently optimizing, training, and testing the iron scoring model with additional cohorts and various AD pathology variations. Preliminary results from a smaller cohort indicate that the model accurately predicts approximately 90% of iron severity scores (R^2). The mean absolute error (MAE) is about 0.2471 units from the actual target values, and large prediction errors are rare (MSE = 0.1229; see Table 1).

MSE	RSME	MAE	R^2
0.1229	0.3506	0.2471	0.9015

Table 1: Preliminary results performances Iron classifier model. MSE = Mean Squared Error, RSME = Root Mean Squared Error, MAE = Mean Absolute Error, R^2 = R-squared

Conclusions: In conclusion, this iron scoring model accelerates the process, enhances reliability by eliminating observer biases, and enables large-scale analysis of iron spread in the brain, crucial for understanding its role in AD progression. The high R^2 value, along with low MSE and MAE, indicates strong model performance with accurate predictions and minimal errors. This suggests the deep learning model is

effective for the regression task, providing insights into the complex relationship between iron and AD that could lead to better diagnosis and treatment strategies.

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SHIFT 02-402

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / OTHER
4-5 April 2025

REDUCED ENDOCANNABINOID RECEPTOR 1 EXPRESSION IN THE BRAIN OF ALZHEIMER'S DISEASE PATIENTS

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Aims: The endocannabinoid system has increasingly been recognized as a promising therapeutic approach for treating neurodegenerative disorders, such as Alzheimer's disease (AD). However, the connection between endocannabinoid receptor 1 (CB1) and the neuropathological progression of AD is still not fully understood and often contradictory. The purpose of this study was to investigate a potential correlation between the progression of AD and the expression of CB1.
Methods: Post-mortem human brain tissue (n=143) was received from the Netherlands Brain Bank (cortex and hippocampus). In addition, to AD patients and controls, samples from Down syndrome patients were included. Furthermore, 5xFAD and Tg4-42 AD mice were also analyzed (n=20). The paraffin-embedded brain samples were cut into 5 µm sections and DAB staining for CB1 was performed on human and mice brain sections.
Results: The expression of CB1 was significantly reduced in AD patients in comparison to the control group in both cortex and hippocampus. Furthermore, the Braak stage and Reisberg score showed a significant negative correlation with CB1. There was no correlation between CB1 and age, gender or apolipoprotein-E-genotype. Consistent with the human data, 5xFAD and Tg4-42 mice exhibited significantly lower CB1 expression in the cortex and hippocampus, respectively, compared to wild-type mice.
Conclusions: CB1 shows promise as a marker for AD, and the observed alterations in the endocannabinoid system suggest it may be a potential target for AD treatment.

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SHIFT 02-403

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - AMYLOID
4-5 April 2025

ASSOCIATION OF APOE GENOTYPE WITH BRAIN AMYLOID QUANTIFIED USING CENTILOIDS IN HISPANIC AND NON-HISPANIC WHITE COHORTS

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Aims: Our recent meta-analysis reported that the Alzheimer's disease (AD) risk allele *APOEε4* was associated with fewer mild cognitive impairment (MCI) cases in Hispanic participants compared to non-Hispanic white (NHW) participants. To further decipher the influence of *APOE* genotype on disease pathology, we are conducting a meta-analysis to determine if there are differences between ethnicities in the association of *APOE* genotype with brain amyloid quantified using Centiloids.
Methods: Source datasets discovered on the Global Alzheimer's Association Interactive Network (GAAIN) include the Anti-Amyloid Treatment in Asymptomatic Alzheimer's (A4) study, the Alzheimer's Disease Neuroimaging Initiative (ADNI), the Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study, and the Standardized Centralized Alzheimer's & Related Dementias Neuroimaging (SCAN) study. The combined dataset consisted of only Hispanic or NHW participants who had a Centiloid measurement from an amyloid PET scan, resulting in 15,587 participants (5% Hispanic).
Results: Hispanic participants had significantly lower mean Centiloid values than NHW participants ($p<0.001$). After separating by diagnosis, there was no difference in mean Centiloid values between ethnicities in the cognitive unimpaired cohort, but there were significant differences between ethnicities in the MCI ($p=0.001$) and AD ($p<0.001$) cohorts. Additionally, after separating by genotype, there was no difference in mean Centiloid values between ethnicities in the *APOEε4*− cohort but there was a significant difference in the *APOEε4*+ cohort ($p=0.01$).
Conclusions: The preliminary results suggest that Hispanic participants have lower brain amyloid load in cases of MCI or AD diagnoses, or having at least one *APOEε4* risk allele. We plan to include additional datasets and run logistic and linear regressions using age, sex, years of education, and data source as covariates to model the relationship between *APOEε4* and Centiloids in Hispanic and NHW cohorts.

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SHIFT 02-405

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - GLUCOSE
4-5 April 2025

ASSESSING THE ROLE OF GENES, ENVIROMENT, AND AGING ON NEUROVASCULAR UNCOUPLING AS AN EARLY DIAGNOSTIC OF DISEASE PROGRESSION

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Aims: OBJECTIVES: Given the mixed etiology of Alzheimer's disease (AD) and related dementia (RD), there is a paucity of predictive diagnostics, thus limiting our understanding of how genes, environment, and aging interact. Here, we highlight the utility of genetic context combined with genetic risk factors and aging to identify early metabolic, inflammatory and vascular contributors to ADRD. We assessed this via novel genetic models of late onset AD (LOAD), combined with high fat/high sugar diet and aging, and assessed them with translational PET/CT of perfusion and metabolism to understand how they contribute to neurovascular dysregulation.
Methods: METHODS: Neurovascular function was assessed in B6, LOAD1 (B6.APOE4.TREM2^{R47H}), LOAD2 (LOAD1.hAβ), LOAD1.PLCG2^{M28L} and LOAD2.PLCG2^{M28L} mice ±HFD at 12 and 18 mos, via PET/CT. Neurovascular uncoupling analysis was performed, where Type 1 (↑ perfusion, ↓ metabolism) , Type 2 (↓ perfusion, ↑ metabolism), and prodromal AD phenotype (↑ perfusion, ↑ metabolism) were assessed.
Results: RESULTS: Uncoupling analysis at 12 mos revealed no effect on B6+HFD; however, LOAD1 and LOAD1+HFD (relative to B6) showed an increase in glucose uptake, without alteration in perfusion. By contrast, LOAD1+HFD and LOAD1.PLCG2^{M28L} (relative to LOAD1) showed Type 1 uncoupling at the same age. Importantly, Type 1 uncoupling was lost in LOAD1.PLCG2^{M28L}+HFD (relative to -HFD), while LOAD2+HFD (relative to -HFD) showed a Type 2 uncoupling. At 18 mos, LOAD2+HFD and LOAD2.PLCG2^{M28L} (relative to LOAD2) showed a prodromal AD phenotype, while LOAD2.PLCG2^{M28L}+HFD (relative to -HFD) regressed to Type 2 uncoupling. These data are indicative of gene by environment by age interaction which results in neurovascular dysregulation.
Conclusions: CONCLUSIONS: This work combines translational PET/CT imaging, with polygenic mouse models, and environmental stimuli across age to drive ADRD, permitting a deeper understanding of stratified risk on neurovascular function.

SHIFT 02-406

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - GLUCOSE
4-5 April 2025

FDG PET FINDINGS ACCORDING TO WANDERING PATTERNS OF PATIENTS WITH DRUG-NAÏVE ALZHEIMER'S DISEASE

Youngsoon Yang
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Aims: To explore anatomic substrate of specific wandering patterns in patients with Alzheimer's disease (AD) by performing positron emission tomography with 18F fluorodeoxyglucose positron emission tomography (FDG PET).
Methods: Drug-naïve AD patients with wandering (n=80) and without wandering (n=262) were recruited. First, the specific pattern of wandering type was operationally classified according to specific wandering score and clinical assessment. Second, brain FDG PET was performed and fluorodeoxyglucose (FDG) uptake differences of specific brain regions according to wandering patterns were compared to those of non-wanderers.
Results: In patients with pacing pattern, FDG PET showed significant lower FDG uptake in both middle cingulum and left putamen cluster compared to non-wanderers. The right precuneus and supplementary motor area in patients with random pattern and left calcarine sulcus, right calcarine sulcus, right middle cingulum, and right post central gyrus in patients with lapping pattern had significantly lower FDG uptake compared to non-wanderers.
Conclusions: This study showed that wandering in patients with AD had three distinct patterns. These specific patterns showed significant lower FDG uptake in specific brain areas compared to non-wanderers.

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SHIFT 02-412

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4-5 April 2025

SEX DIFFERENCES IN NIGROSTRIATAL DOPAMINE TRANSPORTER BINDING OF THE 123I-FP-CIT SPECT IN AUTOPSY CONFIRMED LEWY BODY DISEASE

Toji Miyagawa[1], Scott Przybelski[2], Cynthia Vernon[2], Hoon-Ki Min[2], Leah Forsberg[2], Julie Fields[2], Stuart Mccarter[3], Tanis Ferman[4], Vijay Ramanan[1], Jonathan Graff-Radford[1], David Jones[1], Rodolfo Savica[1], Ross Reichard[1], Dennis Dickson[5], Melissa Murray[6], Gregory Day[7], Neill Graff-Radford[7], Manoj Jain[8], Kejal Kantarci[9], Val Lowe[9], Bradley Boeve[2]
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Aims: We sought to semi-quantitatively assess ^{123}I-FP-CIT SPECT (DaT-SPECT) in autopsy confirmed LBD and Alzheimer's disease (AD) patients and look into sex differences.
Methods: Participants with neurodegenerative syndromes from the Mayo Clinic ADRC who underwent DaT-SPECT and had autopsy with neocortical or limbic LBD and/or AD pathology were included. Nigrostriatal DaT binding and z-scores were calculated using DaTQUANT 2.0 software (GE Healthcare).
Results: Thirty-three patients had LBD pathology (19 without AD (L+/A-) and 14 with AD (L+/A+); 30 neocortical and 3 limbic LBD; 26 male and 7 female) and 12 had AD pathology without LBD (L-/A+). Cut-off value of -0.98 for the DaTQUANT putamen z-score showed 94% sensitivity and 100% specificity in detecting LBD pathology. Age at death, age at DaT-SPECT, MMSE, UPDRS part III, and DaTQUANT z-score of putamen (-3.55±0.97 vs -2.94±1.71) or caudate (-2.77±1.18 vs -2.46±1.48) did not differ between the L+/A- and L+/A+, whereas males were more prevalent in L+A- (95%) than in L+/A- (57%). Age at death, age at DaT-SPECT, interval between DaT-SPECT and death, and MMSE did not differ between the L+ males and females. The L+ females had more AD co-pathology (86% vs 31%), more AD clinical diagnosis during lifetime (29% vs 0%), lower UPDRS part III score (11.4±12.3 vs 23.2±13.0), and less negative z-score of DaTQUANT putamen (-2.17±1.98 vs -3.60±0.97) and caudate (-1.65±1.64 vs -2.90±1.08). All of the L+ females had neocortical LBD pathology, and the two L+ females with AD clinical diagnosis had normal DaT-SPECT and L+/A+ pathology.
Conclusions: DaT-SPECT showed excellent discriminatory power in detecting LBD pathology. Though limited by relatively small number of the LBD females, there were possible differences in sex observed in DaT-SPECT as well as in clinical and pathological findings.

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SHIFT 02-413

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4-5 April 2025

IDENTIFICATION AND PRECLINICAL CHARACTERIZATION OF PET TRACERS FOR IMAGING ALPHA-SYNUCLEIN AGGREGATES IN PARKINSON'S DISEASE AND MULTIPLE SYSTEM ATROPHY

Manolo Mugnaini[1], Stella Vukelic[2], Gero Fink[3], Simone Benninghoff[3], Simon Seifarth[3], Alice Grill[3], Simon Spohr[2], Willi Amberg[2], Sandra Biesinger[3], Carmelina Petrungaro[4], Srirajan Vaidyanathan[5], Aimee Reed[5], Dan Sunnemark[6], Helen Jongsma Wallin[6], Peter Bosch[7], Nadine Ruderisch[7], Hollie Sanders[7], Caitlin Commins[7], Ji-Quan Wang[8], David Reuter[8], Ann Tovcimak[8], Martin Voorbach[8], Yuchuan Zhuang[8], Kyle Wilcox[8], Dustin Wooten[8], Marc Skaddan[8], Sjoerd Finnema[8], Tammy Dellovade[7], Miroslav Cik[3], Robert Comley[8], Frauke Pohlki[2], Stefan Barghorn[3]
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Aims: The aim of this project was to identify a high affinity positron emission tomography (PET) tracer suitable for imaging alpha-synuclein aggregates in individuals with Parkinson's disease (PD). The ideal PET tracer should have excellent selectivity for aggregated alpha-synuclein, low non-specific binding and a favorable PET pharmacokinetic (PK) profile.
Methods: The compound screening funnel included typical drug discovery assays to assess physico-chemical properties and off-target binding. A miniaturized radioligand binding assay using alpha-synuclein aggregate-rich PD brain extracts was utilized to determine binding affinity for alpha-synuclein. Promising compounds were radiolabeled with tritium and evaluated via autoradiography on human PD, multiple system atrophy (MSA) and transgenic alpha-synuclein mouse model brain tissue ex vivo. Pharmacokinetic profiles were determined in rats and from selected lead compounds in non-human primates using PET.
Results: The compound screening campaign has yielded promising lead candidates from structurally different chemical lead-series with high alpha-synuclein affinity. The lead candidate showed excellent selectivity against AD tau, MAO-A/B, neuromelanin and moderate selectivity against amyloid-beta aggregates. Binding to alpha-synuclein aggregates was demonstrated in both PD and MSA human brain tissue, as well as alpha-synuclein mouse model brain tissue. Furthermore, the lead candidate exhibited a favorable PET pharmacokinetic profile.
Conclusions: To identify a high affinity alpha-synuclein PET ligand, we successfully established a compound screening campaign utilizing native alpha-synuclein aggregates extracted from PD brain to evaluate target binding. The current lead exhibited excellent selectivity for alpha-synuclein aggregates, low

non-specific binding, and a favorable pharmacokinetic profile. These findings suggested that the current lead has the potential to be a valuable tool for imaging alpha-synuclein aggregates in PD MSA tissue.

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SHIFT 02-414

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4-5 April 2025

PET IMAGING OF NEUROINFLAMMATION IN COMMON MARMOSETS (CALLITHRIX JACCHUS) IS ASSOCIATED WITH COGNITIVE PERFORMANCE

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Aims: Neuroinflammation, driven by activated microglia, is a key pathological characteristic of Alzheimer's disease (AD).Activated microglia increase expression of the 18kDa translocator protein (TSPO), making TSPO a target for PET imaging of neuroinflammation. Second-generation TSPO ligands, such as 18F-DPA-714, exhibit high affinity and excellent kinetic characteristics during imaging, but are sensitive to gene polymorphism. Thus, individuals must undergo genotyping for expression of TSPO polymorphism and individuals characterized as low affinity binders should be excluded from imaging. Given the interest in marmosets as models for aging and AD, it is important to determine techniques for imaging neuroinflammation and its relation to cognitive performance. We investigated whether PET imaging of microglial activation was associated with cognitive decline in aged common marmosets (*Callithrix jacchus*).
Methods: *Radiosynthesis of ^{18}F-DPA-714.* The radiofluorination of DPA-714 was achieved by nucleophilic substitution of ^{18}F-fluoride using kryptofix (Cryptand 222) in acetonitrile at 100 °C, displacing the tosyl group on a tosylated-DPA714 precursor. The radiosynthetic process was fully automated on a GE-TracerLab FX2N module using Waters Sep-Pak cartridges and an in-house designed reaction and purification sequence. *Marmoset genotyping and PET imaging.* Older marmosets were assessed using ^{18}F-DPA-714 PET as an initial investigation to pave the way for the development of novel imaging biomarkers and novel PET tracers. Eighteen aged marmosets were genotyped for the TSPO polymorphism; approximately half were identified as high or mixed affinity binders. Six of these marmosets expressing high or mixed affinity binding underwent ^{18}F-DPA-714 PET imaging and were tested on executive function and visuospatial integration.
Results: Aged marmosets who performed poorly on cognitive tasks had higher SUV in the hippocampal formation and regions associated with visual and auditory processing than aged marmosets who performed well on these tasks (p<0.05).
Conclusions: 18F-DPA-714 PET was associated with cognition in marmosets.

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SHIFT 02-415

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4-5 April 2025

[11C]PIB PET AS AN IN VIVO MARKER OF DEMYELINATION IN HEALTHY OLDER ADULTS

Claudia Tato Fernández[1,2], Laura Ekblad[1,2,3], Marco Bucci[1,2,4], Jouni Tuisku[1,2], Riitta Parkkola[5,6], Semi Helin[1,2], Juha Rinne[1,2,7], Anniina Snellman[1,2]
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Aims: In this project, we aimed to test 1) whether cognitively healthy *APOE4* carriers who are at genetic risk for Alzheimer's disease (AD) show demyelination measured with [^{11}C]PiB positron emission tomography (PET); and 2) whether myelin integrity is related to axonal microstructure.
Methods: 101 healthy older adults (mean age = 71.3 ± 5.4 years, 59.4% females) underwent [^{11}C]PiB PET and magnetic resonance imaging (MRI) with diffusion tensor imaging (DTI), fluid-attenuated inversion recovery (FLAIR) and T1w sequences. White matter hyperintensities (WMHs) and normal-appearing white matter (NAWM) masks were generated from FLAIR and T1w sequences. PET images were analyzed with an in-house pipeline to estimate standardized uptake value ratios (SUVr) and partial-volume-corrected with the Multiresolution–Multimodal Resolution-Recovery (MM-RR) algorithm. We compared [^{11}C]PiB SUVr within WMHs and NAWM in the whole cohort, and between healthy older adults with different *APOE* genotypes (*APOE2/3* or *APOE3/3*, n=40; *APOE3/4*, n=40, *APOE4/4*, n=21), using t-tests and linear regression. Fractional anisotropy (FA) in WMHs and NAWM was quantified using the DTI sequences. Spearman's coefficient was calculated to assess the correlation between FA and [^{11}C]PiB SUVr.
Results: [^{11}C]PiB retention was lower in WMHs compared to NAWM ($p < 0.001$). There were no differences in [^{11}C]PiB uptake WMHs ($p = 0.12$), nor in NAWM ($p = 0.58$) between non-*APOE4* carriers, *APOE3/4* and *APOE4/4* carriers. Lower FA correlated with lower [^{11}C]PiB SUVr in WMHs ($r = 0.34$, $p < 0.001$), but not in NAWM ($r = 0.11$, $p = 0.30$).
Conclusions: Our findings support the use of [^{11}C]PiB PET as a marker of myelin integrity. However, we did not detect *APOE4*-related demyelination in this cohort of healthy older adults. Myelin levels and axonal microstructure are moderately correlated, but only within white matter lesions.

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SHIFT 02-416

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - OTHER
4-5 April 2025

DEVELOPMENT OF GSDMD INHIBITORS AS IMAGING PROBES AND POTENTIAL THERAPEUTICS

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Aims: Gasdermin D (GSDMD) plays a key role in the process of pyroptosis, one type of inflammasome-dependent cell death. Pyroptosis and neuroinflammation have been implicated in the development of neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson's disease (PD). Although small molecule inhibitors of inflammasomes have been emerging as potential therapeutics for various diseases including AD and PD, however, small molecule GSDMD inhibitors are scarce and only a few compounds that have been reported to show inhibitory activiteis on GSDMD. In additon, there is no GSDMD PET radiotracer has been reported. Therefore, rationally designed and selective GSDMD inhibitors would be valuable to develop novel PET imaging probes and potential therapeutics for disease interventions.
Methods: Based on a hit GSDMD inhibitor, new analogs were prepared, synthesized and characterized for their binding to GSDMD and inhibition on the pore formation and cytokine release. One compound was radiolabeled and PET/CT studies were conducted in mice.
Results: Novel small molecules were identied with proming binding affinity to recombinant GSDMD and inhibitory potency on the release of Il-1beta from cellular models. One compound was selected for radiolabeling. The radiotracer showed rapid brain uptake and quick clearnce in mice. Notably, the parent compound significntly reduced the brain level of the radiotracer, suggesting specific binding in the brain. Furthermore, autoradiography studies in brain tissues of wild type mice and gsdmd-/- mice also demonstrated promising specificity of this radiotracer.
Conclusions: Raditonal design based on a hit GSDMD inhibitor led to the discovery of novel GSDMD inhibitors with improved binbding affinity and inhibitory potency. PET/CT studies of a selected radiotracer in mice demonstrated rapid and specific brain uptake. The results strongly encourage further development of these compounds as imaging probes and potential therapeutics.

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SHIFT 02-420

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4-5 April 2025

EVALUATING COGNITIVE RESERVE IN SUBTYPES OF ALZHEIMER'S DISEASE

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Aims: Past research has identified subtypes of Alzheimer's disease with differences in spatial patterns of neurodegeneration, cognitive decline trajectories and cognitive reserve (CR). In the present study we aim to evaluate an approach to modeling CR that accounts for subtype-specific patterns of neurodegeneration. Within this approach, we will also evaluate fMRI-based functional connectivity measures of CR.
Methods: The current study will implement a CR modeling approach in combination with data-driven clustering of AD-related spatial neurodegeneration patterns in participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI). Specifically, measures reflecting neurodegeneration patterns and its severity will be used in a mixed effects regression model of CR predicting longitudinal cognitive performance. The CR modeling approach will be used to explore residual measures of CR, as well as fMRI-based functional connectivity patterns reflecting a potential brain mechanism of CR.
Results: Within the planned analyses, we will evaluate the CR modeling approach accounting for subtype-specific patterns of AD-related neurodegeneration. Additionally, we will obtain residual and functional connectivity measures associated with CR, and we will compare them with the conventional proxy measure of CR - education. Potential differences of AD subtypes with respect to CR measures will also be tested.
Conclusions: Current ongoing work aims to advance the methods for estimating CR by combining CR modeling with AD subtype measures to account for heterogeneity in patterns of neurodegeneration. The resulting modeling approach will in turn be used to assess residual and functional connectivity measures of CR. This combined approach can contribute to a better estimation of CR with a potential for improved prediction of individual risk of cognitive decline.

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SHIFT 02-421

Poster on Board - Shift 02
β-AMYLOID DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4-5 April 2025

CAN AI-SUPPORTED BRAIN VOLUMETRY (VUNO-MED® DEEPBRAIN®) EFFECTIVELY DIFFERENTIATE AMYLOID POSITIVE/NEGATIVE STATUS IN PATIENTS WITH SUBJECTIVE COGNITIVE DECLINE?

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Aims: Subjective cognitive decline (SCD) is an early risk group for Alzheimer's disease (AD). Predicting amyloid status using MRI could aid early detection without relying on PET or CSF biomarkers. This study aims to evaluate the effectiveness of AI-supported brain volumetry in differentiating amyloid status in SCD patients.
Methods: MRI analysis was performed using VUNO Med®-DeepBrain® with 3D T1-weighted and 2D T2-FLAIR images. Amyloid status was determined by PET, and a machine learning model was created combining volumetric data and demographic factors. Statistical tests identified brain regions with significant volume differences between amyloid positive and negative groups.
Results: Among 184 participants (37 amyloid-positive), volumes of the lingual, entorhinal, medial occipital, and precuneus cortices were significantly smaller in the SCD-Amyloid (+) group ($p<0.05$). Cortical thickness in the parietal/occipital lobes was reduced, though normative percentiles showed no significant difference. The volumes of specific brain regions weakly correlated with amyloid PET SUVR. However, data collection challenges in the SCD-Amyloid (+) group limited the machine learning model's reliability.
Conclusions: AI-supported volumetry can detect structural changes related to amyloid status, but data collection limitations affect the predictive power of machine learning models. Larger datasets and improved models are necessary for accurate early AD prediction.

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SHIFT 02-423

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
4-5 April 2025

BRAIN SHUTTLES TO NOVEL RECEPTORS TO OVERCOME LIABILITIES OF FIRST-GENERATION SHUTTLED ANTI-AMYLOID THERAPEUTICS

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Aims: Delivery moieties that are able to target and cross the blood-brain barrier can improve the dosing, tolerability, accessibility, and efficacy of diverse therapeutic modalities. For example, Roche's trontinemab uses a shuttle to Transferrin Receptor (TfR) to enhance PK and plaque clearance while reducing ARIA of the anti-amyloid beta (anti-Aβ) antibody gantenerumab. Despite the promise of this approach, TfR1-based shuttles have significant peripheral binding and introduce safety liabilities such as hematologic toxicity. The aims of this research are to 1) identify novel BBB targets with greater specificity to the BBB and 2) to create shuttle moieties against them that deliver anti-Aβ antibodies and other neuromedicines to the brain with reduced peripheral safety liabilities.
Methods: We use a high-throughput in vivo screening methodology to identify novel brain shuttles and BBB targets and examine the performance of these shuttles on a clinically validated anti-Aβ antibody. We evaluated the uptake of over 1000 nanobody shuttle candidates across multiple known and novel BBB targets in up to 100-plexed pooled reactions in mice. Top shuttle hits were further validated in terms of brain and plasma kinetics as well as peripheral toxiticies such as reticulocyte depletion and cytokine release upon infusion.
Results: By characterizing dozens of binders per BBB target using high-throughput in vivo screening, we were able identify a shuttle to a novel BBB target. This shuttle enhanced the delivery of an anti-Aβ antibody versus unshuttled controls while reducing cytokine release and hematological toxicity associated with traditional TfR1-shuttles.
Conclusions: Our work demonstrates that liabilities of TfR shuttles can be improved by engaging novel targets on the BBB and further advances a potential shuttle for clinical development that could improve upon the profile of existing TfR-Abeta mAbs such as trontinemab.

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SHIFT 02-424

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
4-5 April 2025

CRYO-EM STRUCTURES OF AMYLOID-B FIBRILS FROM ALZHEIMER'S DISEASE MOUSE MODELS

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Aims: The failure rate of Alzheimer's disease clinical trials regarding therapeutics is high. This might be associated with different factors that may involve differences between animal models of the disease, used in the pre-clinal context and humans. Animal models do not always have the right molecular targets and therefore, the therapeutic outcomes can be different. Hence, the goal of the present study is to compare the ex-vivo amyloid-β (Aβ) fibril structures of murine models of the disease with other known human structures.
Methods: A sarkosyl-based procedure was used to extract fibrils from the brain of six different clinically relevant mouse models of the disease.
Results: The APP/PS1, ARTE10, and tg-SwDI mouse models presented novel Aβ fibril polymorphs. Furthermore, the human type II Aβ structure was solved in the ARTE10, tg-APP_{Swe}, and APP23 murine models. Notably, the tg-APP_{ArcSwe} mouse model is the only one that had the type I Aβ structure which was previously shown to be present in both, familial and sporadic human AD cases. Additionally, the Aβ fibrils extracted from the tg-APP_{ArcSwe} mouse model were immunolabeled by the FDA-approved antibody treatment for AD, Lecanemab, which was originally designed to bind intermediately sized soluble aggregates.
Conclusions: The selection of the adequate mouse model in pre-clinical studies can play an important role in AD therapeutic development, as the molecular binding sites for therapeutics might not be the same in murine models and humans. **Reference:** Zielinski M, Peralta Reyes FS, Gremer L, Schemmert S, Frieg B,

Schafer LU, et al. Cryo-EM of Abeta fibrils from mouse models find tg-APP(ArcSwe) fibrils resemble those found in patients with sporadic Alzheimer's disease. Nat Neurosci. 2023;26(12):2073-80.

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SHIFT 02-425

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
4-5 April 2025

ISOASP7-ABETA – A MAJOR ABETA VARIANT IN ALZHEIMER'S DISEASE, DEMENTIA WITH LEWY BODIES AND VASCULAR DEMENTIA

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Aims: The formation of amyloid beta (Abeta) aggregates in brain is a neuropathological hallmark of Alzheimer's disease (AD). However, there is mounting evidence that specific post-translational modifications (PTMs) of Abeta contribute to its pathogenic profile and that Abeta also plays a pathogenic role in other types of dementia. This study aimed to test the hypothesis that distinct types of dementia are characterized by specific patterns of post-translationally modified Abeta variants.
Methods: We conducted a comparative analysis and quantified total Abeta as well as Abeta with pyroglutamate (pGlu3-Abeta, pGlu11-Abeta), N-truncation (Abeta(4-X)), isoaspartate racemization (isoAsp7-Abeta) and phosphorylation (pSer8-Abeta) modification in *post mortem* human brain tissue from non-demented control subjects in comparison to tissue classified as pre-symptomatic-AD (Pre-AD), AD, dementia with Lewy bodies (DLB) and vascular dementia (VAD). Abeta modification-specific immunohistochemical labelings of brain sections were examined by machine learning-based segmentation protocols and immunoassay analyses in brain tissue after sequential Abeta extraction were carried out.
Results: Our findings revealed that AD cases displayed the highest concentrations of all Abeta variants followed by DLB, Pre-AD, VAD and non-demented controls. With both analytical methods, we identified the isoAsp7-Abeta variant as a highly abundant form in all clinical conditions, followed by Abeta(4-X), pGlu3-Abeta, pGlu11-Abeta and pSer8-Abeta. These Abeta variants were detected in distinct plaque types and, with varying frequencies, in cerebral blood vessels. There was a strong positive correlation between

isoAsp7-Abeta and Thal phase and a moderate negative correlation between isoAsp7-Abeta and MMSE assessment. In aggregation assays, the isoAsp7-Abeta, pGlu3-Abeta and pGlu11-Abeta variants showed instant fibril formation without lag phase.

Conclusions: We conclude that targeting Abeta PTMs, and in particular the highly abundant isoAsp7-Abeta variant, might be considered for diagnostic and therapeutic approaches in different types of dementia.

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SHIFT 02-426

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
4-5 April 2025

LECANEMAB IN EARLY ALZHEIMER'S DISEASE: AN OPTICAL COHERENCE TOMOGRAPHY STUDY

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Aims: The accumulation of soluble and insoluble aggregated amyloid-beta (Aβ) may initiate or potentiate pathologic processes in Alzheimer's disease. Lecanemab, a humanized IgG1 monoclonal antibody that binds with high affinity to Aβ soluble protofibrils, is being tested in persons with early Alzheimer's disease (AD). We explored the retinal changes in early AD patients who received Lecanemab
Methods: We conducted a one-month single center phase 3 trial involving persons 50 to 90 years of age with early AD with evidence of amyloid on positron-emission tomography (PET) or by cerebrospinal fluid testing. Participants were given intravenous lecanemab (10 mg per kilogram of body weight every 2 weeks). The primary end point was to evaluate the retinal structural thickness change from baseline at one month. Optical coherence tomography (OCT) was used to image and measure the retinal structural thicknesses [macula retinal nerve fiber layer (RNFL) and retinal ganglion cell complex (RGC)] in all participants. One eye (the eye with severe neurodegeneration) of each patient was included in the analysis.
Results: A total of 8 participants were enrolled and assigned to receive lecanemab. The mean RNFL and RGC thickness was 38.16 (4.44) μm and 70.30 (3.93) μm respectively. A month of lecanemab, the mean RNFL and RGC thicknesses was 41.28 (5.13) μm and 70.61 (4.39) μm. The mean differences after a month of lecanemab were as follows: RNFL (difference, 3.11, $p = 0.004$) and RGC (difference, 0.31, $p = 0.819$).
Conclusions: Lecanemab reduced markers of amyloid in early AD and resulted in significant thickening of the RNFL (axonal structure of the retina) and thickening of the RGC (neuronal structural associated with visual function in the retina. Longer trials are warranted to determine the efficacy and safety of lecanemab

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SHIFT 02-427

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ABETA, TRUNCATED & PGLU-ABETA
4-5 April 2025

SILYMARIN'S EFFECT ON PERIPHERAL AMYLOID-B OLIGOMERIZATION: A LONGITUDINAL STUDY UTILIZING THE MULTIMER DETECTION SYSTEM-OLIGOMERIC AB (MDS-OAB)

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Aims: Amyloid-beta (Aβ) oligomers are known to play a critical role in the pathogenesis of Alzheimer's disease (AD). Recent research has highlighted the role of silymarin in preventing Aβ oligomerization. This study evaluates the impact of silymarin on Aβ oligomerization, specifically measured by the Multimer Detection System-Oligomeric Aβ (MDS-OAβ), in patients with cognitive impairment.
Methods: This longitudinal observational study aimed to evaluate the effect of silymarin on Aβ oligomerization in patients, as measured by the Multimer Detection System-Oligomeric Aβ (MDS-OAβ). A total of 98 participants were divided into two groups: 51 participants in the silymarin group and 47 in the control group. The silymarin group was further stratified by dosage, with 34 patients receiving a high dosage of 560 mg/day. The change in MDS-OAβ levels was assessed at baseline and follow-up. To assess the impact of silymarin on MDS-OAβ, a regression analysis was conducted, adjusting for age, sex, baseline medication use, and other confounding factors.
Results: The silymarin group showed a statistically significantly greater reduction in MDS-OAβ levels than the control group ($t = 2.15$, $p = 0.034$). The mean change for the silymarin group was -0.115 (SD = 0.208), while the control group showed a mean change of -0.028 (SD = 0.192). Participants receiving 560 mg/day of silymarin showed a larger reduction in MDS-OAβ levels ($p = 0.015$). Adjusting for confounding factors, regression analysis showed a significant reduction in MDS-OAβ levels in the silymarin 560mg group ($p < 0.01$).
Conclusions: While this study provides valuable initial evidence of the potential of silymarin at a dosage of 560 mg/day to reduce peripheral Aβ oligomerization, further research is required to establish whether these changes have a meaningful impact on AD pathology in the brain.

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SHIFT 02-428

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-INFLAMMATORY
4-5 April 2025

UNCOVERING THE ROLE OF COMPLEMENT IN ALZHEIMER'S DISEASE; TARGETING AC1S

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Aims: The complement pathway is a key component of the innate immune system that safeguards the body against pathogens and injured cells and is a strong inducer of neuroinflammation in Alzheimer's disease (AD). Complement-dependent glial-mediated synaptic pruning could be a primary contributor to synapse loss in early AD since there is increased complement activation in AD patient brains, and inhibition of the classical complement cascade has been shown to rescue synapse loss in preclinical models of AD. Genome-wide association studies (GWAS) have identified many AD risk genes encoding complement regulators, including complement associated-complement receptor 1 (CR1), complement regulator clusterin (CLU), and C1S. Therefore, inhibition of the classical complement pathway could represent a key therapeutic strategy for AD.
Methods: To better understand the role of complement in AD, we have established new *in vitro* and *in vivo* tools. We established human iPSC tricultures with Glutamatergic and GABAergic neurons to study the interaction between amyloid beta (Aβ) and complement. *In vivo*, in the 5XFAD AD mouse model, we used proteomic analysis and elisa-based assays to assess complement levels over the course of the disease in these mice.
Results: We found that Aβ (mainly fibrillar Aβ) stimulation can substantially increase complement activation. Importantly, aC1s inhibition decreases Aβ-induced complement activation. Parallel work focuses on assessing the effect of additional AD-related pathological stimuli on complement activation, such as fibrillar Tau. I*n vivo*, in the 5XFAD AD mouse model proteomics analysis and elisa-based assays showed increased complement levels and/or activation in the brain along with increased inflammatory markers starting at 6 months old. Future work will focus on assessing the potential therapeutic benefit of inhibiting aC1s in this model.
Conclusions: Complement inhibition via aC1s could represent a novel therapeutic venue for AD.

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SHIFT 02-429

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-OXIDANTS
4-5 April 2025

PROTECTIVE ACTION OF PHYTOCHEMICALS IN PALMITATE-INDUCED BRAIN MITOCHONDRIAL DYSFUNCTION.

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Aims: Type-2 diabetes mellitus and metabolic diseases are risk factors for Alzheimer's Disease (AD), whose complex multifactorial nature is widely known. Such conditions are characterized by increased circulation of free fatty acids (e.g. Palmitate, PA), which can cross the blood-brain barrier. Inside the brain free fatty acids cause inflammation, ROS overproduction and mitochondrial dysfunction(MitD), leading to neurotoxicity. In such context we evaluated if antioxidant phytochemicals (Quercetin from Ginko Biloba and Indicaxanthin from Opuntia Ficus Indica) could function as mitochondrial enhancers *per se* and thereby counteract PA-linked MitD *in-vitro*.
Methods: Primary mouse cortical neurons were pre-treated with 12.5μM Indicaxanthin or 10μM Quercetin for 2h and then exposed to 60μM palmitate for 24h. Alamar-Blue cytotoxicity kit was used to assess the phytochemicals safety and to screen their protective activity. Mitochondrial function was assessed in a SeaHorse-analyzer measuring oxygen consumption rate (OCR). Intra-mitochondrial ROS production and mitochondrial network fragmentation are currently evaluated by specific fluorescent probes and confocal microscopy.
Results: We show that a relatively low concentration of PA (60μM) can cause neurotoxicity and that both phytochemicals can counteract this. Both Quercetin and Indicaxanthin increased OCR *per se*, showing their potential as mitochondrial enhancers. However, only Indicaxanthin could reverse a decreased OCR induced in PA-stressed neurons. On-going experiments will reveal if the phytochemicals can rescue neurons from PA increased intra-mitochondrial ROS production and mitochondrial fragmentation.
Conclusions: Our study shows how antioxidant phytochemicals could be useful enhancers of mitochondrial function and revert PA-linked MitD in the brain, thus protecting neurons from degeneration and slowing the progression of AD. Interestingly, target-analysis with Quercetin performed in our lab has revealed mitochondrial proteins as potential targets. Further studies will reveal whether the two mitochondria enhancing phytochemicals act via different intracellular pathways.

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SHIFT 02-430

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-OXIDANTS
4-5 April 2025

OXIDATIVE STRESS BIOMARKER PROFILE DYNAMICS ACROSS BLOOD AND CEREBROSPINAL FLUID

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Aims: Numerous studies have highlighted the role of oxidative stress in Alzheimer's disease (AD) development. Yet, the alignment of systemic and central oxidative stress biomarkers is unclear across diverse populations in the AD continuum. This study aims to assess protein damage levels in plasma and cerebrospinal fluid (CSF) within the AD continuum.
Methods: One hundred forty participants without clinical dementia (47 with Mild Cognitive Impairment [MCI] and 93 cognitively unimpaired) from a memory clinic cohort underwent examination for central (CSF) and systemic (plasma) markers of oxidative stress. We measured Total Antioxidant Capacity (TAC), reduced glutathione (GSH), thiobarbituric acid reactive substances (TBARS), and reducing power (RP) using absorbance spectrophotometry (Hitachi U-1500). Pearson's correlations were employed to determine the congruence between the same biomarkers of oxidative stress in CSF and plasma. Factor analysis was performed to ascertain how many antioxidant dimensions they represent.
Results: Table 1 outlines participants' baseline characteristics. Pearson's correlations revealed CSF and plasma RP (r=.+385*) and TBARS (r=-.216*) were correlated (Figure 1). Upon analyzing group-level data, the cognitively unimpaired group showed congruence between CSF and plasma for GSH (r.=-.279*) and TBARS (r=-.287*) but not for TAC (r=+.191) and RP (r=+.202). In the MCI group, only RP (r.=+.640*) demonstrated congruence between CSF and plasma. Factor analysis with CSF biomarkers identified two components in the whole sample (Figure 2). Dimension 1= GSH, and Dimension 2=TAC, TBARS, and RP. Factor analysis with plasma identified two components: Dimension 1=RP and GSH, Dimension 2=TBARS and TAC. Factor analysis for MCI revealed a single component for CSF, while two components for

Table 1. Population Baseline Characteristics

	Total (n=140)	Clinical	
		MCI (n=47)	Cognitively Unimpaired (n=93)
Age (years)	63.47 (10.62)	65.04 (12.71)	62.66 (9.36)
Sex (n, % Male)	47 (33.6%)	18 (38.3%)	29 (31.2%)
Education (years)	13.22 (3.94)	12.34 (3.95)	13.67 (3.89)
CDR-G (score)	.27 (.639)	.652 (.948)	.0870 (.252)
IADL (score)	7.80 (.966)	7.60 (1.362)	7.91 (.661)

CDR-G: Clinical Dementia Rating Scale – Global Score, IADL: Instrumental Activities of Daily Living, MCI: Mild Cognitive Impairment.

plasma.

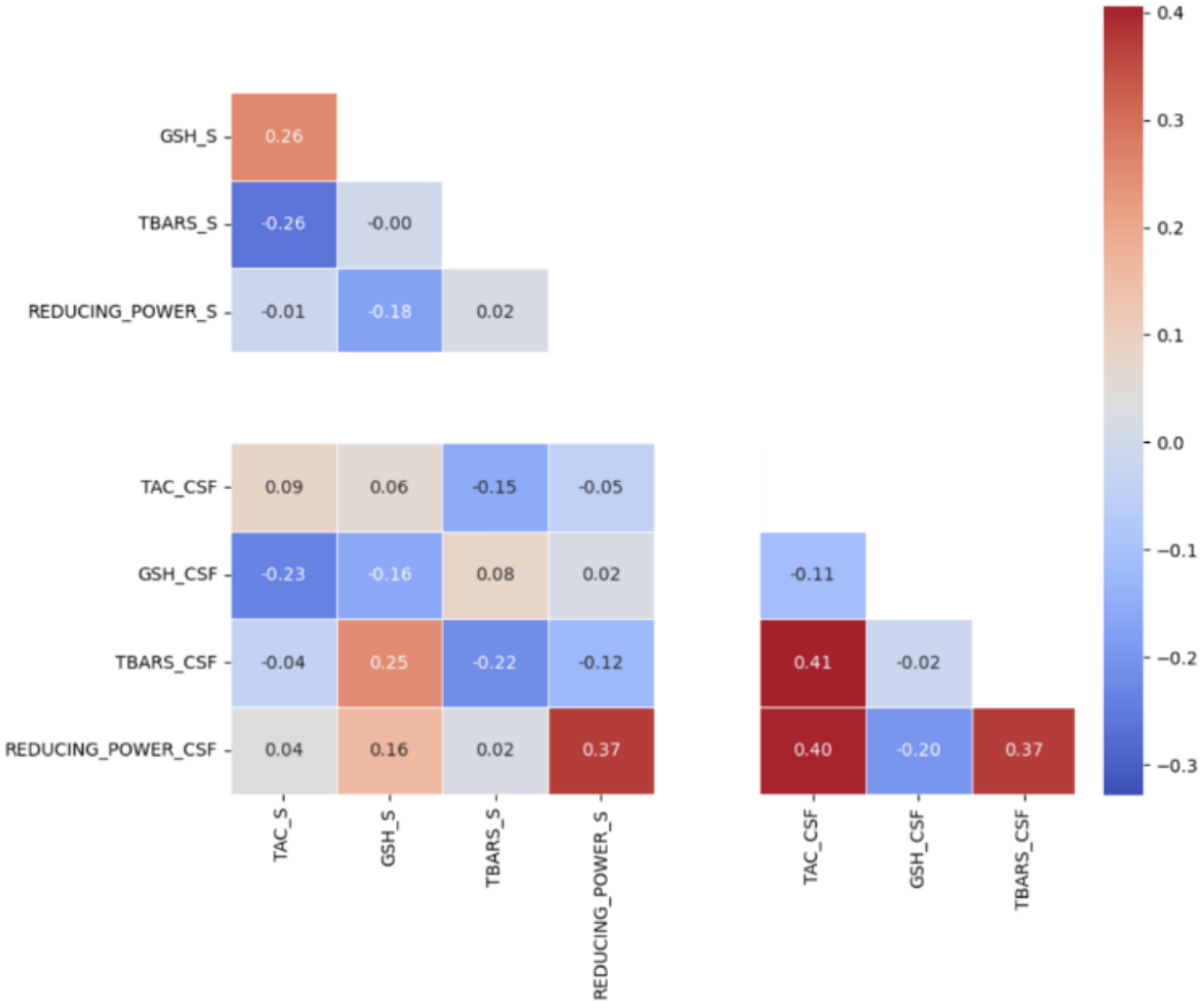

Figure 1. Correlation Matrix with biomarkers of oxidative stress in plasma and cerebrospinal fluid. Total Antioxidant Capacity (TAC), reduced glutathione (GSH), thiobarbituric acid reactive substances (TBARS). S: Plasma, CSF: Cerebrospinal Fluid.

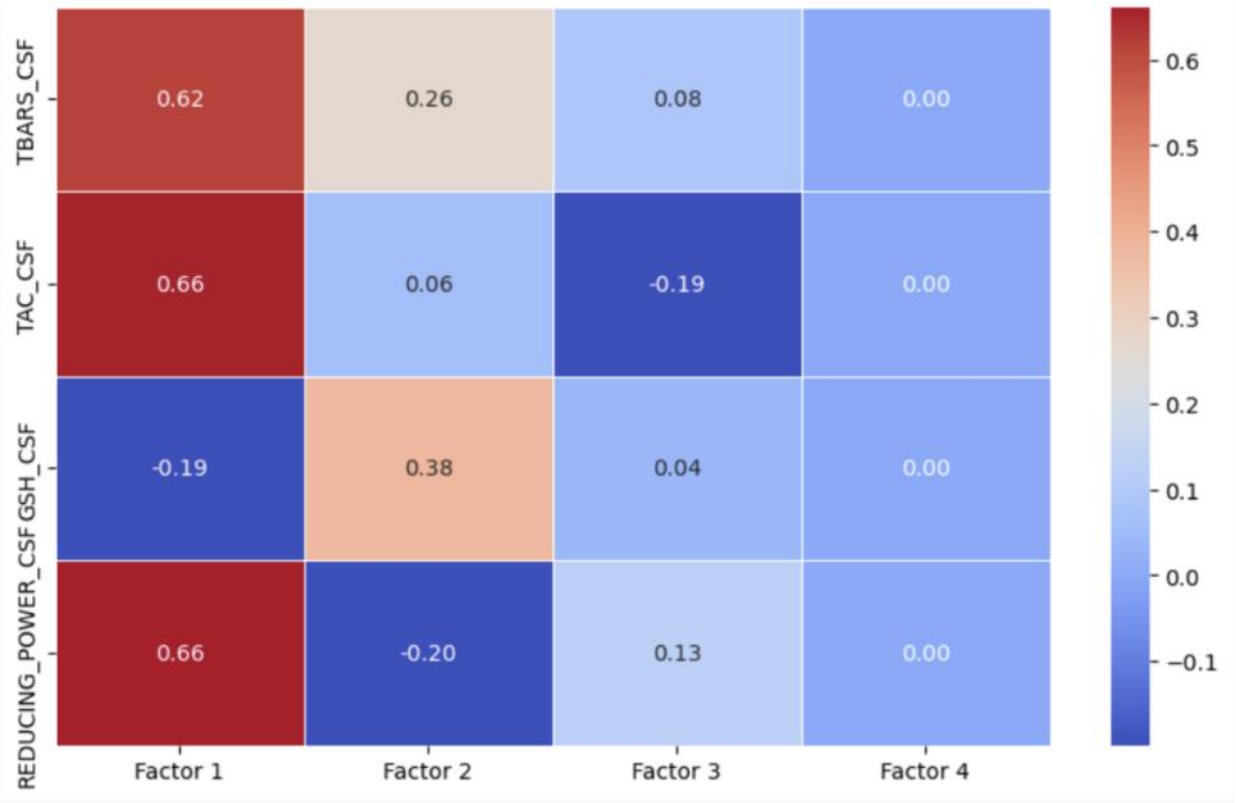

Figure 2. Total sample (n=140) factor loadings for Cerebrospinal Fluid biomarkers of oxidative stress. Total Antioxidant Capacity (TAC), reduced glutathione (GSH), thiobarbituric acid reactive substances (TBARS). CSF: Cerebrospinal Fluid.

Conclusions: Oxidative stress biomarker patterns differ across the AD continuum. Understanding oxidative biomarker evolution can enhance our comprehension of their role in AD and age-related disorders.

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SHIFT 02-431

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-OXIDANTS
4-5 April 2025

NEUROPROTECTIVE AND ANTIOXIDANT ACTIVITY OF NEWLY SYNTHESIZED N-PYRROLYL HYDRAZIDE-HYDRAZONES IN SH-SY5Y CELLS

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Aims: Oxidative stress plays a critical role in the development of neurodegenerative diseases, prompting interest in antioxidants as potential neuroprotective agents. Pyrrole-based derivatives, particularly N-pyrrolyl hydrazide-hydrazones, exhibit promising pharmacological properties, including potent antioxidant activity and inhibition of monoamine oxidase-B (MAO-B), which could benefit neurodegenerative disease treatment strategies. This study aimed to evaluate the neuroprotective properties of newly synthesized N-pyrrolyl hydrazide-hydrazones using in vitro models of neurodegeneration.
Methods: The experiments focused on human neuroblastoma SH-SY5Y cells treated with 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenylpyridinium (MPP+). Oxidative stress and reactive oxygen species (ROS) generation were quantified via a DCFH cytofluorimetric assay.
Results: demonstrated that compounds 7b, 9a, 11, 11b, and 12b significantly reduced cytotoxicity in the 6-OHDA (200 μM) model. Conversely, no statistically significant neuroprotective effects were observed in the MPP+ (1.5 mM) model. Cytofluorimetric analysis revealed that compounds 7b, 11b, and 12b notably reduced intracellular free radical levels by 70.7%, 62.3%, and 56.13%, respectively, compared to the 6-OHDA control. Additionally, flow cytometry analysis showed that compound 7b decreased apoptotic cell levels in the sub-G0/G1 phase to 3.73%, compared to 9.785% in the 6-OHDA control group.
Conclusions: In conclusion, N-pyrrolyl hydrazide-hydrazones, particularly compounds 7b, 11, 11b, and 12b, demonstrate significant antioxidant and neuroprotective effects on SH-SY5Y cells in vitro, warranting further pharmacological exploration in vitro and in vivo.

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SHIFT 02-432

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-OXIDANTS
4-5 April 2025

DINNER SOUPS ARE RICH SOURCES OF CHOLINESTERASE INHIBITORS

Dorota Gajowniczek-Ałasa[1], Dominik Szwajgier[1], Ewa Baranowska-Wójcik[1], Roman Paduch[2], Joanna Grzelczyk[3]
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Aims: Evaluation of the anticholinesterase, antioxidant and anti-inflammatory activities of newly designed dinner soups (undigested and after *in vitro* digestion), created for the supporting of the Alzheimer's disease prevention.
Methods: The anticholinesterase activities of soups were tested using spectrophotometric and calorimetric methods. The inhibiton of SOD, CAT, GPx, GR and COX-2 was tested spectrophotometrically. IL-1β, IL-6, IL-10 levels in the presence of „digested" soups were determined using CCD 841 CoTr and HT-29 cell lines.
Results: Mushroom, asparagus, leek and sea buckthorn soups were chosen among 18 pre-tested soups. The loss ($p<0.05$) of anticholinesterase activities was observed at every stage of "digestion", especially at the end "colon". „Digestion" mostly increased ($p<0.05$) the ability of soups to inhibit the activity of SOD, GR and CAT from the „mouth" until the end of „digestion", GR until the „small intestine" phase and the increase 2h after the bacteria addition in the "colon". COX-2 activity was either decreased (with mushroom, leek and sea buckthorn soups) or unchanged (with asparagus soup) during digestion. Mushroom, asparagus and sea buckthorn soups caused the increase of COX-2 activity during the whole "digestion" (all at $p<0.05$). Digested soups mostly decreased interleukin levels in HT-29 cells: IL-10 in the presence of mushroom, leek and sea buckthorn soups, IL-1β in the presence of mushroom soups, IL-6 in the presence of mushroom and leek soups. However, increased IL-6 levels were observed in the presence of asparagus soup.
Conclusions: *In vitro* digestion of soups caused the loss of the anticholinesterase activity, mostly the loss of so-called „antioxidant" enzymes" and the decrease of IL-1β, IL-6 and IL-10 levels in HT-29 cells in the presence of soups. Mixed results concerning the effect of soups on the COX-2 activity was seen.

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SHIFT 02-434

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / APOE & LIPOPROTEIN-BASED
4-5 April 2025

IN VITRO MODEL OF ALZHEIMER'S DISEASE BASED ON IPSC-DERIVED CELLS WITH APOE4 GENETIC POLYMORPHISMS

Rieko Tanaka[1], Rie Yamoto[1], Tatsuya Sameshima[1], Tetsuya Tanaka[2], Keiki Sugimoto[2], Hosoya Toshihiko[1]
[1]RICOH Company Ltd., Biomedical Business Center, Kawasaki-shi, Kanagawa, Japan, [2]Elixirgen Scientific, Inc., Baltimore, United States of America

Aims: Alzheimer's disease (AD) is the most common form of dementia. Since no animal models fully recapitulate the AD phenotype and drug responses, iPSC-derived cells are a highly valuable tool for the investigation of the AD pathology. The APOE4 gene polymorphism is a strong risk factor for the development of AD. In this study, we asked whether the pathological phenotypes can be observed in neurons and astrocytes generated from APOE4 AD iPSCs by the transcription factor-based technology for rapid differentiation (Quick-Neuron™ Excitatory and Quick-Glia™ Astrocytes).
Methods: We used neurons and astrocytes generated from iPSCs of sporadic AD patients with APOE4 (AD neurons and AD astrocytes). AD neurons were cultured for one to eight weeks with neurons from a healthy donor, and amyloid beta (Aβ) in the culture supernatant and intracellular tau were measured. AD astrocytes were cultured for 1 week, and the amount of intracellular lipid droplet and the glutamate uptake capacity were assessed. In addition, AD neurons were co-cultured with AD astrocytes for 8 weeks and cell viability was evaluated.
Results: After six weeks of culture, the AD neurons exhibited significantly higher accumulation of Aβ40 and Aβ42 in the culture media compared to the control neurons. Tau accumulation and Tau phosphorylation were also significantly higher in the AD neurons after four weeks of culture. AD astrocytes showed a significant increase in the intracellular lipid droplet accumulation and a significant decrease in the glutamate uptake capacity. After 8 weeks of culture, AD neurons co-cultured with AD astrocytes showed decreased cell viability.
Conclusions: Neurons and astrocytes generated from APOE4 AD iPSCs by the transcription factor-based technology exhibit AD-related phenotypes. These cells thus provide a novel opportunity for the investigation of the AD pathology.

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SHIFT 02-435

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ASO AND RNAI
4-5 April 2025

CROSS-SPECIES BBB-PENETRANT IV-DELIVERED AAV GENE THERAPY PROVIDES BROAD AND ROBUST CNS TAU LOWERING IN TAUOPATHY MOUSE AND NON-HUMAN PRIMATE

Wencheng Liu, Hechen Bao, Shiron Lee, Cansu Colpan, Elisabeth Knoll, Ching-Lien Fang, Maneesha Paranjpe, Tyler Moyer, Barbara Bueno, Gretchen Rivera, Brian Ezell, Dillon Kavanagh, Jordan O'brien, Alex Kubiak, Jack Studer, Dhiral Shah, Kyle Grant, Matteo Placidi, Mathieu Nonnenmacher, Dinah Sah, Todd Carter, Rajeev Sivasankaran
Voyager Therapeutics, Neuroscience, Lexington, United States of America

Aims: . Pan-tau lowering in the central nervous system (CNS) was recently shown to have favorable clinical outcomes for the treatment of Alzheimer's disease (AD). However, anti-sense oligonucleotides which reduce tau expression and tau pathology in both preclinical and clinical studies require repeated administration via intra-ventricular or intrathecal administration. In contrast, a one-time, intravenous (IV) administration of a blood-brain barrier (BBB)-penetrant, self-complementary adeno-associated virus (scAAV) gene therapy durably and robustly reduces CNS levels of human tau in a tauopathy mouse model, as we reported previously. Here, we employed a cross-species BBB-penetrant, second-generation TRACER™-derived capsid to deliver via IV administration a vectorized primary artificial microRNA (pri-amiRNA) carrying a potent tau siRNA in hTau mice and non-human primates (NHP). The resultant vector genome (VG) and tau mRNA and protein levels as well as the endogenous miRNA transcriptome in the CNS of htau mice and NHP will be presented.
Methods: Quantitation of VG levels by ddPCR Quantification of tau mRNA by bDNA or qPCR Quantification of tau protein by ELISA Characterization of the endogenous miRNA transcriptome by small RNAseq
Results: The results demonstrated a dose-dependent increase in VG and concomitant tau mRNA knockdown, in multiple brain regions of AAV-treated hTau mice, 2- and 8-weeks post-injection. Total tau protein levels were also significantly reduced by 36% to 87% in multiple brain regions of AAV-treated hTau mice at 8-weeks post-injection. We are currently analyzing VG levels, the reduction of tau mRNA and protein, and the miRNA transcriptome profile in NHP treated with this AAV.pri-amiRNA targeting tau.
Conclusions: The combination of a potent and well-tolerated pri-amiRNA targeting tau and a cross-species BBB-penetrant capsid could represent a promising one-time, IV treatment option for AD and other tauopathies.

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SHIFT 02-436

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
4-5 April 2025

REGULATION OF ENDOGENOUS GENE EXPRESSION VIA UNTRANSLATED REGIONS AS A NEW TREATMENT METHOD FOR ALZHEIMER'S DISEASE

Isabel Runneberger[1], Jaan-Olle Andressoo[2], Bernhard Schmierer[3]
[1]Karolinska Institutet, Department Of Neurobiology, Care Sciences And Society, Huddinge, Sweden, [2]University of Helsinki, Department Of Pharmacology, Faculty Of Medicine, Helsinki, Finland, [3]SciLifeLab and Karolinska Institutet, Crispr Functional Genomics, Department Of Medical Biochemistry And Biophysics, Solna, Sweden

Aims: Develop a new treatment for Alzheimer's disease (AD) by modulating the expression level of naturally expressed therapeutically relevant genes in our brains without altering their spatiotemporal expression pattern via CRISPR-Cas9-based 3'UTR editing.
Methods: First, we created a CRISPR-Cas9-based gene editing screen system to define mutations that upregulate the expression of Becn1 and Dnajb6- proteins believed to have therapeutic potential in AD - by creating small mutations in their 3'UTRs at every NGG site. In collaboration with the SciLifelab CRISPR Functional Genomics unit at Karolinska Institutet, we screened gRNA libraries for the best gRNA candidates for our system and are currently validating these *in vitro*. Next, we will move to *in vivo* testing of our system to examine DNAJB6 and BECN1 protein levels in the brain followed by assessment in AD mouse models.
Results: We found that our libraries contain gRNAs that result in both increased and decreased expression of Becn1 and Dnajb6 – hence our screening platform works. Furthermore, the screening shows that there are nearby gRNAs that provide similar regulation, suggesting that we can change specific regulatory elements in the 3'UTRs.
Conclusions: We have created a CRISPR-Cas9-based tool for editing endogenous gene expression levels. As a first step, we are testing the system by upregulating the expression of two genes that may have therapeutic potential for AD patients – but ultimately, the system could be used to regulate the expression of any endogenous gene. We believe these are important preclinical steps towards a new, endogenous gene-based treatment for AD.

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SHIFT 02-437

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / GENE THERAPY AND GENE EDITING
4-5 April 2025

PGC1ALPHA GENE THERAPY IN AGED MICE RESULTS IN IMPROVEMENTS IN COGNITION INDEPENDENT OF CHANGES IN AMYLOID-BETA DEPOSITION

Magdalena Sastre, Bibiana Mota, Robertas Aleksynas, Nelofer Syed, Nicole Kocurova,, Ceri Pickering, Nicholas Mazarakis
Imperial College London, Brain Sciences, London, United Kingdom

Aims: PPARγ coactivator-1α (PGC-1α) is a transcriptional regulator of genes involved in metabolic function (such as mitochondria biogenesis and glucose and lipid metabolism) and amyloid pathology, regulating the transcription of BACE1. We published previously that PGC-1α gene therapy delivered at early stages of the disease (before appearance of Amyloid-β (Aβ) deposition and memory deficits) in the APP23 mouse model of amyloidosis led to reduced Aβ generation, decreased neuronal loss and improved memory. The objective of this study was to investigate potential changes in gene profile caused by PGC-1α gene therapy in aged wild-type and APP23 mice, at stages with neuronal and memory loss.
Methods: We conducted gene delivery of either CMV-hPGC-1α or CMV-eGFP lentiviral vectors in frontal cortex and hippocampus of 12 m.o. female APP23 and WT C57Bl6 littermate mice. We determined changes in their memory and cognition 3 months after injection, at 15 months of age. We then conducted RNAseq in the frontal cortex and Aβ staining in the APP23 mice
Results: Our results suggest that PGC-1α gene delivery leads to improvements in recognition memory in old APP23 and WT mice, without changes in Aβ deposition. In addition, RNAseq in frontal cortex of WT mice highlighted changes in pathways related to metabolic processes, mitochondrial markers, as well genes involved in long-term potentiation, long-term depression and neurotransmission. RNAseq in the brains of the APP23 mice revealed alterations in metabolic processes, markers of synaptic vesicles as well genes involved in PPAR signalling
Conclusions: Our results suggests that PGC-1α gene delivery in the brain is neuroprotective in aged animals and this effect may not be dependent on changes in Aβ deposition, but affecting metabolic and mitochondrial pathways.

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SHIFT 02-441

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
4-5 April 2025

SNP234, A NOVEL POTENT, AGGREGATE SELECTIVE ANTI-ABETA ANTIBODY, AS NEXT GENERATION ANTI-AMYLOID IMMUNOTHERAPY AMICABLE FOR SUBCUTANEOUS ADMINISTRATION

Yuka Martens, Jakob Samsel, Mary Elizabeth Curtis, Young Park, Zusheng Li, Gang An, Min Li
SciNeuro Pharmaceuticals, Rockville, United States of America

Aims: Alzheimer's disease (AD) is a progressive neurodegenerative disorder that represents the most common cause of dementia in aged individuals. Given the central role of Aβ aggregation in AD, therapeutic strategies have focused on targeting Aβ to promote its clearance. Recent advances highlighted the need for antibodies with high selectivity for aggregated forms of Aβ, such as soluble Aβ (sAβ) aggregates and fibrils, while minimizing binding to monomeric Aβ. Monoclonal antibodies which selectively target aggregated forms of Aβ or amyloid aggregates which contain pyroglutamate modified Aβ have shown promising results in clinical trials, leading to their FDA approval despite the concerns for increased risks for vascular-related side effects for certain groups of patients. However, there remains an ongoing need for more potent binding agents that selectively target aggregated forms of Aβ peptides and can be used for the diagnosis, prevention, and treatment of AD and other disorders characterized by Aβ aggregation.
Methods: Here, we describe the development of SNP234, a highly selective monoclonal antibody against sAβ aggregates that is more potent than currently available anti-amyloid therapeutic antibodies. Its binding affinities to different species of Aβ were assessed using direct and competition binding assays. The antibody-mediated Aβ clearance activity of SNP234 was also investigated.
Results: SNP234 was one of several novel antibodies identified with high selectivity, exhibiting sub-nanomolar affinity, for sAβ aggregates while maintaining low binding to monomer Aβ. It displayed excellent developability profiles amicable for subQ formulation. SNP234 is efficacious in removing human amyloid plaques.
Conclusions: SNP234 demonstrates high selectivity against toxic form of Aβ and promotes efficient removal of disease-associated Aβ. These findings support further development of SNP234 as a potential next generation best-in-class anti-amyloid immunotherapy agent with subcutaneous administration.

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SHIFT 02-442

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
4-5 April 2025

LECANEMAB DEMONSTRATES HIGHLY SELECTIVE BINDING TO ABETA PROTOFIBRILS ISOLATED FROM ALZHEIMER'S DISEASE BRAINS

Malin Johannesson, Linda Söderberg, Olof Zachrisson, Nicolas Fritz, Helen Kylefjord, Eleni Gkanatsiou, Emily Button Button, Anne-Sophie Svensson, Adeline Rachalski, Patrik Nygren, Gunilla Osswald, Lars Lannfelt, Christer Möller
BioArctic, Stockholm, Sweden

Aims: Immunotherapy against Aβ has been shown as a promising treatment option for Alzheimer's disease (AD). In a phase 3 clinical trial in early AD subjects, lecanemab demonstrated disease-modifying effects on clinical endpoints and clearance of Aβ plaques in the brain. Lecanemab is a humanized IgG1 monoclonal antibody, selectively targeting Aβ protofibrils. Soluble Aβ protofibrils are believed to be the most toxic species of Aβ. The present study investigated lecanemab's interactions with various Aβ species isolated from post mortem AD brain tissue.
Methods: The present study prepared extracts of post mortem brain samples from AD patients and non-demented elderly controls, characterized the forms of Aβ present, and investigated their interactions with lecanemab. Aβ levels and aggregation states in soluble and insoluble extracts, and in fractions prepared using size-exclusion chromatography or density gradient ultracentrifugation, were analyzed using combinations of immunoassay, immunoprecipitation (IP), and mass spectrometry.
Results: The majority of Aβ in temporal cortex was found in the insoluble fraction. Aβ42 was the most abundant form present, particularly in AD subjects, and most soluble Aβ42 was in soluble aggregated protofibrillar structures. Aβ protofibril levels were much higher in AD subjects than in controls. Protofibrils captured by lecanemab-IP contained high levels of Aβ42 and lecanemab bound to large, medium, and small Aβ42 protofibrils in a concentration-dependent manner. Immunohistochemistry showed that lecanemab bound readily to Aβ plaques (diffuse and compact) and to intraneuronal Aβ in AD temporal cortex.
Conclusions: Lecanemab preferentially targets soluble aggregated Aβ protofibrils. These are largely composed of Aβ42, and lecanemab binds less readily to the Aβ40-enriched fibrils found in the cerebral vasculature.

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SHIFT 02-443

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
4-5 April 2025

INVESTIGATING THE "PERIPHERAL SINK" MECHANISM OF BRAIN AB REMOVAL THROUGH PASSIVE IMMUNOTHERAPY IN ALZHEIMER'S DISEASE USING NOVEL MOUSE MODELS

Urszula Swierczek, Nicole Hentschel, Marina Jendrach, Frank Heppner
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Aims: Amyloid beta (Aβ) is one of the hallmarks of Alzheimer's disease (AD). Recently, passive immunotherapy with anti-Aβ antibodies emerged as a promising disease-modifying treatment in AD, leading to the breakthrough approval of three anti-Aβ antibodies by the FDA. Still, low efficacy and high occurrence of adverse effects of these treatments raise concerns, while their mechanisms of action have not been fully explained. One contributing mechanism could be the "peripheral sink", namely the reallocation of Aβ from brain tissue to the blood. To assess this mechanism, we generated two transgenic mouse models, producing anti-Aβ antibodies restricted to the periphery.
Methods: We crossed the Aβ-depositing AD-like APPPS1 mouse model to the novel AB9u or DelS mice. We verified the production of anti-Aβ antibodies by ELISA. To determine the effect of the anti-Aβ antibodies in the periphery on AD pathology, plaque load, neuroinflammation and microglia activation were quantified with a range of biochemical and histological methods. Serum Aβ levels were quantified to assess the efflux of Aβ from the brain.
Results: We verified the production of anti-Aβ antibodies in the novel APPPS1.AB9u and APPPS1.DelS mice. Aβ40 and Aβ42 levels in their brains and serum were measured by electrochemiluminescence at two different time points, namely at the beginning of amyloid beta pathology and at a later stage, when Aβ plaque pathology has reached a plateau. In addition, we quantified neuroinflammation and microglia activation.
Conclusions: Our data reveal the effect of anti-Aβ antibodies in the periphery on AD pathology in the AD-like APPPS1 mice, showing the potential contribution of the "peripheral sink" mechanism of AD immunotherapy.

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SHIFT 02-447

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE
4-5 April 2025

DISCOVERY AND PRE-CLINICAL DEVELOPMENT OF A NOVEL RAC1 ACTIVITY INHIBITOR FOR TREATING ALZHEIMER'S DISEASE

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Aims: Rac1 (Ras-related C3 botulinum toxin substrate 1) -mediated active forgetting plays an important role in memory deficits of Alzheimer's disease (AD), and screening drugs that can effectively inhibit Rac1 activity is expected to provide a new direction for the treatment of AD. Therefore, The objectives of this study is the discovery and pre-clinical development of Rac1 inhibitors with new structures for future studies.
Methods: Through phenotypic screening with fly model, we found a hit compound JKF-012. we optimized that hit through medicinal chemistry, fly model phenotypical study, mice model validation and found a candidate compound 50561. We performed further ADME, GLP toxicity and other pre-clinical studies to demonstrat whether 50561 have unique potential for clinical development. Finally, we manufacture GMP tablets for its clincial development.
Results: 50561 is an excellent candidate as a novel Rac1 inhibitor for treatment AD. It has an IC50 of 87 nM in cells and can completely reverse memory defect in both APP/PS1 and APP/PS1/Tau mice models in several well accepted paradigms. It also has a unique inhibitory mechanism, by disassembling Actin-PAK1 complex and release Rho-GDI. 50561 also has a good ADME and toxicity profile and has obtains IND permission in both China and USA.
Conclusions: We found a novel small-molecular inhibitor of Rac1 activity, 50561 and we'll develop it in clinical trials.

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SHIFT 02-448

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / NEUROTROPHIC, SYNAPTIC PLASTICITY, REPAIR, REGENERATIVE MEDICINE
4-5 April 2025

SMALL UBIQUITIN MODIFER THERAPY MITIGATES AMYLOID TOXICITY LEADING TO PRESERVATION OF SYNAPTIC ACTIVITY

Kanayo Satoh[1], Nadeeja Wijesekara[1], Elentina Argyrousi[2,3], Shinsuke Matsuzaki[4,5,6], Hirotnori Takamura[6], Kyung Han[1], Agnieszka Staniszewski[2,3], Erica Acquarone[2,3], Taichi Katayama[6], Ottavio Arancio[2,3], Luana Fioriti[2,7], Paul Fraser[8]
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Aims: Amyloid-β oligomers are key factors in the etiology and synaptotoxicity in Alzheimer's disease (AD) and have been the target for several therapeutic intervention strategies. The goals of this research are to examine the impact of small ubiquitin modifier (SUMO) proteins on AD-related pathology and synaptic loss as well as to develop a biologic that mimics SUMO2 activity as therapeutic for Alzheimer's disease and related disorders.
Methods: Treatment with a recombinant biologic SUMO2 analogue, SBT02, were assessed in an APP transgenic mouse model of AD pathology (TgCRND8). Recombinant SBT02 and an inactive analogue were expressed and purified from E.coli and used to treat APP transgenics were treated at a dose of 20 mg/kg for three months. Cognitive function was determined by fear conditioning and synaptic plasticity evaluated by electrophysiology. Immunofluorescence and immunoblotting analyses for a number of pre- and post-synaptic markers were used to assess spine survival in the treated animals.
Results: Systemic administration of the recombinant biologic SUMO2 mimetic, SBT02, exhibited high brain bioavailability and prophylactically halted the progression of AD-associated deficits in TgCRND8 mice. The SBT02 biologic was equally capable of reversing the cognition deficits and synaptic impairments in the equivalent of late-stage amyloid pathology relevant to a clinical setting. Mechanistically, SUMO2 and the SBT02 biologic do not alter Aβ processing or clearance, instead they mitigate synaptotoxicity in the presence of high amyloid loads. Analysis of synaptic markers indicated the preservation of synaptic integrity and density in the areas dominated by the amyloid pathology.
Conclusions: Enhanced SUMO2 conjugation induced by the SBT02 biologic is a promising therapeutic

strategy to not only counteract but also reverse the synaptotoxic effects of Aβ oligomers and amyloid pathology in AD.

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SHIFT 02-453

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

RETHINK-ALZ PHASE 3 CLINICAL TRIAL OF SIMUFILAM IN MILD-TO-MODERATE ALZHEIMER'S DISEASE: ENHANCING TRIAL INTERGRITY BY QUALITY REVIEW AND INDEPENDENT CHAIN OF CUSTODY

Antonio M Hernandez[1], Lindsay Burns[2], Anton Porsteinsson[3], Raymond Turner[4], Jon Durrani[5], Roger Clarnette[6], David Miller[7], Erica Appleman[7], Sumati Raghavan[8], James Kupiec[1], Tracy Owen[1], Emmalee Crow[1], Melissa Snyder[1]
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Aims: Simufilam is an oral drug candidate in two pivotal phase 3 trials for mild-to-moderate Alzheimer's Disease (AD) dementia. Simufilam targets filamin A to reduce $Abeta_{42}$-mediated tau hyperphosphorylation and neuroinflammation. Oversight trial design safeguards and an independent chain of data custody were implemented for RETHINK-ALZ.
Methods: Signant Health conducted a quality review of all screening MMSEs. Premier Research, an independent contract research organization, conducted a Pre-Enrollment Eligibility Review (PEER) of initial patients at each clinical site. Clario, an independent imaging analysis vendor, reviewed all screening MRIs. Patients without historical confirmation of AD pathology had plasma P-tau181 measured by Neurocode, a CAP-accredited laboratory. The chain of custody of all trial data is independent of the Sponsor, and efficacy data flowed from trial sites to Premier to Pentara, an independent statistics vendor.
Results: Signant's quality review of 2271 screening MMSEs resulted in score changes for 401 patients (17.7%) and exclusions of 20 and 11 patients, respectively, on the low and high ends of the entry criterion range (16-27). Without this review, 31 patients with more severe or overly mild disease may have been erroneously enrolled due to scoring errors. In the PEER review of 248 eligibilities, frequently requiring investigator feedback and additional documentation, 36 (14.5%) were not approved, preventing enrollment of patients with exclusionary concerns and providing guidance to sites. Clario's review of screening MRIs revealed 66 patients (4.5%) did not meet eligibility criteria. Finally, of 1446 patients screened for plasma P-tau181 levels, 219 patients (15.2%) had levels below the pre-specified cutoff.
Conclusions: The RETHINK-ALZ trial was designed and executed with quality oversight of eligibility criteria and an independent chain of custody of all trial data to enhance clinical trial integrity.

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SHIFT 02-454

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

MICROBIOME-BASED L-DOPA TREATMENT MODULATES GLIAL RESPONSE AND NEUROBEHAVIORAL SYMPTOMS IN APP-KI MICE

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Aims: Alzheimer's disease (AD) is the most common cause of dementia, and no effective treatments exist to alleviate the progression and clinical symptoms. Monoamine neurotransmitter systems, including norepinephrine (NE) and dopamine (DA), are increasingly recognized to play a crucial role in AD. This study evaluates therapeutic efficacy of oral administration of our novel genetically engineered L-DOPA bacterial live-therapeutic (LDBL). This strategy is designed to maintain stable therapeutic levels of plasma L-DOPA, hence increases brain DA and NE to rescue clinical symptoms.
Methods: To evaluate its therapeutic efficacy, we administered LDBL treatment every 12 hours for 2 weeks to 11-12 month-old APP^{NL-G-F}-KI and strain-matched wild-type mice. We then assessed their memory function and depressive-like behavior using contextual fear conditioning and forced swim tests, respectively.
Results: We found that LDBL-treated APP-KI mice performed significantly better than vehicle-treated mice. These positive behavioral outcomes were also supported by restoration of firing frequency at single neuronal cell levels in the hippocampus of the treated mice. Interestingly, histopathological analysis revealed that Aβ pathology was mostly unchanged. However, notable differences were observed in glial cells between the two groups. Despite the total areas covered by various glial markers (Iba1, Clec7a, Tmem119, CD68, GFAP, C3, Ferritin) remaining similar between groups, detailed analysis revealed the engagement and phagocytic activity of microglia were significantly increased around plaques in the LDBL-treated mice.
Conclusions: These findings provide a better understanding of the immunological mechanisms underlying AD and highlight the critical contribution of LDBL to activate immune response modulation in the brain. Moreover, these results open the door to further refinement and enhancement of our proposed microbiome-based live biologic therapy to alleviate neuropsychological deficits in AD.

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SHIFT 02-455

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

REDUCED REGIONAL LEVELS OF SIGMA 1 RECEPTOR IN ALZHEIMER'S DISEASE BRAIN

Jana Nussbaumer[1], Marine Bruttin[1], Cinzia Maschio[2], Tunahan Kirabali[2], Uwe Konietzko[2], Axel Rominger[3], Christoph Hock[4], Zhude Tu[5], Roger Nitsch[4], Ruiqing Ni[2]
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Aims: Sigma-1 receptor (σ1R) plays an important role in Alzheimer's disease (AD) and is a promising therapeutic target in the treatment of AD. However, alterations in the levels of σ1Rs in the AD brain are not yet clear. Here, we aimed to evaluate the levels of σ1R in the postmortem AD brain and its associations with amyloid-beta, tau, synaptic markers, and gliosis.
Methods: Immunohistochemical staining for σ1R and synaptophysin was performed on postmortem frontal cortex, temporal cortex, entorhinal cortex and hippocampus slices from 46 AD patients and 46 nondemented controls. Correlation analysis was performed between σ1R and amyloid-beta (4G8), Braak stage, phospho-tau (AT-8), synaptophysin, synaptic vesicle glycoprotein 2A (SV2A), glial fibrillary acidic protein (GFAP), and ionized calcium binding adaptor molecule 1 (Iba1).
Results: Reduced levels of σ1Rs in the hippocampus, entorhinal, frontal and temporal cortex were detected in the AD group compared with nondemented control group. No difference was observed in the levels of σ1Rs between APOE ε4 carriers and non-carriers. Moreover, σ1R levels in the entorhinal cortex were lower in male AD patients than in female AD patients. Negative correlations between σ1R levels and the levels of amyloid-beta, phospho-tau, and Braak stages were observed.among AD patients and nondemented controls. Positive correlations between σ1R and synaptic markers, as well as astrocytic GFAP and microglial Iba1 levels in the hippocampus and entorhinal cortex were observed among AD patients and nondemented controls.
Conclusions: This study provides postmortem evidence for reduced levels of regional σ1R in the brain of AD patients compared with nondemented controls, and associations between σ1R with amyloid-beta and tau pathologies.

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SHIFT 02-456

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

RATIONAL DESIGN, SYNTHESIS AND IN VITRO EVALUATION OF POTENTIAL THERANOSTIC FLUORESCENCE PROBES FOR ALZHEIMER'S DISEASE

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Aims: 'Theranostics' is emerging as a promising tool for the simultaneous diagnosis and therapy of multifactorial diseases like Alzheimer's disease (AD). To develop theranostic fluorescence probes for the detection of Aβ aggregates and inhibition of cholinesterase enzymes, which are primary targets for the development of therapeutics for the treatment of AD.
Methods: A novel series of theranostic agents have been designed with amalgamation of the structural features from potential anti-AD agents and fluoroprobes with the **architecture of electron donor-acceptor**. The designed derivatives were synthesised, characterized and tested on different spectroscopic, *in silico* and *in vitro* biological parameters.
Results: The potential dual-targeting inhibitory profile was displayed by the synthesized derivatives against both acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE). (compound **1,** (*ee*AChE IC_{50} = **0.886 ± 0.068** mM) and, compound **2,** (*ee*AChE IC_{50} = **0.806 ± 0.0431** mM; *eq*BuChE IC_{50} = **9.908 ± 0.017** mM) possessed most significant inhibitory profile among all the sixteen synthesised derivatives. Additionally, the lead compounds evaluated with PAMPA assay, showed significant blood–brain barrier (BBB) permeability. The interaction of optimal compound **1** with Aβ aggregates showed noticeable enhancement in fluorescence intensity. The binding profile of the compound with AChE and Aβ was accessed through the molecular docking studies.
Conclusions: AChE and BuChE inhibition assays and structure-activity relationship studies showed all the tested compounds endowed with potential anti-cholinesterase activity. In addition to the excellent spectroscopic properties as contrast fluorescent agent, *in-vitro* investigations evidenced compound **1,** bearing *N*-aryl piperazine**,** as a potential lead for AD.

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SHIFT 02-457

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

RTMS (REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION) FOR ALZHEIMER'S DISEASE TREATMENT: IDENTIFICATION OF MICRORNAS AS BIOMARKERS OF THERAPEUTIC EFFICACY.

Barbara Tanno[1], Eleonora Colantoni[2], Francesca Camera[1], Lucia Mencarelli[3], Francesco Di Lorenzo[3], Sonia Bonnì[3], Giacomo Koch[3], Arianna Casciati[1], Caterina Merla[1]
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Aims: Alzheimer's disease (AD) is the main cause of dementia. There is no cure for AD. Repetitive transcranial magnetic stimulation (rTMS) is an emerging non-invasive therapeutic treatment against AD. rTMS-stimulation has been demonstrated to slow down cognitive and functional decline in patients. In this study, we connected clinical positive outcomes of AD-rTMS treated patients with molecular mechanisms, investigating microRNAs involved in synaptic plasticity and long-term potentiation known to be deregulated in early stages of disease. MicroRNAs are secreted and can easily be quantified in all biological fluids, these features make them potential biomarkers of response to therapy.
Methods: First, we performed dosimetry on rTMS-treated AD patients using specialized software to develop a dosimetric model able to scale the human exposure for in vitro studies (using Sim4Life). Then, an AD cellular model (differentiated SH-SY5Y cells, treated with β-amyloid) was used to identify microRNAs modulated following TMS exposure (q-PCR). These microRNAs were also analyzed in AD patient serum, and ADAS-cog tests were administered before and after treatment to assess efficacy of the treatment.
Results: In our *in vitro* AD model we demonstrated that a single session of TMS treatment significantly reduced the expression of miR-26b, miR-125b, miR-181c and miR-146a, compared to untreated AD-mimicking group, restoring healthy control group expression. Furthermore, analysis of the same microRNAs in the serum of patients, treated with rTMS, revealed a modulation of expression post-treatment in some of them. In patients with cognitive improvement or stable maintenance following rTMS treatment, only miR-125b expression was significatively restored post treatment as in healthy subjects.
Conclusions: The role of miR-125b in synaptic plasticity and the restoring of expression level as in healthy subjects suggests it as a potential biomarker of therapeutic efficacy for rTMS.

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SHIFT 02-458

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

DIETARY INTAKE OF N-6 POLYUNSATURATED FATTY ACID IS ASSOCIATED WITH ALZHEIMER'S DISEASE PATHOLOGY IN A MEMORY CLINIC POPULATION

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Aims: Dietary fatty acids, associated with an increase in plasma cholesterol levels, could be highly relevant to the development of Alzheimer's disease, as cholesterol plays a central role in Alzheimer's disease. This study aimed to evaluate the association between fatty acid intake and cerebral amyloid-β burden in memory clinic population.
Methods: Sixty-two older participants who underwent Food Frequency Questionnaire (FFQ) assessment and ^{18}F-florbetaben (FBB) positron emission tomography (PET) were included in this study. The intake of n-6 polyunsaturated fatty acids was evaluated based on a computerized assessment of the FFQ. Cerebral amyloid-β (Aβ) burden was quantitatively evaluated using ^{18}F-FBB PET images. The Controlled Oral Word Association Test *(*COWAT) was used to assess cognitive function.
Results: Intake of n-6 polyunsaturated fatty acids was significantly higher in the Aβ-positive group than in the Aβ-negative group (P = 0.040). Multiple linear regression analysis revealed that the intake of n-6 polyunsaturated fatty acids was significantly associated with cerebral Aβ burden (β = 0.284, P = 0.019). Additionally, the intake of n-6 polyunsaturated fatty acids was significantly associated with the COWAT score (β = -0.251, P = 0.041).
Conclusions: The intake of n-6 polyunsaturated fatty acids is associated with cerebral Aβ accumulation and cognitive function. These findings suggest that high intake of n-6 polyunsaturated fatty acids may contribute to the development of Alzheimer's disease.

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SHIFT 02-459

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

BLOCKING FSH ACTION IMPROVES MEMORY IN MOUSE MODELS OF ALZHEIMER'S DISEASE

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Aims: High post–menopausal levels of the pituitary gonadotropin follicle–stimulating hormone (FSH) are strongly associated with the onset of Alzheimer's disease (AD). We have shown recently that FSH directly activates the hippocampal FSH receptors (FSHRs) to drive AD–like pathology and memory loss in mice. To unequivocally establish a role for FSH in memory loss, we studied the effect of the loss of function of FSH in *3xTg* mice, either genetically by deleting FSHR or pharmacologically through the use of an FSH–blocking antibody.
Methods: Female *3xTg*;*Fshr* mutant mice were ovariectomized and underwent Morris Water Maze for spatial memory testing. In separate experiments, *3xTg* and *APP/PS1* mice were injected with FSH–blocking antibody, following which neurobehavioral testing was performed.
Results: The loss of memory acquisition and retrieval in *3xTg*;*Fshr*$^{+/+}$ mice at 5 months of age was rescued in *3xTg*;*Fshr*$^{-/-}$ mice and, to a lesser extent, in *3xTg*;*Fshr*$^{+/-}$ mice. Sham–operated *3xTg*;*Fshr*$^{-/-}$ mice showed better memory performance, further suggesting that *Fshr* deletion prevents age–related progression of memory deficits. There was also a gene–dose–dependent reduction in the amyloid β40 isoform in whole brain extracts. Serum FSH levels <8 ng/mL in 16–month–old *APP/PS1* mice were associated with better retrieval of spatial memory. Finally, the FSH–blocking antibody rescued recognition memory and spatial learning loss in *3xTg* and *APP/PS1* mice in a context– and time–dependent manner.
Conclusions: Collectively, the data provide compelling genetic and pharmacologic evidence for a protective effect of inhibiting FSH signaling on the progression of spatial memory deficits in mice and lay a firm foundation for the use of an FSH–blocking agent for the early prevention of memory loss in postmenopausal women.

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SHIFT 02-460

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
4-5 April 2025

TARGETING EPITRANSCRIPTOMIC MECHANISMS IN THE REGULATION OF ALZHEIMER'S DISEASE PATHOGENESIS

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Aims: The accumulation of microtubule-associated protein tau (tau) aggregates closely parallels cognitive decline in Alzheimer's disease (AD) and related tauopathies, underscoring its critical role in mediating neurodegeneration. However, the precise mechanisms through which tau aggregation induces neuronal toxicity remain unclear. Our recent research demonstrated that oligomeric tau (oTau) sequesters N6-methyladenosine (m6A)-modified RNA, leading to translational inhibition and neuronal dysfunction. Current study aims to further elucidate the role of RNA modification in AD by (1) examining the dynamics of m6A-RNA in AD progression, (2) determining the impact of RNA methylation on AD pathogenesis, and (3) evaluating the therapeutic potential of inhibiting excessive RNA methylation in models of tauopathy.
Methods: To investigate RNA modifications, we performed RNA dot blots on post-mortem brain tissues from AD patients and age-matched control to quantify levels of m6A, 5-methylcytosine (m5C), and N7-methylguanosine (m7G). Primary glial cell cultures derived from P0 mouse pups were treated with STM2457, a small-molecule inhibitor of METTL3, a key m6A 'writer' enzyme. Immunocytochemistry was then conducted on these cells to assess changes in m6A, tau, astrogliosis, and microglial activation.
Results: Preliminary findings reveal a significant increase in m6A levels in AD and intermediate disease states, with m6A distinctly elevated compared to other RNA modifications such as m5C and m7G. Treatment with STM2457 led to a balanced microglial and astrocyte populations in culture with oTau spreading, suggesting a potential role for m6A in glial activation and neuroinflammation.
Conclusions: Our study highlights the potential of targeting m6A modifications in oTau-associated neurodegeneration. These findings support the development of m6A-focused therapeutics for AD and related tauopathies. Future work will involve DART-seq to further characterize m6A interactions with tau, identifying novel therapeutic targets for AD.

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SHIFT 02-461

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, MISFOLDING, CHAPERONES
4-5 April 2025

DEVELOPMENT OF COMPOUNDS THAT TARGET THE MOST ABUNDANT AMYLOID KNOWN AS MEDIN

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Aims: Medin amyloid is likely to be found in the vasculature of almost everyone over 50 years. Its deposits are linked to reduced arterial elasticity and altered structure of vessel walls. Medin aggregation has also been reported to cause neurodegeneration by inducing neuroinflammation and accelerating ß-amyloidosis and cerebral amyloid angiopathy (CAA). Thus, disassembly of pathogenic medin aggregates by specific ligands might be of therapeutic relevance in cerebrovascular diseases. The aim of this project is the selection and validation of ligands targeting monomeric medin for the further development of a strategy against vascular damage in CAA and vascular dementia.
Methods: We performed phage display selections against full-length L- and D-Medin and peptide sequences were identified from the next generation sequencing data. The binding interactions of compounds with medin were validated *in vitro*. The methods included surface plasmon resonance (SPR), and *de novo* and seeded aggregation kinetics analysis using thioflavin T (ThT) assays.
Results: Two selection courses yielded an L-enantiomeric and an D-enantiomeric compound, termed MVL and MVD, respectively. Using SPR, binding affinities for medin in the low micro- to nanomolar range were determined. The ThT assays revealed concentration-dependent inhibitory effects of the compounds on medin *de novo* fibril formation. Seeded aggregation of medin was also considerably reduced after treatment with both peptides.
Conclusions: Two promising candidates were discovered that interfered with medin aggregation and could be used for further development as a new therapeutic approach against CAA, vasculopathies and related dementia.

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SHIFT 02-464

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
4-5 April 2025

MODULATION OF MT5-MMP IN ALZHEIMER'S DISEASE USING VIRAL-MEDIATED TRANSGENIC STRATEGIES

Thais Lestra[1], Shweta Sonawane[1], Nicolas Jullien[1], Pedro Belio-Mairal[1], Laure Fourel[1], Kevin Baranger[2], Laurence Louis[1], François Roman[1], Eric Di Pasquale[1], Emmanuel Nivet[1], Christine Manrique[1], Santiago Rivera[1]
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Aims: Membrane-type 5 matrix metalloproteinase (MT5-MMP) plays an important role in amyloidogenesis by cleaving APP and promoting the production of the toxic C-terminal fragment C99 as well as Aβ. MT5-MMP knock-out can diminish neuropathological markers of Alzheimer's disease (AD) while preserving cognition in 5xFAD mice. The aim of this study is to investigate the effect of mutant forms of MT5-MMP encoded by AAVs (AAVs-MT5), which could modulate the pathological mechanisms in AD. Our aims are: To determine the impact of AAVs-MT5 variants in 5xFAD mice in the prodromal-like phases. To determine the impact of AAVs-MT5 in human iPS-derived neurons.
Methods: 5xFAD mice were injected with AAVs-MT5 variants at P1. Four months later, behavioral tests were performed to evaluate their cognitive abilities. Immunostaining of amyloid plaques, astrocytes, microglia, MT5-MMP and intracellular Aβ were compared between mice injected with different variants or a PolyA control to non-injected mice. AAVs-MT5 variants and C99 are currently being transduced in hIPSc lines. We will study the subcellular distribution of C99 depending on the modulation of MT5-MMP using proximity ligation assay, immunocytochemistry and microscopy.
Results: Injection of full-length MT5-MMP protein reinforces amyloid pathology as well as neuroinflammation in 5xFAD mice, in contrast with the effects observed for other MT5-MMP variants. We expect specific MT5-MMP variants to influence spatial learning and memory while reducing amyloid pathology and neuroinflammation. Finally, in our cellular model, we expect to observe changes in in the localization of C99 depending on the AAVs-MT5 variant.
Conclusions: Our study should provide insights on the role of specific domains of MT5-MMP in APP metabolism. It should also help validate MT5-MMP as a potential therapeutic target which could ultimately pave the way for new treatments in AD.

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Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
4-5 April 2025

NEURON-SPECIFIC GENE 1 (NSG1) AS A KEY MODULATOR OF ADAM10-DRIVEN PROTEOLYSIS

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Aims: We have discovered that the Neuron-Specific Gene 1 (NSG1) protein regulates ADAM10-dependent proteolytic cleavage of the Alzheimer's disease (AD)-linked sortilin receptor, while its family member NSG2 does not share this function. We aim to elucidate the mechanism by which NSG1 modulates the proteolytic processing of sortilin and determine whether it functions as a molecular switch, capable of controlling activity and substrate selectivity of ADAM10.
Methods: These studies are performed in HEK-cell-based assays by transiently overexpressing the proteins and constructs of interest. A library of NSG1 and NSG2 chimeric constructs based on structural differences between the two proteins was generated with seamless cloning. Postmortem human brain samples from Frontotemporal Dementia (FTD) and AD patients were used to investigate NSG1 and NSG2 expression levels.
Results: We have identified key structural domains that underlie the divergent functions of NSG1 and NSG2. The transmembrane domain (TMD) of both proteins serves as the primary interaction site with sortilin. Notably, single-point mutations within the TMD can inhibit the ability of NSG1 to modulate sortilin ectodomain shedding by switching its preferred binding interface. An extreme helix in the C-terminus of NSG1 is responsible for its modulatory function but it does not drive the interaction itself. Interestingly, this modulatory role can be adopted by NSG2 by introducing the C-terminal helix of NSG1 to the protein. Furthermore, we have linked NSG1 to AD and FTD by showing that NSG1 is significantly downregulated in post-mortem brain tissue from AD and FTD patients.
Conclusions: Regulation of ADAM10 function via NSG1 represents an entirely new way of approaching AD pathology, thus presenting an unexploited potential for drug development.

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SHIFT 02-466

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / SECRETASES, PROTEASES
4-5 April 2025

TSPAN14-MEDIATED REGULATION OF ADAM10 PROTEOLYSIS AND ITS IMPLICATIONS FOR ALZHEIMER'S DISEASE

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Aims: Recent genetic studies have identified numerous Alzheimer's disease risk genes, many of which are predominantly expressed in microglia. Among these is tetraspanin 14 (*TSPAN14*), whose physiological role in the brain remains unexplored. Our study aims to elucidate TSPAN14's function in microglia and its impact on Alzheimer's disease-related molecular pathways.
Methods: We employed a combination of biochemical, molecular, and proteomic methods using human induced pluripotent stem cell (iPSC)-derived microglia and BV2 mouse microglia as *in vitro* models.

Results: Research suggests that TSPAN14 acts as functional regulator of ADAM10, a transmembrane protease that cleaves multiple substrates in the brain, including the Alzheimer's disease-associated microglial protein TREM2. Our results indicate that TSPAN14 regulates ADAM10-mediated proteolysis of TREM2, and therefore plays a role in modulating TREM2 function.
Conclusions: Our findings help to elucidate the physiological and pathophysiological relevance of TSPAN14 in the brain. These results have the potential to uncover new pathways relating to Alzheimer's disease pathogenesis and to highlight novel therapeutic targets.

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SHIFT 02-467

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TREM2
4-5 April 2025

USING IPSC MODELS TO INVESTIGATE THE IMPACT OF TREM2 VARIANTS ON THE MICROGLIAL RESPONSE TO AMYLOID-BETA

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Aims: The *TREM2* variants *R62H* and *R47H* are linked to increased risks of Alzheimer's disease (AD). TREM2 is a microglial receptor for endosomal uptake of amyloid-β oligomers (oAβ) and inflammatory modulator. Our group previously showed that AD patients carrying *R62H* or *R47H* display increased expression of proinflammatory genes in microglia. Here, we aimed to test for impaired modulation of proinflammatory cytokine release in *R62H* and *R47H* microglia *in vitro*.
Methods: Human isogenic iPSC lines carrying the *TREM2* common variant (CV), *R62H, R47H*, or a *TREM2* KO were differentiated into iPSC-derived microglia (iMG). iMG cultures were treated for 24h with oAβ generated from synthetic amyloid-β monomers or with 100 ng/ml lipopolysaccharide (LPS). Interleukin-6 (IL-6) concentration was measured in the supernatant of these cultures via ELISA.
Results: Preliminary data suggests that mean IL-6 concentration was similar in untreated *TREM2*-CV (9 pg/ml; n=3), *R62H* and *R47H* iMG cultures (11 and 7 pg/ml; n=2) but 4-times higher in *TREM2*-KO cultures (43 pg/ml; n=2). oAβ induced a dose-dependent increase in IL-6 production in all iMG lines. After treatment with 3 μM oAβ, IL-6 concentration was similar in *TREM2*-CV (565 pg/ml; n=3) and *R47H* iMG cultures (763 pg/ml; n=2), but 2- and 6-fold greater in *R62H* and *TREM2*-KO cultures (1303 and 3374 pg/ml; n=2). All iMG lines secreted IL-6 following stimulation with LPS. Supernatant IL-6 levels showed little difference between LPS-treated cultures of *TREM2*-CV (21365 pg/ml; n=3) and *R47H* iMG (23297 pg/ml; n=2) but were >55% higher in *R62H* and *TREM2*-KO cultures (34854 and 33661 pg/ml; n=2).
Conclusions: These results indicate that TREM2-mediated modulation of proinflammatory cytokine responses of microglia to oAβ is impaired by the *R62H* variant but not by *R47H in vitro*. Additional data collection is continuing.

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SHIFT 02-468

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TREM2
4-5 April 2025

TOWARDS A CONSISTENT AND ROBUST MEASUREMENT OF STREM2 USING THE FULLY AUTOMATED LUMIPULSE® G PLATFORM

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Aims: Soluble triggering receptor expressed on myeloid cells 2 (sTREM2), found in cerebrospinal fluid (CSF) and blood, is a promising biomarker associated with neuroinflammation and microglial activity in Alzheimer's disease (AD) and other neurodegenerative conditions. sTREM2 concentrations can provide insights into TREM2-mediated microglial activation, supporting research and pharmaceutical drug development. Fujirebio has developed the Lumipulse® *G* sTREM2 prototype assay for CSF and blood to enhance accessibility for sTREM2 quantification. This study evaluates the analytical performance of this assay in both matrices.
Methods: The LUMIPULSE *G* System, an automated chemiluminescent enzyme immunoassay platform, processes CSF, plasma (K2EDTA) and serum samples in about 30 minutes using 20 µL of sample. This assay uses a specific 2-step format with antibodies targeting the human sTREM2 ectodomain and was assessed for sensitivity, precision, dilutional linearity, and lot consistency. The calibration range spanned 0–40,000 pg/mL, and sample dilution was evaluated to improve matrix interference. A comparison with the Simoa sTREM-2 Advantage PLUS Kit (HD-X) provided insights into cross-platform comparability.
Results: The Lumipulse® *G* sTREM2 prototype assay, in development for a commercial RUO product, met all analytical performance criteria. Analytical sensitivity was determined with all clinical samples exceeding the lower limit of quantification (LLoQ). Imprecision was determined to be below 15% CV across matrices, and dilutional linearity was within ±20%. A method comparison showed a high correlation ($r \geq 0.90$) with the Simoa assay. Stability testing under stressed conditions demonstrated promising results, with real-time stability testing ongoing.
Conclusions: The Lumipulse® *G* sTREM2 prototype assay is a potential robust and reliable tool for sTREM2 quantification in blood and CSF on a globally available fully automated immunoassay system, showing the necessary analytical performance in blood and CSF.

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SHIFT 02-469

Poster on Board - Shift 02
β-AMYLOID DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TREM2
4-5 April 2025

CORRECTING THE GENETIC DEFICITS OF BLOOD MONOCYTES CARRYING TREM2R47H MUTATION AND ITS THERAPEUTIC POTENTIAL IN AN AD MOUSE MODEL

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Aims: The arginine-47-histidine (R47H) mutation in triggering receptor expressed on myeloid cells 2 (TREM2) confers a significant risk for Alzheimer's disease (AD), but the underlying mechanisms remain unclear. Dysfunction of blood monocytes has been implicated in the development of AD. Ageing and genetic deficits contribute to monocyte dysfunction. Previous studies have primarily focused on the impact of the $TREM2^{R47H}$ mutation on microglia. Less attention has been paid to blood monocytes in terms of their role in the development of AD and their therapeutic potential when carrying the $TREM2^{R47H}$ mutation.
Methods: Flow cytometry was performed to evaluate monocytic phagocytosis. To investigate whether blood monocytes carrying the $TREM2^{R47H}$ mutation contribute to AD pathogenesis, APP/PS1 mice with wild-type (Wt) TREM2 gene were transplanted with bone marrow cells (BMCs) from APP/PS1 mice with the $TREM2^{R47H}$ mutation (AD-$T^{R47H\rightarrow Wt}$). To explore therapeutic potential of replacing mutant monocytes, APP/PS1 mice carrying the $TREM2^{R47H}$ mutation were transplanted with BMCs from APP/PS1 mice with Wt TREM2 gene (AD-$T^{Wt\rightarrow R47H}$). Additionally, a gene-editing strategy was employed to correct the $TREM2^{R47H}$ mutation in BMCs, and its therapeutic potential was also investigated.
Results: Mouse monocytes carrying the $TREM2^{R47H}$ mutation showed compromised Aβ phagocytosis. AD-$T^{R47H\rightarrow Wt}$ mice exhibited increased Aβ levels in blood and brain, aggravated AD-type pathologies, and worsened cognitive function. Moreover, AD-$T^{Wt\rightarrow R47H}$ mice showed the restored monocytic Aβ phagocytosis, reduced Aβ levels in blood and brain, and ameliorated AD-type pathologies. Correcting the $TREM2^{R47H}$ mutation in BMCs using the base-editing technique recovered monocytic Aβ phagocytosis and rescued AD-type deficits, with minimal ratio of off-targets.
Conclusions: Our study reveals that blood monocytes carrying the $TREM2^{R47H}$ mutation contributes to the pathogenesis of AD, and correcting the $TREM2^{R47H}$ mutation in BMCs represents a potential therapeutic approach for individuals carrying this mutation.

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SHIFT 02-471

Poster on Board - Shift 02
COVID-19 / IMPACT ON BRAIN NEURODEGENERATIVE DISEASES / EPIDEMIOLOGY OF COVID-19 IN PATIENTS WITH NEURODEGENERATIVE DISEASES
4-5 April 2025

MAPPING PERIPHERAL IMMUNE CELL MECHANISMS FOR NEURODEGENERATIVE DISEASES AND COVID-19 PHENOTYPES USING MENDELIAN RANDOMISATION

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Aims: This project aims to integrate genomic data with advanced statistical techniques to elucidate causal pathways underlying brain diseases, COVID-19 susceptibility, and healthy brain ageing, ultimately identifying potential biomarkers and/or drug targets for risk mitigation. The objectives are: 1. To identify single-cell genetic anchors, consisting of immune cell expression quantitative trait loci (eQTLs) and brain cell eQTLs, in both peripheral immune and brain cells. Peripheral immune cell data will be sourced from available datasets, including single-cell RNA-seq data of activated CD4+ naïve and memory T cells (N=655,349) and resting T cells (N=1,267,768), including CD4+, CD8+, regulatory, and MAIT T cell subtypes. 2. To utilise single-cell eQTL analysis, genetic colocalization, and Mendelian randomisation to identify cell-type-specific causal genes for various brain disorders, COVID-19 phenotypes, and potential therapeutic targets or biomarkers. 3. To integrate proteomics data with genetic traits to identify causally involved proteins and subsequently protein biomarkers.
Methods: We utilize colocalisation analysis combined with univariate two- sample Mendelian randomization to inform potential causal relationships between peripheral immune cells and Brain & COVID-19 phenotypes.
Results: We mapped single cell-type eQTLs in unstimulated and stimulated PBMCs and integrated these with GWAS data related to 30 diverse central nervous system (CNS) phenotypes, including neurodegenerative diseases, behavioural traits, and structural brain traits. Focusing on CD4+ T cells, we identified genes (eGenes) regulated by one or more SNPs (eSNPs). We uncovered 683 significant putative causal inferences (i.e., putatively causal gene>CD4+>trait triplets) across 14 CNS traits, including Alzheimer's Disease, Parkinson's Disease and COVID-19-related phenotypes.
Conclusions: The translation of GWAS loci into viable therapies requires understanding causal genes and their directional impact on disease susceptibility. Our results suggest links between neurodegenerative diseases, COVID-19 infection, and immune cell types, highlighting potential novel approaches to treating and mitigating brain disease.

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SHIFT 02-472

Poster on Board - Shift 02
DEMYELINATING DISEASES / ANIMAL MODELS
4-5 April 2025

ALLEVIATION EFFECT OF EXPERIMENTAL AUTOIMMUNE ENCEPHALOMYELITIS BY THE IMMUNE REGULATION OF REDUCTION IN IL-17/TH17 IN TOXOPLASMA GOONDII-INFECTED MOUSE

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Aims: Experimental autoimmune encephalomyelitis (EAE) is a mouse model of multiple sclerosis (MS), a demyelinating autoimmune disease caused by the infiltration of a harmful autoreactive Th1 and Th17 cells. The objective of the present study is to analyze the effect of *T. gondii* infection on the onset of EAE.
Methods: C57BL/6 mice were intraperitoneally injected with *T. gondii* cysts (ME49 strain). Mice at 10 wk after *T. gondii* infection were subcutaneously immunized in both flanks of the back with complete Freund's adjuvant (CFA) emulsion and myelin oligodendrocyte glycoprotein 35-55 (MOG35-55). Experiments were performed for the clinical manifestation, phenotypes of immune cells recruited to the brain, neuropathy with demyelination, immune response in T. gondii infected EAE mouse.
Results: *T. gondii* infection in the brain increases SOCS3 expression and decreases the phosphorylation of STAT3, **and** to reducing IL-17A and IL-23, which suppress the differentiation and expansion of pathogenic Th17 cells, accelerating MS development. These immune responses resulted in a reduction in the clinical scoring of EAE induced by MOG_{35-55} immunization. In the EAE group with *T. gondii* infection (Tg+EAE-group), Th17-related immune responses that exacerbate the onset of EAE were reduced compared to those in the EAE group, and it was confirmed that the immunomodulatory effects caused by *T. gondii* infection inhibited the progression of EAE.
Conclusions: This study suggests that the alleviation of EAE after *T. gondii* infection is regulated in a SOCS3/STAT3/IL-17A/blood brain barrier (BBB) integrity-dependent manner. Our study provides a new promising approach for MS therapy through specific immune modulation based on CNS infection by the parasite *T. gondii*.

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SHIFT 02-473

Poster on Board - Shift 02
DEMYELINATING DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

DEVELOPMENT OF A PROTOTYPE CHLIA AND A RESEARCH-USE ONLY ELISA FOR THE DETECTION OF LIGHT CHAIN NEUROFILAMENT (NFL) IN CSF

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Aims: Increased levels of the light chain of neurofilament (NfL) in human cerebrospinal fluid indicate axonal damage. Their determination can support laboratory diagnosis and monitoring of neurological diseases associated with axonal damage. We developed a prototype chemiluminescence assay (ChLIA) and an enzyme-linked immunoassay (ELISA, research use only) to detect NfL and report their analytical agreement with an established ELISA.
Methods: Agreement between the established NF-light ELISA (UMANDiagnostics) and the Neurofilament Light (NfL) ELISA (EUROIMMUN) as well as the prototype NfL ChLIA (EUROIMMUN) was determined using 19 internal reference samples containing native NfL, with NfL levels distributed across the measurement range of the NF-light ELISA. Possible bias between methods was estimated with Passing-Bablok regression and Kolmogorov-Smirnov CUSUM test.
Results: Comparison of NF-light ELISA and Neurofilament Light (NfL) ELISA indicated a small proportional deviation with NF-light ELISA values being higher than Neurofilament Light (NfL) ELISA values (regression: y=-163.9+0.97x, 95% CI intercept: [-490.8, -79.67], CI slope: [0.89, 1.05], r=0.98, CUSUM test p=0.6). Comparison of Neurofilament Light (NfL) ELISA and prototype NfL ChLIA indicated a small shift with ChLIA values being higher than ELISA values, especially in the upper end of the measurement range (regression: y=13.73+1.14x, CI intercept: [-140.9, 97.05], CI slope: [1.07, 1.23], r=0.98, CUSUM test p=0.6).
Conclusions: The results of analytical agreement between NfL levels determined by the ELISA and the prototype ChLIA in comparison to the established ELISA show promise regarding their performance characteristics. Being limited by the small sample size, these results will be followed up by a larger method comparison and validation study.

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SHIFT 02-474

Poster on Board - Shift 02
DEMYELINATING DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

OPAL SENSOR EQUIVALENCY TO CAPTURE MOBILISE-D DIGITAL MOBILITY OUTCOMES

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Aims: Mobilise-D was an IMI-funded project producing validated and accepted digital mobility outcomes (DMOs) to monitor the daily life gait of people with various mobility disorders, including Parkinson's disease (PD), multiple sclerosis (MS), and others. The project used 2 wearable sensor companies (McRoberts and Axivity) to capture and validate data, prior to releasing sensor specifications (accelerometer & gyroscope @ 100hz) for broader scale dissemination. We conducted a study with the objective of demonstrating Opal sensor (APDM) equivalency to the Axivity sensor previously used in the project to capture DMOs.
Methods: 10 participants with MS (18-64 y.o.) with an EDSS <6 participated. Medical & MS history, EDSS, MSFC, NeuroQoL, MS Impact Scale, MAIA, Postural Awareness Scale, Visual Functioning Scale were completed. Additionally, a 2-Minute Walk Test was performed over a 7m walkway with 180 degree turns while wearing adhered Opal and Axivity sensors on the lower waist. The following week, participants wore the same sensors during waking hours for 7 continuous days in the real-world. Participants returned sensors to the site via mail upon completion for data analysis.
Results: Ten individuals had gait data collected over an average of 6 days (12 hrs/day). The Opal and the Axivity sensors consistently provided statistically equivalent results. Average absolute percent difference was 1.249% (with a range of 0%-3%) for all 25 real-world DMO measures of gait quality, turning and activity.
Conclusions: Opal wearable sensors can be used to collect Mobilise-D DMOs during daily life. Additionally, Clario global-scale services enable real-world mobility data capture alongside eCOA, Imaging, Cardiac, and Respiratory endpoint capture for a wholistic patient view in global clinical trials.

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SHIFT 02-475

Poster on Board - Shift 02
DEMYELINATING DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

CORRELATION BETWEEN ECHO INTENSITY AND ABNORMAL SPONTANEOUS ACTIVITY IN CUBITAL TUNNEL SYNDROME: A PRELIMINARY STUDY

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Aims: -**Cubital tunnel syndrome** is upper limb neuropathy, and ultrasonography (US) is now widely used for its diagnosis and treatment. -**Echo intensity (EI)** is one of the quantitative ultrasonographic muscle evaluation techniques, which uses the fact that the echogenicity of the muscle **increases due to fibrosis or fatty change** when the muscle **denervation** occurs. -Several studies have explored the differences in EI between affected muscles and healthy controls in peripheral neuropathy but have not compared EI with other existing diagnostic parameters. -Therefore, through this preliminary study, we tried to find out the **correlation between the EI** of the abductor digiti minimi (ADM) muscle, which is most affected in cubital tunnel syndrome, and the **abnormal spontaneous activity (ASA) degree of ADM** observed in needle EMG.
Methods: -Patients with **unilateral** cubital tunnel syndrome were enrolled in this study. -We measured and calculated the mean and standard deviation (SD) of **ADM EI**

$$\text{ADM EI ratio} = \frac{\text{EI of affected ADM}}{\text{EI of ipsilateral thenar muscle}}$$

ratio. -The mean EI was obtained by **repeating 10 times** from one patient, and EI of the muscles were analyzed using **ImageJ software.** -Electrodiagnostic studies were done by standardized techniques using Nicolet Viking IV electrodiagnostic system (Nicolet Biomedical, Madison, WI, USA). -ADM needle EMG was done to evaluate the degree of ASA.

Results: -ADM의 ASA는 8명 중 4명에서 관찰되었으며, ASA 정도는 2+에서 4+의 분포를 보였다. -EI 비율은 5명의 환자 중 1보다 컸습니다. -ASA가 높은 ADM은 초음파 EI 비율이 크다. - 그러나 ASA의 유무와 EI **비율의 크기 사이에는 통계적으로 유의한 상관관계가 없었다[Table**

Table 1. Comparison of ASA and EI ratio in affected ADM muscle

Case	Hand side	Needle EMG (ASA)	EI ratio (Mean ± SD)
1	Rt.	+++	1.02±0.05
2	Lt.	−	0.52±0.13
3	Lt.	++	0.37±0.08
4	Lt.	++	1.05±0.17
5	Rt.	++++	1.50±0.41
6	Rt.	−	1.11±0.13
7	Rt.	−	0.67±0.11
8	Lt.	−	1.06±0.08
			p = 0.775

EMG, electromyography; ASA, abnormal spontaneous activity; EI, echo intensity; ADM, abductor digiti minimi; SD, standard deviation

1].

Conclusions: -This preliminary study examined the correlation between ASA degree and muscle EI ratio, with the anticipation of meaningful results as more patient data is accumulated, despite the lack of statistically significant findings thus far.

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SHIFT 02-476

Poster on Board - Shift 02
DEMYELINATING DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4-5 April 2025

ESTABLISHMENT AND VALIDATION OF AN IN VITRO CO-CULTURE MODEL TO STUDY MYELINATION USING HUMAN IPSC-DERIVED GLUTAMATERGIC NEURONS AND OLIGODENDROCYTES

Malika Bsibsi[1], Abeera Popalzij[1], Matteo Zanella[1], Lieke Geerts[1], Mark Musters[1], Stefan Kostense[1], David Fisher[2], Ludovico Buti[1], Tony Oosterveen[3], Ines Ferreira[3], Marijn Vlaming[1]
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Aims: Oligodendrocytes wrap their cell membrane around axons to support rapid nerve impulse conduction. Oligodendrocyte progenitor cells (OPC) react in human adult CNS to injury by proliferation and migration. Oligodendrocyte dysfunction and disrupted myelin is involved in the pathogenesis of neurodegenerative disease such as multiple sclerosis (MS) and Alzheimer's disease (AD). Although microglia and astrocytes have been extensively characterized in neurodegeneration, oligodendrocytes have received less attention due to the complexity of primary oligodendrocyte isolation and culturing. Induced pluripotent stem cells (iPSCs)-derived oligodendrocytes can provide a suitable solution to study differentiation and maturation of oligodendrocytes as well as myelination.
Methods: Here, we characterised commercially available iPSC-derived oligodendrocytes (ioOligodendrocyte) generated by bit.bio using the opti-ox technology from human iPSCs. We developed a co-culture in vitro model with the iPSC-derived glutamatergic neurons (ioGlutamatergic Neurons, bit.bio) to evaluate the myelination processes and oligodendrocyte maturation.
Results: Immunofluorescent staining of ioOligodendrocyte cells at different time points showed positive staining for key oligodendrocyte lineage markers including Olig2, O4, and SOX2 and myelin markers, including myelin-binding protein (MBP) and myelin proteolipid protein (PLP). At day 3 post seeding the O4+ cells displayed a typical OPC-like morphology. They mature into oligodendrocyte-like cells with characteristic multiple branched processes. Co-culture of ioGlutamatergic Neurons and ioOligodendrocyte cells resulted in increased number of MBP+ cells compared to monocultures of oligodendrocytes in a time-dependent manner. Importantly, MBP+ cells surrounded axons in the co-culture, indicating myelination of neuronal axons.
Conclusions: Taken together, we successfully established a relevant in vitro mono- and co-culture myelination model using the iPSC-derived ioOligodendrocyte cells and ioGlutamatergic Neurons. These models enable the screening of compounds that modulate oligodendrocyte maturation and myelination, supporting drug development for neurodegenerative and demyelinating diseases, such as multiple sclerosis.

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SHIFT 02-477

Poster on Board - Shift 02
DEMYELINATING DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4-5 April 2025

AN IPSC DERIVED NEUROINFLAMMATION IN VITRO MODEL OF NEURONS AND GLIAL CELLS

Malika Bsibsi[1], Abeera Popalzij[1], Matteo Zanella[1], Lieke Geerts[1], Mark Musters[1], Stefan Kostense[1], David Fischer[2], Ludovico Buti[1], Tony Oosterveen[3], Ines Ferreira[3], Marijn Vlaming[1]
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Aims: Neuroinflammation occurs in most neurodegenerative and inflammatory diseases. Mono in vitro cultures of astrocytes and microglia are powerful tools to study specific molecular pathways involved in neuroinflammation. However, more complex neuronal in vitro models are required to capture the effects of cellular communication on neuroinflammation in a human-based model which reduces animal testing in the early stages of drug discovery.
Methods: We have established a complex in vitro culture model of neurons, astrocyte, microglia and oligodendrocytes, for which we used a variety of iPSC-derived neuronal and glial cells (ioGlutamatergic Neurons, IoMicroglia, ioOligodendrocytes, iCell Astrocytes). We evaluated and validated the co-cultures by immunocytochemistry, multi-parametric high content imaging and multi-variate data analysis and the release of cytokine TNF-α as read-outs for neuroinflammation. Additionally, we triggered neuroinflammation and neurotoxicity in this model with LPS, nigericin and beta amyloid fibrils, followed by electrochemiluminescence-based detection to measure Neurofilament light chain (NfL), an established biomarker for neurotoxicity and neurodegeneration.
Results: Co-cultures of neurons, astrocytes and oligodendrocytes increased branching of neuronal dendrites and astrocytes process. Maturation of Oligodendrocytes, however, seem to be reduced in the presence of astrocytes, treatment with Tasin-1 (a well-known inducer of oligodendrocyte differentiation and myelination) promoted the maturation and myelin-binding protein (MBP) production in oligodendrocytes. Adding microglia to the cultures could inhibit maturation and differentiation of neurons and oligodendrocytes. Treatment with LPS, nigericin or beta amyloid fibrils leads to damage of neurons and oligodendrocytes as quantified by high content imaging and by the release of TNF-α and NfL.
Conclusions: Taken together, we successfully established and characterized a complex in vitro culture model using iPSC derived neuronal and glial cells which we consider as a highly valuable tool for modeling neurodegenerative and inflammatory disease in drug discovery programs.

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SHIFT 02-479

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / ANIMAL MODELS
4-5 April 2025

NEUROTOXIC CONSEQUENCES OF CHRONIC EXPOSURE TO CONCENTRATED AMBIENT FINE AND ULTRAFINE PARTICULATE MATTER IN A NOVEL MOUSE MODEL OF LATE-ONSET ALZHEIMER'S DISEASE

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Aims: Recent epidemiological studies identified individuals living in areas with heavy air pollution have substantially greater risk for cognitive decline, dementia and Alzheimer's disease (AD). Studies using animal models by us and others also demonstrate that traffic-related air pollution, specifically, particulate matter (PM) exacerbates cognitive decline, neuroinflammation and AD-like neuropathology. However, key underlying mechanisms by which air pollution or PM instigates neurotoxicity and neurodegeneration leading to the clinical onset of AD remain largely unexplored. In this study, we used a novel mouse model of late-onset AD (hAβ-KI) to examine the risk of chronic exposure to concentrated ambient fine and ultrafine PM on cognition, neuronal function and development of AD-like pathology in the brain.
Methods: Both hAβ-KI and strain-matched wildtype (WT) mice at 6 months of age were exposed to concentrated ambient PM for 7 or 13 months (5 hrs/day, 4 days/week) using a versatile aerosol concentration enrichment system (VACES). At the end of the exposure period, all animals were tested with open field (OF), object location memory (OLM) and novel object recognition (NOR) tests. A subset of animals were then used for electrophysiological recordings of long-term potentiation (LTP).
Results: We found that hAβ-KI and WT mice exposed to PM had substantially impaired LTP in the CA1 hippocampus. On the other hand, neurobehavioral tests are showing mixed outcomes. While NOR was significantly impaired in WT mice and had a trend to be impaired in hAβ-KI mice, no obvious difference was observed in OF or OLM tests.
Conclusions: Our findings strongly indicate harmful impact on neuronal function, but more investigation will be required to unveil its neurotoxic consequences on AD-like phenotypes in hAβ-KI mice.

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SHIFT 02-481

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4-5 April 2025

AGGREGATION OF DISC1 AND RELATED PROTEINS IN MENTAL ILLNESS OCCURS ACROSS THE BRAIN, BUT IS NOT HOMOGENOUS

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Aims: Protein aggregation, a key mechanism in neurodegenerative disorders like Alzheimer's, has recently been linked to mental illnesses such as schizophrenia. Proteins like Disrupted in Schizophrenia 1 (DISC1), Collapsin Response Mediator Protein 1 (CRMP1), and Trio and F-actin Binding Protein (TRIOBP-1) have been found to aggregate in patients with schizophrenia and major depressive disorder. However, most studies focus on single brain regions, potentially overlooking broader patterns. Our aims were to investigate the aggregation of these proteins across multiple brain regions in schizophrenia, major depressive disorder, and Alzheimer's disease, and assess the heterogeneity in protein insolubility across different regions and hemispheres.
Methods: In this study, we analyzed protein insolubility in 20 post-mortem brain tissue samples from a single individual diagnosed with both schizophrenia and Alzheimer's disease. We then conducted follow up analysis in smaller sample sets from other individuals, including those diagnosed with major depressive disorder, Alzheimer's disease, and victims of suicide.
Results: Our analysis revealed that insoluble DISC1 was present in multiple regions of the brain but with significant variation in the levels of insolubility across different areas, including corresponding regions in opposing hemispheres. The follow up analysis in other patients revealed a similar pattern: when insoluble proteins such as DISC1, CRMP1, or TRIOBP-1 were found in one brain region, they were often present in other regions as well. However, the distribution of these aggregates was highly heterogeneous.
Conclusions: Our findings suggest that current studies may be underestimating the prevalence of protein aggregation in mental illnesses due to the variation in insoluble protein distribution across the brain. Future research should take this heterogeneity into account to gain a more comprehensive understanding of the role of protein aggregation in mental disorders.

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SHIFT 02-482

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

ABNORMAL BRAIN DEVELOPMENT IN BETA-PROPELLER PROTEIN-ASSOCIATED NEURODEGENERATION ORGANOID MODEL

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Aims: Human brain development is a complex process in which embryonic precursors of the nervous system rapidly proliferate, migrate, and differentiate to develop connectivity patterns. Thus, abnormal neurodevelopment and differentiation processes are associated with neurodevelopment disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Beta-propeller protein-associated neurodegeneration (BPAN) caused by mutations in the WDR45 (WD Repeat Domain 45) gene is an inherited neurodevelopmental disorder with brain iron accumulation. To identify the role of WDR45 in neurodevelopment processes, we investigated neurodevelopmental abnormalities in BPAN model with WDR45 gene mutation.
Methods: For the study, we used induced pluripotent stem cells (iPSCs) carrying WDR45 gene mutation. We generate the WDR45 mutant iPSC model (WDR45 CRISPR/Cas9: c.17-18delinsAAA) using CRISPR/Cas9-mediated gene editing. Patient-specific iPSC model (WDR45 patient: c.1035-1036delCA) was reprogrammed from peripheral blood mononuclear cells (PBMCs) of BPAN patient into iPSCs using transcription factors. In this study, we analyzed the abnormal neuronal development during 2D (neural stem cell to neurons) and 3D (cerebral organoids) differentiation in two iPSC lines carrying WDR45 gene mutation.
Results: We observed impaired neural stem cells (NSCs) population with reduced self-renewal ability in WDR45 mutant NSCs. Our results show that the WDR45 gene mutant affects the regulation of NSC state and increases abnormal NSCs, consequently reducing the differentiation of excitatory neurons. In addition, abnormal ventricular zone, neuronal migration, and layer formation were confirmed in WDR45-mutant cerebral organoids at 20- and 40-days using immunohistochemistry and ultrastructural analysis. Therefore, the ventricular zone with abnormal neural progenitors resulted in neurodevelopmental abnormalities.
Conclusions: These early neurodevelopmental abnormalities will disrupt the differentiation of mature neurons and glial cells and the formation of synapses. Our results will be key data for studying the role of WDR45 gene in neurodevelopment.

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SHIFT 02-492

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

TOWARDS GENERALIZING IMAGE SEGMENTATION ON NEUROMELANIN-SENSITIVE MRI ACROSS SITES

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Aims: Neuromelanin (NM)-sensitive MRI of the substantia nigra (SN) is a promising imaging biomarker for Parkinson's disease (PD), but there is a lack of publicly available tools for segmenting the NM hyperintensity. Simultaneously, investigations tend to focus on images acquired from a single site and protocol, with little regard to generalization. To fill this gap, we created a segmentation model by addressing cross-site generalizability, and published it as an open source research tool.
Methods: The SN was hand drawn on NM-weighted MRIs from a mixture of PD patients and controls from a Norwegian cohort (N=82), a Canadian cohort (N=27) and PPMI (N=22). A convolutional neural network was trained on the Norwegian cohort, while generalization capability was evaluated on the other two. To force the network to learn a more general representation of the inputs, we trained it on multiparametric MRIs, while aggressively applying data augmentation. Our method was compared to a a low-augmentation uniparametric model in terms of Dice overlap, and clinical utility was established using contrast-to-noise ratio of the SN to a background region.
Results: On test data from the same site of the training data, the low- and high-augmentation models barely differed in performance (Dice=0.75). However, the low-augmentation uniparametric model failed to generalize to the Canadian and PPMI datasets (Dice=0.007/0.36 respectively), while our approach improved generalization considerably (Dice=0.68/0.56). ROC-analysis yielded an AUC of 0.83 from our model on the test set, compared with 0.85 from manual segmentations.

Conclusions: Image segmentation models tend to under-perform on out-of-distribution data, despite good results on the test set. Models should always be trained on heterogeneous data, but we can further improve generalization with data augmentations and multiparametric training, as well as encouraging open sharing of code.

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SHIFT 02-493

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

QUANTIFICATION OF NF-L IN CEREBROSPINAL FLUID BY MASS SPECTROMETRY: TOWARDS IMPLEMENTATION OF A REFERENCE MEASUREMENT PROCEDURE

Christopher Mcelroy[1], Emanuele Scollo[1], Salomé Coppens[2], Christopher Hopley[1], Heidi Goenaga-Infante[1], Luise Luckau[1]
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Aims: Neurofilament light chain (Nf-L) is a biomarker detectable in cerebrospinal fluid (CSF) and blood, used to monitor axonal damage associated with neurodegenerative diseases. Nf-L is often quantified using immunoassays due to their sensitivity. However, different immunoassays lack comparability and the measurement uncertainty is generally large (Holcombe, 2024). Therefore, standardization of Nf-L measurements is essential and can be achieved with reference measurement procedures (RMPs) using certified reference materials (CRMs). Here we describe the development of a quantification method for Nf-L peptides in CSF using mass spectrometry, thereby facilitating CRM production.
Methods: A selected reaction monitoring method using a Xevo TQ-XS mass spectrometer coupled to capillary flow liquid chromatography was developed to quantify Nf-L tryptic peptides first using an *Escherichia coli* expressed protein and then in artificial CSF.
Results: Following value assignment of an NF-L protein standard *via* amino acid analysis and isotope dilution mass spectrometry against NMIJ amino acid CRMs, a mass fraction content of the calibrator stock solution of 1 nmol/g ± 0.02 nmol/g (error represents combined expanded uncertainty) was obtained. Surrogate CSF spiked with the calibrator at different levels enabled determination of the method LOQ for 2 peptides: peptide 1 at 0.1 µg/L and peptide 2 at 1 µg/L.
Conclusions: A robust mass spectrometry method for quantifying Nf-L peptides in CSF was developed and validated for accuracy, precision, and sensitivity. This method will support standardization of Nf-L measurements through value assignment of pooled CSF materials, aiding future interlaboratory comparisons and enhancing diagnostic consistency. References: Holcombe. (2024). Clinically and industrially relevant incurred reference materials to improve analysis of food allergens, milk, egg, almond, hazelnut and walnut. *Food Chemistry, 434*, 137391.

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SHIFT 02-494

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

CASE REPORT OF A PARKINSONISM PATIENT PRESENTING WITH DYSARTHRIA ONLY

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Aims: Parkinsonism is a general term used to describe a set of movement disorders that resemble the symptoms of Parkinson's disease. These symptoms typically include tremors, bradykinesia, rigidity, and postural instability. In some cases, speech impairment can be the initial symptom in a patient with Parkinsonism, but various Parkinsonian features may appear later. We describe a case of a Parkinsonism patient who presented with dysarthria only.
Methods: A 58-year-old man presented with dysarthria that started two years ago. At that time, his only symptom was dysarthria, which progressed gradually. There were no other Parkinsonian features or non-motor symptoms. The initial United Parkinson's Disease Rating Scale (UPDRS) Part III score was 1.
Results: Brain magnetic resonance imaging showed no significant focal parenchymal lesions. Dopamine transporter scans revealed decreased uptake in the dorsal posterior putamen. Other neurologic tests, including nerve conduction studies and electromyography, were normal. The patient received dopaminergic replacement therapy, resulting in mild improvement of the dysarthria. One year later, only mild dysarthria was sustained, without any other Parkinsonian features.
Conclusions: Despite various neurologic laboratory tests showing no abnormalities, if symptoms continue to progress, dopamine transporter scans may be necessary to differentiate other neurodegenerative diseases such as Parkinsonism.

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SHIFT 02-495

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

A REVIEW OF THE UTILITY OF SPEECH AND LANGUAGE ANALYTICS FOR SCREENING ALZHEIMER'S DISEASE AND SCHIZOPHRENIA

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Aims: Efficient participant screening is essential in neuroscience clinical trials to reduce costs and streamline recruitment. Traditional identification and diagnostic methods are costly, invasive and limit access, especially for diseases like Alzheimer's disease (AD) and schizophrenia. Speech and language changes occur as part of the symptom complex in both conditions. Aim is to examine the relationship between speech and language function in AD and schizophrenia. Data are designed to inform analytics pipelines for screening these common neurological conditions.
Methods: Databases including PubMed, Scopus, and Google Scholar were searched for studies related to speech and language, Alzheimer's disease, Schizophrenia, and digital speech analysis. Data were synthesized thematically, focusing on natural history studies describing speech and language function in AD or Schizophrenia.
Results: Individuals with AD present with memory-related speech and language impairments such as word finding difficulties, reduced vocabulary, and frequent pauses. Communication of individuals with schizophrenia is characterized by disorganized and incoherent speech. Studies focused on describing spectral, prosodic, lexical, semantic, and syntactic features of speech and language. Advances in digital speech analytics, machine learning and natural language processing offer innovative methods for screening early-stage AD and schizophrenia patients.
Conclusions: Speech and language analysis is a promising tool for improving participant screening in clinical trials for neurological disorders, potentially accelerating drug development and reducing healthcare burdens. There remain, however, challenges relating to cohort variability, linguistic diversity, privacy concerns, and standardization.

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SHIFT 02-496

Poster on Board - Shift 02
HUNTINGTON'S AND OTHER NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

CNS PROTEOMICS IDENTIFY POTENTIAL BIOMARKERS OF ACUTE AND CHRONIC TRAUMATIC BRAIN INJURY.

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Aims: Traumatic Brain Injury (TBI) is a heterogeneous condition involving multiple pathophysiological processes. High-dimensional protein assays or proteomics are particularly well-suited for validation and discovery of TBI fluid biomarkers given the wide-reach across mechansisms of injury and recovery.
Methods: Under IRB approved protocols, participants with a history of multiple TBIs and self-reported cognitive complaints ("chronic-mixed,"), severe TBI patients admitted to the intensive care unit ("acute-severe," GCS 3-8) and cognitively intact controls were included in the study. CSF and plasma from a single time-point were analyzed using the Alamar NULISASeq™ CNS Disease Panel 120.
Results: There were 22 chronic-mixed (40±8.5yrs, 19% female, 5.8±3.3 TBI incidents, 10.6±6.7yrs post-injury), 34 acute-severe (46±21yrs, 21% female, 4d post-injury) and 8 control (38±6.1yrs, 13% female) participants. In the chronic-mixed group, differential expression analysis identified 8 proteins in plasma (7 up, 1 down) and 2 in CSF (1 up, 1 down) that were signficantly differenent compared to controls. In the acute-severe group, 63 plasma (52 up, 11 down) and 57 CSF (42 up, 15 down) proteins were significantly differentially expressed from controls. Notably, plasma neurofilament light (NfL), was elevated in both chronic-mixed and acute-severe cohorts (fold change, p-value vs. control: 1.40, $p=0.0061$; 30.1, $p<0.0001$, respectively) and was significantly different in acute-severe patients with poor (GOS-E≤2) and good (GOS-E≥5) outcomes ($p=0.004$). Three additional proteins were elevated in plasma in both TBI groups (SAA1, TREM2, CX3CL1).
Conclusions: CNS-specific proteomics identified differentially expressed proteins in plasma and CSF of patients with chronic-mixed and acute-severe TBI. Across the TBI temporal and severity continuum, this method confirmed the utility of hallmark TBI plasma markers as well as highlighted potential novel targets for further investigation.

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SHIFT 02-501

Poster on Board - Shift 02
LYSOSOMAL STORAGE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

PROGRANULIN-SORTILIN 1 PATHWAY-RELATED ENDO-LYSOSOMAL ALTERATIONS IN SORT1 GENETIC RISK VARIANT-CARRYING HUMAN MICROGLIA

Elena Ppali[1], Tomi Hietanen[1], Dorit Hoffmann[1], Roosa-Maria Willman[2], Eino Solje[3,4], Ville Leinonen[5], Anna Mäki-Petäjä-Leinonen[6], Mikko Hiltunen[2], Annakaisa Haapasalo[1]
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Aims: Several variants of the SORT1 gene, encoding for sortilin 1, a sorting receptor in the endo-lysosomal system, have been associated with increased risk of Alzheimer's disease and frontotemporal dementia. However, the underlying molecular mechanisms of the risk effect remain unclear. One of the identified risk variants, rs141749679, results in a single nucleotide polymorphism at the suggested ligand-binding site of sortilin 1. Our aim is to gain insights into how the SORT1 rs141749679 risk variant affects the endo-lysosomal pathway in human microglia, specifically focusing on the interaction of sortilin 1 with progranulin, a protein associated with several neurodegenerative diseases.
Methods: Skin, blood, CSF, and brain tissue biopsy samples are obtained from SORT1 rs141749679 carriers and control individuals from an idiopathic normal pressure hydrocephalus (iNPH) patient cohort at Kuopio University Hospital, Kuopio, Finland. Skin fibroblasts were reprogrammed into induced pluripotent stem cells and differentiated into microglia cells (iMGs). Blood and CSF samples will be analyzed for altered protein levels and brain biopsy samples will be used for immunohistochemical analysis. iMGs will undergo detailed phenotypic and functional characterization, including immunocytochemistry, protein analysis, and endocytosis assays.
Results: Our preliminary immunocytochemical staining results show that sortilin 1 co-localizes with the lysosomal protein Lamp2a in the iMGs. Furthermore, sortilin 1-containing vesicles appear larger and contain more sortilin 1 protein in the SORT1 rs141749679-carrying iMGs compared to the control iMGs, despite similar overall fluorescence intensities.
Conclusions: Our initial data suggest potential endo-lysosomal alterations in SORT1 rs141749679-carrying iMGs. Understanding the role of sortilin 1-progranulin interactions in the context of neurodegeneration may lead towards more accurate diagnosis and the development of preventative and therapeutic treatments for neurodegenerative diseases.

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SHIFT 02-502

Poster on Board - Shift 02
LYSOSOMAL STORAGE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4-5 April 2025

THE BRI2 BRICHOS DOMAIN, A POTENTIAL DRUG TRANSPORTER ACROSS THE BLOOD-BRAIN BARRIER FOR NEUROLOGICAL DISORDERS

Cloé Moëlo[1], Willem Hendrik Molenkamp[1], Nikolett Nemcova[1,2], Gefei Chen[1,3], Axel Abelein[1], Nina Kronqvist[1], Jan Johansson[1]
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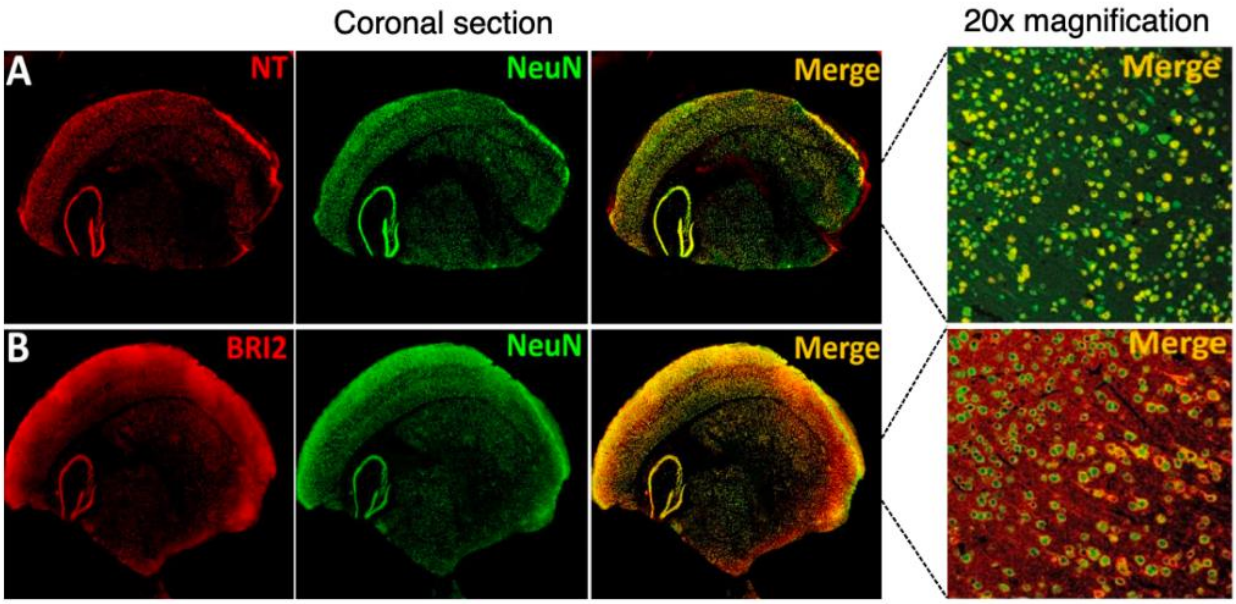
Aims: The BRICHOS domain from the Bri2 protein has molecular chaperone-like properties by preventing protein misfolding into toxic amyloid aggregates and can pass the mouse blood-brain barrier (BBB). This project aims to **(i)** understand how recombinant human (rh) Bri2 BRICHOS crosses the BBB and **(ii)** explore its potential as a therapeutic delivery system for neurological diseases, particularly lysosomal storage disorders.
Methods: (i) rh Bri2 BRICHOS fused to cargo proteins (spider silk protein N-terminal domain (NT), mCherry, nanobodies and nanoluciferase) were expressed in *Escherichia coli* and tested for BBB crossing *in vitro* using a human endothelial cell BBB model and *in vivo* in mice. Their brain distribution was analyzed by immunofluorescent co-staining with NeuN (neurons) and EAAT (endosomes). **(ii)** Lysosomal enzymes require glycosylation, which bacteria cannot provide. Hence, we expressed rh Bri2 BRICHOS-lysosomal enzyme fusion proteins in mammalian cells. Their ability to cross the BBB will be tested in the same human BBB model and in mice.
Results: (i) Bri2 BRICHOS fusion proteins showed passage across the BBB *in vitro*, while the cargo proteins alone did not. When injected to mice, the fusion protein NT-Bri2 BRICHOS was detected in the brain cortex, hippocampus and cerebellum, and colocalized with neurons (Fig.1) and early endosomes. **(ii)** For the first time, we successfully expressed rh Bri2 BRICHOS in mammalian cells. We are now focusing on producing lysosomal enzymes fused to rh Bri2 BRICHOS in the same



conditions.

Conclusions: Focusing on Bri2 BRICHOS' ability to cross the BBB and carry other proteins, this project could provide a method for delivering drugs to neurons, enabling more effective treatments for neurological disorders.

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SHIFT 02-503

Poster on Board - Shift 02
LYSOSOMAL STORAGE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4-5 April 2025

EXPLORING GCASE-LIMP-2 INTERACTION FOR THERAPIES IN PARKINSON'S DISEASE

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Aims: Genetic variants of GBA1, encoding the lysosomal enzyme beta-glucocerebrosidase (GCase), are well-known risk factors for Parkinson's disease. The interaction of GCase with its transporter, the lysosomal integral membrane protein 2 (LIMP-2), is essential for its lysosomal delivery and enzymatic activity in the lysosome, making this protein complex a promising therapeutic target for GBA1-linked PD. We investigated the interaction between GCase and LIMP-2 in the context of selected disease-associated GBA1 variants (E326K, N370S, L444P), with a focus on the role of LIMP-2 in GCase activity and delivery.
Methods: For this, we overexpressed full-length LIMP-2 and GCase variants in HEK 293T cells, and analyzed the lysosomal enrichment and activity of the different variants. We co-expressed untagged GCase variants and a novel His-tagged LIMP-2 shuttle construct in HEK293F cells, and successfully co-purified functional LIMP-2/GCase complex from the cell supernatant.
Results: Overexpression of LIMP-2 increased lysosomal abundance and enzymatic activity of selected GCase variants, including the PD-associated E326K variant. Co-purification experiments confirmed functional binding and trafficking between LIMP-2 and GCase variants. Based on our findings, we developed a lysosome-targeted peptide derived from LIMP-2 to enhance GCase activity in patient-derived cells. This LIMP-2 peptide significantly improved lysosomal GCase activity in particular in PD patient cells harbouring the GBA1-E326K variant.
Conclusions: Our study reveals LIMP-2 as an activator of GCase, emphasizing the significance of GCase-LIMP-2 complex formation in a disease context. These findings offer valuable insights into the molecular mechanisms underlying Parkinson's disease and pave the way for development of targeted treatments that harness the GCase-LIMP-2 interaction.

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SHIFT 02-504

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
4-5 April 2025

EFFECT OF BEHAVIORAL ACTIVATION USING SOCIAL ROBOT ON DEPRESSION IN HIGH-RISK OLDER ADULT

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Aims: This study aimed to evaluate the effect of behavioral activation with a social robot on depressive symptoms and cognitive function in older adults at high risk of mental illness. Depression is a major risk for cognitive decline, highlighting the importance of mental health management.
Methods: The study used a single-group pre-post-follow-up design with 229 adults aged 65 and older, who were living alone or had PHQ-9(Patient Health Questionnaire-9) of ≥10. Of these, 135 participants who completed all assessments were analyzed. Participants interacted with a social robot using a behavioral activation-based monitoring scenario. Assessments were made at baseline, post-intervention, and follow-up using CIST(Cognitive Impairment Screening Test), SSI(Beck Scale for Sucide Ideation), GDS(Geriatric Depression Scale), PHQ-9, BADS(Behavioral Activation for Depression Scale), VQ(Valuing questionaire), WHODAS-12(WHO Disability Assessment Schedule-12), and UCLA(University of California, Los Angeles) Loneliness Scale. The Friedman test and Wilcoxon signed-rank test were used.
Results: The average age of the participants was 80.69±5.24 years with 64(47.4%) having no education and 128(94.8%) living alone. All measurements differed significantly across the three time points. CIST(rank-biserial correlation(r_{rb})=-0.5), UCLA loneliness scale(r_{rb}=-0.3), GDS(r_{rb}=-0.5), BADS(r_{rb}=-0.3) and VQ(r_{rb}=0.2) showed significant changes between baseline and post-intervention. Moreover, CIST(r_{rb}=-0.6), UCLA loneliness scale(r_{rb}=-0.3), GDS(r_{rb}=-0.4), BADS(r_{rb}=-0.4) and VQ(r_{rb}=0.3) showed significant changes between baseline and follow-up. WHODAS-12 demonstrated significant differences between baseline and post-intervention(r_{rb}=-0.3), as well as between post-intervention and follow-up(r_{rb}=-0.2). SSI showed significant difference across all time points but effect size were small. PHQ-9 showed significant reductions from baseline to follow-up(r_{rb}=-0.3) and from post-intervention to follow-up(r_{rb}=-0.2).
Conclusions: Social robot interventions improve depressive symptoms and cognitive function in older adults, showing promise as a non-drug treatment in geriatric care. Further research is needed to confirm whether these effects stem from the socially assistive robot or the behavioral activation.

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SHIFT 02-505

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
4-5 April 2025

EXPLORING SPATIAL NAVIGATION CHALLENGES IN MCI SUBTYPES: INSIGHTS FROM VIRTUAL REALITY TESTING

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Aims: Missing and getting lost are frequently seen in people with Alzheimer's disease (AD). The underlying mechanisms are believed related to hippocampal dysfunctions. At cell level, grid cells and place cells play a critical role in spatial navigation; both are present in the hippocampi and the related structures where are damaged in the early stage of AD. People with non-AD are at risk of missing as well. The mechanisms, however, may be different.
Methods: We invited 30 cognitively unimpaired (CU), 30 mild cognitive impairment due to AD (AD MCI) and 25 MCI due to non-AD (non-AD MCI) to join this study. The core experiment was Pai-Jan virtual reality (PJVR) test, which assesses sense of location. Linear deviation (LD) in meters and vector deviation (VD) in degrees were the variables for comparison. The Questionnaire on Everyday Navigational Ability (QuENA) was also assessed.
Results: The overall QuENA scores showed no difference between the CU and non-AD MCI, and these two groups were better than AD MCI. AD MCI had a larger LD (95.70 [43.33], mean [SD]) than non-AD MCI (62.70 [41.26]) and the CU (28.01 [24.17]) ($p<0.000$). In the same way, AD MCI had a larger vector deviation (67.86 [47.31] than did non-AD MCI (40.58 [28.65] and the CU (26.22 [24.89]) ($p<0.000$). The LD and the QuENA scores are well correlated ($p<0.000$). Moreover, AD MCI took more time to complete the tasks, indicating a more severe spatial navigation deficit.
Conclusions: As expected, the AD-MCI performed the worst PJVR parameters among the three groups, while non-AD MCI manifested worse results than the CU. Obviously, Non-AD MCI also faces wayfinding challenges, which is contrast to previous impression and reveals potential overlooked deficits in this subtype of MCI.

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SHIFT 02-506

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
4-5 April 2025

EFFICACY OF SODIUM VALPROATE IN BEHAVIORAL AND PSYCHOLOGICAL SYMPTOMS OF DEMENTIA: A RETROSPECTIVE OBSERVATIONAL STUDY FROM PUMCH DEMENTIA COHORT

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Aims: This study aims to assess the effectiveness of valproate preparations in addressing Behavioral and psychological symptoms of dementia (BPSD), with a specific focus on managing agitation symptoms in individuals with dementia.
Methods: A retrospective analysis was conducted at Peking Union Medical College Hospital (PUMCH) on patients diagnosed with BPSD who received valproate preparations between 2013 and 2023. Patients were classified into 'effective', 'ineffective' and 'unknown' group based on their response to valproate treatment, and the distribution of BPSD symptoms between the effective and ineffective groups was compared.
Results: Among the 116 patients studied, 62.1% exhibited effective responses, 12.1% showed ineffectiveness, and 25.9% had uncertain outcomes with valproate therapy. While the effective group displayed a higher prevalence of agitation symptoms and other behaviors like wandering, restricted and repetitive behaviors, and sleep disturbances compared to the ineffective group, these differences did not reach statistical significance ($p = 0.156$, 1.000, 0.899, 0.283). Patients in the ineffective group were more likely to experience aggression with comorbid psychotic symptoms compared to those in the effective group ($p = 0.023$).
Conclusions: The findings suggest that tailored valproate treatment at low doses may be beneficial in managing agitation-related BPSD in the Asian population. Further validation through randomized controlled trials is essential to substantiate these observations.

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SHIFT 02-515

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION / SUPPORT DEVICES & MONITORING
4-5 April 2025

A MULTIMODAL LIFESTYLE INTERVENTION MANAGEMENT SYSTEM FOR POPULATIONS AT RISK OF COGNITIVE DECLINE

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Aims: Digitally supported clinical trials constitute the most contemporary advancements in monitoring and guiding multimodal lifestyle interventions, effectively exploiting advantages of technology. To that end, based on the LETHE clinical trial, we present a novel digital lifestyle intervention and monitoring framework, that acts within the LETHE Platform, with its primary purpose being the federation and classification of study participant's weekly performance on a wide spectrum of lifestyle behaviors including physical activity, app usage, cognitive exercise, diet, and cardiovascular risk. The system already facilitates the explicit purpose of supporting the LETHE clinical trial.
Methods: LETHE, conducting a highly digital multimodal lifestyle interventional clinical trial designs and implements a novel, patient-centered, lifestyle management system that federates, guides, and motivates in a personalized manner beneficial lifestyle behavioral changes. A total of 160 individuals aged 60-77 years with risk factors for dementia were recruited and randomized 1:1 to structured multimodal lifestyle intervention. Practical applications were devised to facilitate participant engagement in remote monitoring and modification of lifestyle behaviors, while enabling the monitoring of engagement to delineated weekly pathways (green, yellow, or red).
Results: The results of the Digital Intervention component through the first year of the trial depict a prominent differentiation between control and intervention group, where the latter group achieves

consistently higher weekly classification scores, essentially proving that engagement and adherence are actively advocated by the system in place.

Conclusions: Adherence and engagement constitute dynamic evaluations of the lifestyle behavioral modifications across various dimensions. Digital Monitoring Frameworks of this order, unveil a true shift in the paradigm of behavioral change as they can offer monitoring, guidance, increase motivation, and address adherence issues not only in clinical trials, but also when implementing lifestyle changes overall.

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SHIFT 02-516

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT
4-5 April 2025

UPTAKE OF COGNITIVE SCREENING AMONG OLDER ADULTS WHO CARE FOR PEOPLE WITH ADRD: A US NATIONAL SURVEY

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Aims: Caregivers for patients with Alzheimer's Disease and related dementias (ADRD) experience substantial burden and have a higher rate of subjective memory complaints. However, studies also show that they have negative attitudes towards the disease and are reluctant to getting screened for cognitive impairment. Little is known on how these countervailing factors affect their uptake of cognitive screening in comparison with individuals who do not care for ADRD patients.
Methods: We analyzed data from a US nationally representative survey on individuals aged 65 years and older who care for ADRD patients, caregivers for non-ADRD patients, and non-caregivers, regarding their uptake of cognitive testing during a doctor's visit in the past 12 months.
Results: Among 2,353 participants aged 65+, 195 (8%) cared for an ADRD patient, 761 (32%) for a non-ADRD patient, and 1397 (59%) did not provide care. Adjusting for demographics (age, sex, race/ethnicity, education, and yearly household income), logistic regression shows that ADRD caregivers were more likely ($p<0.05$) to have had a cognitive test (26%), compared to non-ADRD caregivers (20%) or non-caregivers (19%). Results were similar after further adjusting for two factors predictive of one's likelihood to take a cognitive test: subjective memory complaints (odds ratio [OR]=1.60, $p<0.001$) and having a primary source of care (OR=1.59, $p=0.003$).
Conclusions: Older adults caring for people with ADRD report a significantly higher uptake of cognitive screening than those who do not care for ADRD patients, after consideration of their subjective memory complaint and access to regular care, but only by a small margin. Efforts to reduce their reluctance to screen are needed to increase the uptake, such as destigmatization, better education, and support from their physician, social circle, and the general public.

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SHIFT 02-517

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: CAREGIVER SUPPORT
4-5 April 2025

MAYA ANGELOU CENTER FOR HEALTH EQUITY CAREGIVER COLLEGE (MC2): FOCUS GROUP FEEDBACK FROM TIER 1 AND TIER 3 COUNTIES IN NORTH CAROLINA

Takiyah Starks[1], Allison Caban-Holt[2], Doreen Fortune[2], Ashley Sanderlin[3], Charlene Brown[2], Tonnette Artis[2], Shawnta Lloyd[2], Ashley Gregory[2], Brian Kunkle[4], Farid Rajabli[4], Scott Williams[5], William Bush[5], Rufus Akinyemi[6], Jonathan Haines[7], Christiane Reitz[8], Giuseppe Tosto[9], Jeffery Vance[4], Margaret Pericak-Vance[10], Goldie Byrd[2]
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Aims: Objective: Determine the caregiving and health education needs of Black informal dementia caregivers in Tier 1 (most-distressed) and Tier 3 (least-distressed) counties in North Carolina, USA.
Methods: Methods: The North Carolina Department of Commerce ranks the state's 100 counties based on economic well-being and assigns the most-distressed counties as Tier 1, and least-distressed as Tier 3. Focus groups were conducted with community stakeholders in Tier 1 and Tier 3 counties. Focus group attendees were engaged in discussion on topics including a review of local resources to support caregiving, barriers that AD caregivers face, educational needs of caregivers and preferred format of a MACHE Caregiver College (MC2) event.
Results: Results: Focus group participants (N = 15; most-distressed county residents = 8, least-distressed county residents = 7) were Black (100%), with professional and community roles including clergy, caregivers, nursing, teaching, manager, community health worker, and local city officials.
Findings suggested that significant needs in the most-distressed county include lack of geriatric\AD specialists, few caregiver support resources, and little qualified in-home care assistance. In the least-distressed county, structural barriers and physical access to resources were named as difficulties. A common issue for both counties was confusion regarding what medical insurance plans cover.

Conclusions: Conclusions: Needs in most-distressed and least-distressed counties differ. Caregivers facing economic challenges may have less access to resources that may reduce caregiver burden. Both groups need help navigating medical insurance. Understanding diverse community needs assist in customizing educational offerings to meet the expressed needs of stakeholders in each county type.

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SHIFT 02-518

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
4-5 April 2025

LONGITUDINAL EFFECTS OF MOBILE APPLICATION-BASED COGNITIVE TRAINING ON OLDER ADULTS WITH MILD COGNITIVE IMPAIRMENT: A 15-MONTH FOLLOW-UP STUDY

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Aims: Mild cognitive impairment (MCI) is defined as an intermediate state between normal cognitive aging and dementia, characterized by a subjective impression of cognitive decline and objectively detectable memory impairment. Early intervention through mobile based-cognitive training may help older adults with MCI maintain or even improve their cognitive function. While recent studies have examined the short-term effects of cognitive training applications, little research has explored their long-term impact. This study aims to investigate the longitudinal effects of a cognitive training application on older adults with MCI.
Methods: A total of 28 older adults with MCI participated in cognitive training. The training was delivered via a mobile application called "Cogthera", designed to enhance memory encoding through attention, imagination, and association techniques. Participants used the application twice daily for 3 months, with 9 participants continuing for an additional 12 months. The primary outcome was cognitive function, measured by the Alzheimer's Disease Assessment Scale-cognitive subscale 14 (ADAS-cog 14) at baseline, 3 months, and 15 months. The secondary outcome was health-related quality of life, assessed using EQ-5D-5L, which covered domains such as mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
Results: Participants showed a decrease in ADAS-cog 14 scores over time, indicating improved cognitive function. Specifically, there was a significant difference in ADAS-cog between baseline and 15 months ($p < 0.001$), while the difference between baseline and 3 months was not significant. EQ-5D-5L also decreased over time, suggesting improvements in quality of life. Significant improvements were observed in mobility and anxiety/depression between baseline and 3 months ($p < 0.05$), with marginal improvements in pain/discomfort and composite score.
Conclusions: These findings highlight the potential of mobile-based cognitive training as a long-term, non-invasive intervention for managing cognitive health in older adults.

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SHIFT 02-519

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
4-5 April 2025

PROGRESS ON A NEUROMODULATION TREATMENT USING UPPER ALPHA NEUROFEEDBACK FOR AMNESTIC MILD COGNITIVE IMPAIRMENT: THE ESPERANZA PROJECT

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Aims: Patients with Alzheimer's Disease show reduced alpha oscillation power and frequency, correlating with poorer cognitive performance. In Mild Cognitive Impairment (MCI), these changes are linked to cognitive deficits. EEG-based neurofeedback (NF) provides real-time feedback on brain activity, enabling users to modulate their brain patterns, showing promise for enhancing cognition in both the general population and MCI patients.
Methods: The ESPERANZA study (Phase 2b), a double-blind, placebo-controlled trial, will investigate NF effects on 64 aMCI patients at home. The intervention involves 48 sessions over three months, aiming to increase upper-alpha (UA) activity. Primary outcomes will assess electrophysiological changes, and secondary outcomes will evaluate cognitive function improvements, specifically in episodic and working memory. We hypothesize that increased UA activity will enhance memory performance.
Results: Previous studies (Phase 1 and 2a) with 40 healthy elderly individuals and 20 aMCI patients have included over 750 sessions. Findings indicate that NF is safe, well-tolerated, and effective at increasing UA activity, even in self-administered formats. Notably, cognitive improvements in working and episodic memory have been observed in the aMCI population.
Conclusions: This NF intervention has the potential to mitigate alpha power declines in MCI patients and may enhance cognitive function, particularly memory. This approach offers a promising non-pharmacological symptomatic treatment for MCI and Alzheimer's patients.

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SHIFT 02-520

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: COGNITIVE TRAINING
4-5 April 2025

STUDY OF A MULTI-SESSION ANTI-AGING STANDARD FOREST HEALING PROGRAM WITH FOREST VISITS ON COGNITIVE AND PHYSICAL HEALTH IN OLDER ADULTS

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Aims: The Anti-Aging Standard Forest Healing Program (ASFHP), which utilizes forest therapy, has been shown to improve psychological, physical, and cognitive functions. However, direct visits to forest sites can be challenging for some individuals. This study aimed to examine the impact of a multi-session ASFHP involving visits to forest facilities on mental and physical health in older adults, comparing it with the same program conducted indoors.
Methods: Participants aged 70 years and older, who had concerns about cognitive decline, were recruited from dementia support centers and divided into control and experimental groups. A total of 33 individuals underwent the ASFHP under the guidance of a forest therapy instructor. The control group completed the program indoors, while the experimental group visited a forest healing center, with the program repeated over 20 weeks.
Results: The multi-session ASFHP significantly improved Cognitive Impairment Screening Test (CIST) total scores, memory, the Korean version of the Repeatable Battery for the Assessment of Neuropsychological Status (K-RBANS) total scores, immediate recall, visuospatial/construction abilities, language, forest healing standard questionnaire total scores, and overall cognitive function, regardless of whether the program was conducted indoors or outdoors. However, forest visits showed additional benefits, improving orientation, delayed recall, emotional stability, physical activity, and overall health. Improvements in the memory domain of the CIST were the strongest indicator of the program's effectiveness.
Conclusions: The 20-week multi-session ASFHP with forest visits resulted in significant cognitive improvement as well as enhanced physical and emotional stability compared to indoor-only sessions. This suggests that incorporating forest visits into therapeutic programs for older adults may offer additional benefits.

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SHIFT 02-521

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: MOBILE APPLICATIONS, SOCIAL NETWORKS
4-5 April 2025

THE EFFECTIVENESS OF MOBILE-BASED MULTIDOMAIN PREVENTION OF DEMENTIA IN COMMUNITY-DWELLING AT-RISK MIDDLE-TO-OLDER ADULTS: A MULTI-CENTER RANDOMIZED SINGLE-BLINDED TRIAL

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Aims: This study examined the effectiveness of a mobile-based dementia prevention program in a community-dwelling population aged 55 and older with normal cognition over 12 weeks.
Methods: A total of 150 cognitively normal individuals aged 55 and older who visited seven community centers for dementia in South Korea were enrolled in the study. Participants were randomly assigned in a 1:1 ratio to the intervention group or active control (usual care). The mobile-based intervention encompassed physical activities, cognitive training, dietary management, and mental health monitoring. All activities were monitored by coaches with feedback through a real-time web platform. During the initial 12 weeks, participants received weekly feedback (intensive phase), followed by monthly feedback during the 12-week maintenance phase. The primary outcome was assessed through the dementia risk factor score by blinded evaluators at baseline, 12, and 24 weeks. A mixed-design analysis of variance was performed to examine group differences over time.
Results: A total of 127 participants were included in the analysis (intervention, n=60; active control, n=67), with a mean age of 69.1 years, of which 87% were female. A significant interaction effect on modifiable risk composite score was observed between the time and group assignment (F=4.569, p=.011). The significance was maintained in a model with adjustment for baseline risk score, age, sex, community center, and baseline global cognitive function. Especially the intervention led to significant improvements in physical, cognitive, and social activity after the intensive phase, and steady increases in cognitive and social activity were observed after the maintenance phase.
Conclusions: Our remote dementia prevention program effectively reduced modifiable dementia risk factors in cognitively normal adults. It is expected that mobile-based interventions can be utilized to expand dementia prevention services even in low-income countries.

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SHIFT 02-522

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
4-5 April 2025

THE DORIAN GRAY PROJECT: A PERSONALIZED RISK STRATIFICATION AND HOLISTIC MANAGEMENT FOR PREVENTION OF COGNITIVE IMPAIRMENT

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Aims: The overarching ambition of the DORIAN GRAY project is to uncover the mechanisms bridging MCI with CVD, and develop an integrated digital approach, which aims to promote resilience and improve overall health in the ageing population.
Methods: The driving concept of the project is to start from the analysis of data available in patients with CVD, such as heart failure (HF), in which mechanisms leading to MCI are enhanced, and thereafter to define the factors aggravating the onset and progression of cognitive impairment in the general population with cardiovascular risk factors (CVRF). The same factors will be used in a multifactorial assessment, integrating RWD from multiple sources (i.e smartwatch, smartphone, Tablets, PCs) and employing multi-modal trustworthy artificial intelligence (AI), to enable risk stratification and personalised treatment. An avatar-based coaching exergaming (ABCE) will be developed that will serves a dual purpose; a cognitive enhancement tool in the exergame component and a lifestyle intervention in the coaching system.
Results: The DORIAN GRAY solution will be employed in i) Pilot two-arms randomised controlled Trial in patients with HF and MCI and ii) Implementation study in patients with MCI and CVRF that will be conducted across five and four different countries respectively. The trials will assess the feasibility and adherence to the digital treatment and ABCE as well as the efficacy and acceptability of the intervention and the improvement on quality of life, respectively. The ultimate target concurrently is through the AI and Causal modeling to assess the changes in blood and imaging biomarkers to uncover disease mechanisms and progression.
Conclusions: The DORIAN GRAY project, through AI-powered Digital Twin model for risk stratification, enables the early identification of individual patterns, of potential MCI progression, and devises a paradigm shift in healthcare, applicable to other NCDs.

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SHIFT 02-523

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
4-5 April 2025

AUDITORY SIMULATION DURING SLEEP AS A POTENTIAL TREATMENT FOR AMNESTIC MILD COGNITIVE IMPAIRMENT - THE NANA STUDY

Javier Minguez[1,2,3], Eduardo López-Larraz[1], Sergio Clemente Jiménez[1], Galit Fierro[1], David Oriol[1], Almudena Robledo-Menéndez[1], José María Perez-Trullén[4,5], Elena Muñoz-Farjas[6], Pedro Modrego[4,7], Antonio Lobo[4,8], Jorge De Francisco Moure[4,7], Carmen Almárcegui[4,7], Esperanza Jubera-García[1,9]
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Aims: Cognitive decline in mild cognitive impairment (MCI) is linked to sleep impairments, specifically deteriorations in slow oscillations and sleep spindles, neural rhythms crucial for memory consolidation. Their disruption is associated with memory decline and structural brain changes. A promising technique, "auditory stimulation during sleep" uses short tones during Non-Rapid Eye Movement (NREM) sleep to boost slow oscillations and spindles, enhancing declarative memory in healthy adults. Demonstrating similar memory benefits in MCI patients could pave the way for developing a non-pharmacological treatment.
Methods: In a pre-registered, double-blind, placebo-controlled trial, 34 patients with MCI will receive auditory stimulation during NREM sleep in a sleep lab. The intervention uses a comfortable EEG headband designed for long-term, self-applied use at home. A calibration night will personalize the stimulation. Each patient will experience one night of real and sham stimulation, respectively. Memory tests before and after sleep, and again one week later, will measure differences in sleep-related memory consolidation between conditions. We expect improved memory performance following the stimulation night.
Results: Several pilots with healthy older adults and aMCI patients confirmed the feasibility of this approach. Across pilots, 68 nights were conducted with 32 participants (including 17 individuals over 60 and 4 aMCI patients). The procedure consistently induced slow oscillations and spindles in all participants. The final trial is set to begin in 2025.
Conclusions: The upcoming trial marks one of the first large-scale investigations of auditory sleep stimulation's potential memory benefits in MCI patients. If successful, it will be a key step toward developing the first non-pharmacological therapy for MCI, potentially paving the way for future long-term studies.

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SHIFT 02-524

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
4-5 April 2025

CLINICAL AND EPIDEMIOLOGICAL PROFILE OF DEMENTIA WITH LEWY BODIES: ANALYSIS OF A COHORT FROM RIO DE JANEIRO/BRAZIL

Vanderson Neri[1], Matheus Barros[2], Gabriela Nascimento[2], Gesildo Neto[2], Yasmim Toledo[3], Lara Ribeiro[2]
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Aims: To apply the diagnostic criteria for Dementia with Lewy Bodies **(**DLB) in a cohort of patients with parkinsonian syndromes in the North of Rio de Janeiro; to estimate the prevalence and analyze the clinical profile, pharmacological treatment and neuroimaging of this group of patients.
Methods: Application of the diagnostic criteria for DLB (McKeith et al. 1996) in patients with parkinsonism and cognitive impairment (after neuropsychological assessment). Selection of patients who met criteria for DLB, clinical and laboratory evaluation of this group.
Results: In a cohort of 750 patients with parkinsonian syndromes (prospectively followed from May 2010 to June 2022), 22 patients met the criteria for diagnosing DLB (2.9% of the total). Average age was 78.36 (SD ± 7.9); 12 (54.5%) were men. Mean time neurological symptoms 1.77 years (± SD 0.81). MMSE: average 11.3 (SD ± 8.86), MOCA: average 9.43 (SD ± 7.2). Most prevalent motor symptoms: bradykinesia (90.9% of cases) and bilateral muscle stiffness (90.9%). After clinical, laboratory and imaging evaluation, it was concluded that secondary causes were excluded. 100% of cases presented impairment in more than one domain of cognition, impacting their daily activities. Treatment: 18 (81.8%) used levodopa / benseraside, 4 (18%) pramipexole, 13 (59%) quetiapine, 8 (36.5%) donepezil, 3 (13.6%) rivastigmine and 1 (4, 5%) galantamine. Neuroimaging: MRI morphometric evaluation showed predominance of diffuse cerebral atrophy 21 (95.5%), dilated cerebral ventricles 15 (68.2%), and preservation of temporal lobe structures 17 (77.3%).
Conclusions: We observed a prevalence of 2.9/100 DLB patients in this cohort. Significant cognitive impairment with few years of evolution, predominance of rigidity and bradykinesia on neurological examination and clinical manifestation started in the seventh decade of life were more specific results found.

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SHIFT 02-525

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
4-5 April 2025

PARTICIPATION IN CME EDUCATION RESULTS IN MORE PATIENTS GETTING DIAGNOSED WITH ALZHEIMER'S DISEASE IN REAL WORLD PRACTICE

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Aims: Despite advances in Alzheimer's disease (AD) understanding, many clinicians underutilize biomarkers and are not diagnosing patients with early AD in a timely manner. To address this gap, 2 accredited continuing medical education (CME) activities were developed. This study aimed to assess if CME education could improve AD diagnosis rates and biomarker use in real world clinical practice.
Methods: A retrospective, matched case-control study examined changes in clinical care among primary care physicians (PCPs), neurologists, geriatricians, and psychiatrists. 'Learners' (who participated in at least one activity[1,2] from September to December 2023 and treated at least 1 patient aged 60+) were matched to non-learner controls by exposed month, specialty, geography, and number of patients with AD coded and the number of patients they diagnosed with AD in the 6 months prior to participation, based on a claims database licensed through Komodo. Results compare 3-month pre-/post-CME period using ANCOVA in SAS 9.4. Outcomes assessed included cognitive assessments, neurologist referrals (for non-neurologists), biomarker referrals, and biomarker orders. Tukey comparisons examined effects across different physician groups. 1. https://www.medscape.org/viewarticle/989301; 2. https://www.medscape.org/viewarticle/997712
Results: 1697 learners and 1697 matched control non-learners were included in the analysis. 3 months after participating in at least one CME activity, controlling for number of patients at pre, the CME learner group was 38% more likely to have patients with cognitive assessment, specialist referral, and biomarker testing than control ($P < .001$). Ultimately, 11% more patients received at least one desired outcome in the CME group than control.
Conclusions: This study showed that participation in at least 1 of 2 CME activities about Alzheimer's disease identification and biomarker testing is predictive of real-world practice change.

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SHIFT 02-526

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / DEMENTIA AND COGNITIVE DYFUNCTION: OTHER
4-5 April 2025

ASSOCIATIVE ATTRIBUTION OF INTRACEREBRAL HEMORRHAGE EVENTS TO CEREBRAL AMYLOID ANGIOPATHY OR HYPERTENSIVE COMORBIDITIES IN ALZHEIMER'S DISEASE FROM REAL-WORLD DATABASES

Ying Wang[1], Joel Reisman[2], Dan Berlowitz[2], Peter Morin[3], Vanesa Carlota Arasa[4], Brant Mittler[5], Raymond Zhang[6], Amir Tahami Monfared[6], Michael Irizarry[6], Quanwu Zhang[6], Weiming Xia[3]
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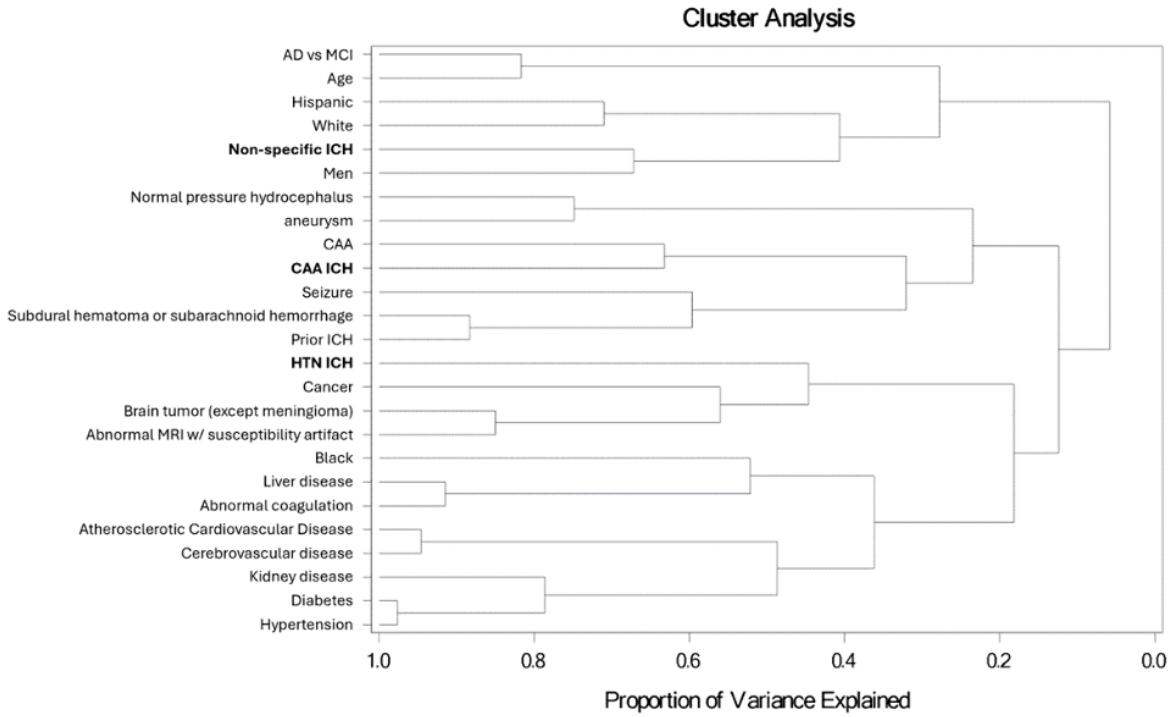
Aims: This study examines the feasibility of differentiating cerebral amyloid angiopathy vs hypertensive intracerebral hemorrhage (ICH) based on comorbidities from electronic healthcare records of patients with mild cognitive impairment (MCI) or Alzheimer's dementia (AD).
Methods: Patients with MCI or AD were identified using clinical notes or diagnostic codes in the US Veterans Affairs Healthcare System (VAHS) databases. Inpatient ICH events were identified (2016–2023) using principal ICD-10 codes and classified as: cerebral amyloid angiopathy (CAA-ICH), hypertensive (HTN-ICH), or non-specific-ICH. The incidence of ICH events after MCI/AD was summarized. Cluster Analysis was used to examine whether real-world data correlations are consistent with the above ICH classifications.
Results: Out of 523,924 patients with MCI/AD (mean age 79 years; 13,289 [2.5%] women; 55,150 [10.5%] Black), we found 1,190 (0.23%) CAA-ICH, 178 (0.03%) HTN-ICH, and 1,324 (0.25%) non-specific-ICH events. The correlation patterns of ICH types and their respective risk factors were hierarchically clustered until each attribute became a unique cluster. The first level clustering immediately separated non-specific-ICH with patient demographics and Alzheimer's disease from the remaining patient attributes. The second level clustering separated CAA-ICH with brain/neurologic conditions from HTN-ICH with predominantly cardiometabolic disorders, resulting in 3 distinctive clusters with respective ICH type and associated health conditions, which explained approximately 20% of the variations in the correlation



matrix.

Conclusions: The estimated incidence of ICH events over the study period was 5 out of 1,000 patients. Furthermore, the analytic findings supported differential CAA vs hypertensive ICH classifications based on ICD coding in electronic health records. Specifically, distinct brain/neurological and cardiometabolic clusters were observed in patients with MCI/AD in the VAHS.

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SHIFT 02-528

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / BEHAVIORAL & PSYCHIATRIC SYMPTOMS
4-5 April 2025

QUALITATIVE PATIENT EXPERIENCE OF ADVANCED PARKINSON'S DISEASE: A CONCEPTUAL MODEL OF SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE IMPACTS

Nicola Williamson[1], Milton Biagioni[2], Thomas Morel[2], Aoife Lydon[3], Molly Clifford[3], Patrick Cronin[3], Helena Bradley[3]
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Aims: Parkinson's disease (PD) is a progressive neurodegenerative condition, characterized by motor symptoms (MS) and non-motor symptoms (NMS). While no universal definition of advanced PD exists, people in advanced stages typically experience diverse and severe symptomatology, which significantly impacts their health-related quality of life (HRQoL). There is a need to understand the most frequent symptoms and HRQoL impacts experienced by this population. This qualitative study explored the experience of advanced PD from patient and clinician perspectives to identify key concepts for assessment in clinical trials.
Methods: A targeted review of literature, and qualitative concept elicitation interviews with people with advanced PD (n=20; defined as persons with PD diagnosed ≥5 years experiencing ON/OFF motor fluctuations despite levodopa therapy and are classified as modified Hoehn and Yahr stages 2-4) and expert clinicians (n=3) in the US, were conducted to identify symptoms of advanced PD and their impact on HRQoL.
Results: A total of 65 symptoms (48 NMS, 17 MS) were identified across the reviewed literature and qualitative interviews. Most frequently reported MS included tremor, rigidity, balance issues, and slowness of movement. Beyond cardinal PD MS, a high frequency of NMS was reported, including fatigue, cognitive dysfunction (e.g., difficulty thinking), neuropsychiatric symptoms (e.g., apathy), pain, sleep problems, urinary dysfunction, autonomic dysfunction, excessive daytime sleepiness, gastrointestinal dysfunction, and sensory dysfunction. HRQoL impacts included impacts on daily activities, emotional well-being, physical functioning, social functioning, work/study, and financial well-being. Most bothersome and important to treat symptoms were reported.
Conclusions: This study provides in-depth insights into the symptoms and HRQoL impacts experienced by people with advanced PD. Findings informed the development of a comprehensive conceptual model to support identification of concepts for assessment in PD clinical trials.

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SHIFT 02-529

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / CAREGIVER SUPPORT
4-5 April 2025

DEMOGRAPHIC AND PSYCHOSOCIAL ASSESSMENT OF 105 CAREGIVERS OF PATIENTS WITH PARKINSON'S DISEASE FROM RIO DE JANEIRO/BRAZIL

Vanderson Neri[1], Glaucia. Licassali[2], Daniele Vianna[2], Elvira Reinaldo[2], Eleny Guimaraes[2]
[1]Hospital da Lagoa, Neurology, Rio de Janeiro, Brazil, [2]Centro de Doença de AlZheimer e Parkinson, Neurology, Campos dos Goytacazes, Brazil

Aims: Evaluate demographic profile, psychosocial aspects and knowledge about the disease in caregivers of patients with PD from Rio de Janeiro. Propose interdisciplinary activities that address the quality of life of caregivers.
Methods: Evaluation performed through a questionnaire after the medical consultation in the period from July to December 2023. Individualized interview conducted by the psychology team, using The Informal caregiver burden assessment questionnaire, validated for Brazil.
Results: 105 caregivers were interviewed. 82% were women and 18% men. 89.4% were relatives: 43.6 were children and 29.7% were spouses. Mean age 51.85 years (ranging from 16 to 83 years). Schooling: 67.2% studied over 10 years, average of 8.3 years of study. Financial income: 33.3% receive up to U$ 1.200,00/month and 29.2% do not have income. Disease: tremor and muscle stiffness were considered the most important and disabling symptoms by 54.2%, bradykinesia was reported by 42%. In free answers, 46% said they had knowledge to care for the patient. 84% say they seek information about the disease: 63% use the internet, 32% TV programs, and 51% consult their doctor with questions. Psychosocial aspects: 49% considered psychologically shaken by caring for a parkinsonian, 51.2% changed their life plan after this activity, however, 89% said they feel better about caring for a parkinsonian.
Conclusions: There are few studies with caregivers of patients with PD. In our sample, we observed a predominance of family members as caregivers and a large proportion (29%) with no financial remuneration. Although 46% claim to be able to be a caregiver, almost half confirm that they are psychologically affected by it. New strategies for treatment and psychotherapeutic support should be included in medical care centers to improve caregivers' quality of life.

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SHIFT 02-532

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / MOTOR COORDINATION & EXERCISE
4-5 April 2025

COMPARISON OF THE EFFECTS OF CHRONIC AEROBIC EXERCISE AND TAI CHI CHUAN INTERVENTIONS ON ANTIOXIDANT ACTIVITY IN PATIENTS WITH PARKINSON'S DISEASE

Chia-Liang Tsai[1], Tsu-Kung Lin[2], Chien-Yu Pan[3], Tsai-Chiao Wang[4], Yu-Ting Tseng[5], Chung-Yao Chien[1]
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Aims: This study aimed to compare the effects of different exercise types on antioxidant levels in patients with PD.
Methods: Fifty-one participants were randomly divided into one of three groups: aerobic exercise (AE), Tai Chi Chuan (TCC), or control. Blood samples were collected before and after 12 weeks of intervention to assess antioxidant markers, including glutathione (GSH), oxidized glutathione (GSSG), glutathione peroxidase (GSH-Px), catalase (CAT), superoxide dismutase (SOD), and uric acid (UA).
Results: While no significant changes were observed in GSH-Px, GSSG, or SOD activity in the AE and TCC groups, the 12-week AE intervention led to a significant increase in GSH and CAT levels and a notable decrease in UA levels in PD patients. In contrast, the TCC intervention significantly elevated GSH levels. However, SOD activity significantly decreased in the control group after 12 weeks.
Conclusions: These findings suggest that chronic AE and TCC training could be effective complementary measures alongside medical treatments and alternative therapies for reducing oxidative damage in PD, with AE offering greater benefits than TCC.

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SHIFT 02-533

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
4-5 April 2025

TECHNICAL SUPPORT PROVISIONS FOR TIMELY REGISTRATION TO PARTICIPANT PORTAL: IMPACT UPON PARTICIPANTS INVOLVED IN STUDIES AIMED AT PARKINSON'S DISEASE (PD) PREVENTION

Lynell Lemon, Bridget Mcmahon, Arianna Faraday, Margaret Mcmahon, Julia Nevins, Molly Nygard, Amaya Cunningham, Benjamin Mcqueeney, Hannah Hargrave, Brianne Smith, Jacob Ewart, Jacqueline Carley, Laura Kruchkow, Brittney Henry, Zeina Singh
Institute for Neurodegenerative Disorders, New Haven, United States of America

Aims: To discuss the development and benefit of an individual approach to provide clinical study participants access to a clinical study participant portal. In 2024 the Parkinson's Progression Markers Initiative (PPMI), a longitudinal, observational study, sponsored by Michael J. Fox Foundation for Parkinson's Research (MJFF) launched *myPPMI*, an individualized online portal for participants to access recent relevant scientific publications, general study information, view study test results, and connect with parallel sub studies. Barriers related to technology use among the study population, slowed registration and participation in the new digital platform. A modified support framework was developed to meet the particular needs of study participants.
Methods: To augment efforts of five full-time employees, nine undergraduate students, studying biological sciences and nursing in the United States (US) were engaged as interns. Each provided 5-10 hours/week to conduct technical support to study participants within US and United Kingdom (UK). Study participants were emailed invitations to register for *myPPMI* participant portal and provided a link to schedule a video/phone call to assist them in the process. Study staff and interns conducted calls over a five-month period. Advanced technical issues were escalated to specialists for additional personalized instruction and resolution. Innovative solutions were devised throughout project implementation to ensure timely response to participant requests.
Results: In five months, staff completed 427 US and UK participant support calls. Registration for digital platform increased from 43% to 80.3% in US and UK. Part-time intern work totaled 720 hours upon project completion.
Conclusions: Incorporation of participant support mechanisms provide timely response and engagement of new digital platforms utilized in clinical research. Student interns provide a cost-effective approach to complete fundamental study tasks and yield innovative solutions to team challenges.

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SHIFT 02-534

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
4-5 April 2025

PARTICIPANT ENGAGEMENT INITIATIVE: IMPACT OF CENTRALIZED INTERN PROJECT TO COLLECT PARTICIPANT FEEDBACK FOR CLINICAL STUDY AIMED AT PARKINSON'S DISEASE PREVENTION

Lynell Lemon, Bridget Mcmahon, Arianna Faraday, Benjamin Mcqueeney, Brianne Smith, Hannah Hargrave, Amaya Cunningham, Julia Nevins, Margaret Mcmahon, Molly Nygard
Institute for Neurodegenerative Disorders, New Haven, United States of America

Aims: To examine the benefit of an instrument to enhance clinical study participant experiences while familiarizing student interns to clinical research practices and professions. In clinical research, particularly longitudinal studies such as the Parkinson's Progression Markers Initiative (PPMI), an observational study sponsored by Michael J. Fox Foundation for Parkinson's Research (MJFF), participant retention is an essential criterion to ensure study validity and credibility. Rapport with the study team including personalized care and collecting participant input, may be valuable but time-consuming for sites with limited resources.
Methods: Implementation of an online undergraduate internship program initiated collection of participant feedback. Nine part-time student interns, studying biological sciences and nursing in the United States (US), completed engagement calls with participants within the US. Interns created talking points and a script to identify themes in the participant study experience, communication, site visits, travel assistance, and appreciation events. Additional interview time was allocated for voluntary feedback. Participants received email invitations to schedule phone interviews with PPMI interns. Calls were also conducted for unscheduled participants. Retrieved data was transcribed into reports and shared with study stakeholders and clinical sites for awareness and process improvement.
Results: Interns made 6,389 attempts to complete calls with 892 (36%) PPMI participants from 31 clinical sites. Part-time work hours for the interns totaled 1,125 over the 7-month period. Improvements for travel, time management, procedural discomfort, and research test results surfaced for implementation.
Conclusions: Rapport between study personnel and participants is vital to overcome participant retention challenges. Adopting processes for participant feedback may lend to improved retention as input is realized**.** Implementation of a student internship program may be a cost-effective approach to obtain participant feedback, enhance participant experiences, and introduce students to clinical research practices.

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SHIFT 02-535

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
4-5 April 2025

MYPPMI: A WEB PORTAL FOR ENHANCING PARTICIPANT ENGAGEMENT AND DATA COLLECTION IN PARKINSON'S DISEASE CLINICAL TRIALS

Craig Stanley[1], Christina Destro[2], Maggie Kuhl[2], Amanda Miller[3], Laura Heathers[3], Tatiana Foroud[3], Auldyn Matthews[1], John-Michael Talarico[1], Cailey Fitzgerald[1], Zeina Singh[1], Erinn Bryan[1], Jacqueline Carley[1], Brittney Henry[1], Antonette Gerrity[1], Emily Flagg[1], Thomas Tropea[4], Kimberly Fabrizio[1], Ken Marek[1]
[1]Institute for Neurodegenerative Disorders, New Haven, United States of America, [2]The Michael J. Fox Foundation for Parkinson's Reseach, New York, United States of America, [3]Indiana University School of Medicine, Indianapolis, United States of America, [4]Perelman School of Medicine at the University of Pennsylvania, Department Of Neurology, Philadelphia, United States of America

Aims: As telehealth and decentralized clinical trials become more prevalent, patient portals need to accommodate a wide range of users, considering different technological abilities and varying backgrounds. The new myPPMI platform centralizes data collection and provides personalized, participant-centric content. Currently in use for the Parkinson's Progression Markers Initiative (PPMI), myPPMI may provide a platform or model for other clinical studies.
Methods: Here we implement a human-centered design approach, arising from in-person and virtual research sessions combined with technical optimization, to realize a newly envisioned portal. Using a generalizable clinical data model, centered on remote trial data, we populate the portal with direct data insights into participants' contributions, connecting the participant to their individual study journey. Iterative design cycles developed personalized dashboards, and technical improvements ensured accessibility on various devices and low-bandwidth conditions.
Results: From initial launch, over 300 updates were made, achieving over 80% usage (n=TK) among the U.S. clinical population. Key features include a personalized dashboard showing (i) previous participant contributions, (ii) informational multimedia content, and (iii) new opportunities for participants to interact within the PPMI study, including reviewing their own research information. The platform supports invitations to both in-person and virtual events.
Conclusions: The updated myPPMI portal illustrates how focusing on participant-centered design and incorporating technical upgrades can enhance engagement and data collection in decentralized trials. This method offers a scalable model for extensive clinical research while providing a unified view of a participant's trial experience.

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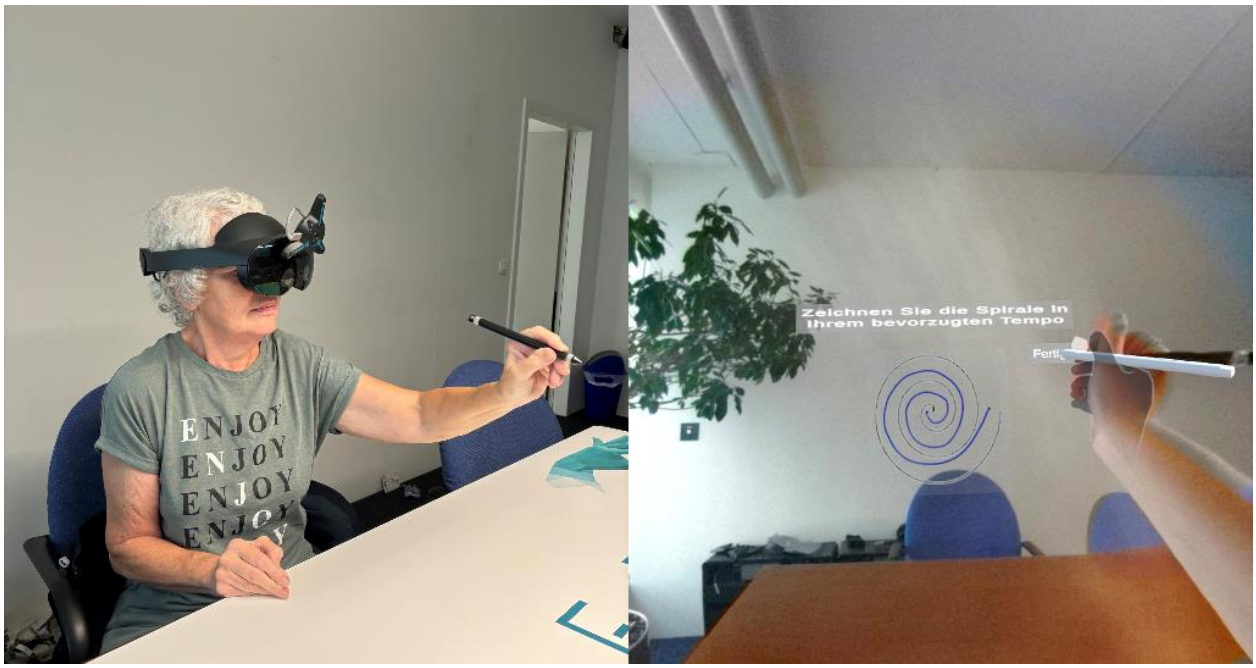
SHIFT 02-536

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / OTHER
4-5 April 2025

NEW ASSESSMENT OF UPPER LIMB MOTOR FUNCTION IN PARKINSON'S DISEASE: SPIRAL DRAWING WITH SMART STYLUS IN AUGMENTED REALITY

Tim Vanbellingen[1], Marije Zeillemaker[1], Manuela Pastore-Wapp[1], Rolf Adelsberger[2], Hagen Seifert[2], Erwin Van Wegen[3]
[1]ARTORG Center for Biomedical Engineering Research, Gerontechnology And Rehabilitation, Bern, Switzerland, [2]Sensoryx, Zurich, Switzerland, [3]Amsterdam UMC, Vrije Universiteit Amsterdam, Department Of Rehabilitation Medicine, Amsterdam, Netherlands

Aims: This pilot study explored the use of the Maliang Magic Pencil, a smart stylus, within an augmented reality (AR) environment to assess upper limb motor function in Parkinson's disease (PD) patients. Aim was to identify performance metrics that could distinguish between PD patients and healthy participants.
Methods: Three PD patients and five healthy participants drew 16 Archimedean spirals on a table surface and in the air. Various performance metrics, including trajectory length, number of changes in acceleration (NCA), and variance in pen altitude and azimuth, were evaluated. Test-retest reliability was assessed, along with correlations between metrics and clinical tests such as the Nine Hole Peg Test (NHPT).
Results: The system demonstrated usability above the threshold (SUS mean score 71.3%) and significant test-retest reliability, except for Spectral Arc Length (SPARC). Key metrics such as NCA correlated with NHPT performance, particularly in spirals drawn with the dominant hand in the air (r=0.42, p=.01) and non-dominant hand on the table (r=0.75, p=.03). PD patients exhibited unique motor patterns, including increased movement irregularity and reduced



smoothness. Figure: Drawing of a big spiral in the air, visible as seen through the AR headset.

Conclusions: The use of a smart stylus in AR shows promise for assessing motor function in PD patients. Larger studies with age-matched cohorts are needed to confirm the results and refine the assessment protocol for early diagnosis and disease monitoring.

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SHIFT 02-537

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / SUPPORT DEVICES & MONITORING
4-5 April 2025

DETECTING ISOLATED REM SLEEP BEHAVIOUR DISORDER (IRBD) FROM A WEARABLE SENSOR ON THE LOWER BACK

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[1]Tel Aviv Medical Center, Tel Aviv, Israel, [2]Tel Aviv University, Tel Aviv, Israel

Aims: Isolated rapid-eye-movement (REM) sleep behavior disorder (iRBD) is caused by motor disinhibition during REM sleep and is a strong early predictor of Parkinson's disease (PD). Recent studies have shown promise in detecting iRBD by measuring sleep-related motor activity from wrist-worn devices in the home setting. This study explored the accuracy of machine learning (ML) based analysis of mobility measures in classifying iRBD from a lumber worn sensor.
Methods: The study included 166 subjects: 13 individuals with iRBD, 67 health controls and 86 recently diagnosed patients with PD (40 with RBD). Participants slep one night in a polysomnographic laboratory and were asked to wear a wearable sensor (AX6, Axivity Ltd.) on their lower back (L4-5) for additional six nights. Mobility features were calculated from the accelerometer data.
Results: Mobility measures were able to classify PD from healthy controls with high accuracy 84.5% (sensitivity 82.5%, specificity 86.9%). Among the most prominent features were activity count and twitch activity. ML model based on seven digital measures distinguished iRBD from healthy controls with an accuracy of 76.8%, long immobile bouts was the most prominent feature. Within the PD group, the model distinguished between PD-RBD and PD-no RBD with accuracy of 55.8% (sensitivity 69.2%, specificity 44.6%).
Conclusions: Our proposed iRBD classifier achieved high accuracy in detecting iRBD based solely on wearable sensor data collected from an axial position. Using wearable sensors in the home setting for screening iRBD could assist in detecting individuals in the prodromal stage of neurodegeneration .

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SHIFT 02-538

Poster on Board - Shift 02
PATIENT CARE AND SUPPORT / MOVEMENT DISORDERS / SUPPORT DEVICES & MONITORING
4-5 April 2025

LONGITUDINAL PROGRESSION OF GAIT DECLINE IN INDIVIDUALS AT RISK FOR DEVELOPING PARKINSON'S DISEASE

Tal Tzfoni[1], Noa Levanon[1], Gadi Maayan Eshed[1], Nir Giladi[1], Jesse Cedarbaum[2], Roy Alcalay[1], Jeffrey Hausdorff[3], Anat Mirelman[3]
[1]Tel Aviv Medical Center, Tel Aviv, Israel, [2]Coeruleus Clinical Sciences, Yale University department of Neurology, Woodbridge, United States of America, [3]Tel Aviv Medical Center, Faculty of Medicine and Health Sciences, Tel Aviv University, Tel Aviv, Israel

Aims: Subtle motor gait alternations have been reported in the prodromal stage of Parkinson's disease (PD). The progression of gait changes in these cohorts is less known. This study aimed to investigate changes over time in selected gait measures in individuals at risk for developing PD.
Methods: The study included 145 adults. The MDS prodromal likelihood ratio score was calculated to assess the risk of developing PD. Study participants underwent an in-clinic gait assessment while wearing sensors adhered to their lower back, bilateral ankles, and wrists. Participants walked in a 15-meter corridor for 1 minute under two walking conditions: (1) preferred walking speed and (2) walking while engaging in a cognitive task (dual-task). They also performed the timed up-and-go test (TUG). Participants were assessed twice, 4 years apart.
Results: Forty-four participants were considered high-risk (i.e., LR>50, mean age 61.4±9.8yrs, 59%males) and 101 were low risk (59.9±8.5yrs, 42%males). Gait speed, step length and stride variability were similar between groups with similar changes over time. Group x time interactions were observed in the mean reduced amplitude of the arm swing in DT (mean change high-risk group: 8.5±2.11 vs. low-risk: 0.15±0.11deg; p=0.039) as well as longer TUG turn duration (mean change high-risk group: 0.23±0.01 vs. low r-risk group: 0.04±0.00sec; p<0.001).
Conclusions: Measures obtained from challenging walks (eg, dual task and turning) unmask mobility impairments in the prodromal stage of PD. Features relating to coordinative asymmetrical movements such as arm swing and turns appear to be especially sensitive to the relatively early stages of the neurodegenerative process.

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SHIFT 02-539

Poster on Board - Shift 02
PRION DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

IDENTIFICATION OF AN ION CHANNEL UNDERLYING A MULTI-MODAL VACUOLATION PHENOTYPE THAT CAN ALSO BE OBSERVED IN PRION-INFECTED MICE

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Aims: We revisited data from over 50 years ago, which had revealed similarities in a vacuolation phenotype observed in rodents poisoned with cardiac glycosides (CGs)—antagonists of NKAs—and spongiform degeneration seen in prion diseases. At the time, this hypothesis was dismissed because the vacuoles in prion diseases are observed in neurons, while CG poisoning of rodent brains led to astrocytic vacuoles. We hypothesized that this difference might be an idiosyncrasy of rodents and set out to investigate if we can alter this paradigm to make it useful for understanding molecular events underlying vacuolation and cell death in prion diseases.
Methods: We assessed whether mice expressing a humanized NKA α1 subunit develop neuronal vacuoles following CG treatment. We also used a variety of biomedical techniques to uncover the molecular mechanisms underlying this vacuolation phenotype. Using rAAV vector-mediated delivery of a fluorescent organelle marker, we examined if this marker could label vacuoles in prion-infected mouse brains.
Results: Acute CG treatment induced neuronal vacuolation in humanized NKA α1 expressing mice. Several lines of evidence, generated with pharmacological agents, ion-specific dyes, and truncated expression constructs, pointed toward a specific ion channel as being central to the vacuolation phenotype. We documented that vacuoles in late-stage prion disease can be filled with an organelle-specific fluorescent marker.
Conclusions: We demonstrate that acute CG poisoning of rodents expressing a humanized NKA α1 can induce a vacuolation phenotype that extends to neurons. The phenotype can also be triggered in cell culture by several specific insults and appears to depend on a specific ion channel. Using a fluorescent reporter, we document that this phenotype can also be observed in late-stage prion-infected rodents in vivo, suggesting it contributes to the spongiform degeneration seen in prion diseases.

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SHIFT 02-541

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4-5 April 2025

NOMAD® GENETICALLY ENCODED BIOSENSORS FOR DOPAMINE RECEPTORS FUNCTIONAL ASSAY

Patricia Villace, Rosa Mella, Meritxell Roura, Elisabete Hernández-Imaz
INNOPROT, Molecular And Cellular Biology, DERIO, Spain

Aims: Nomad biosensors comprise a platform for multiplexing GPCR functional assays using genetically encoded fluorescent biosensors and label-free receptors. This new technology allows the detection of changes in different GPCR signaling pathways (Ca2+, cAMP, DAG and Arrestin) in one single assay (Fig 1). In this work, we show a cell based assay using stable cell lines coexpressing cAMPNomad biosensor and Dopamine receptors (DRD1,2,3, 4 and 5). Dopamine receptors are implicated in many neurological processes, including motivation, pleasure, cognition, memory, learning, and fine motor control, as well as modulation of neuroendocrine signaling. After the screening campaign, positive compounds were chosen for further testing, based on the strength of the initial response and the lack of cytotoxicity.
Methods: U2OS cell line stably expressing cAMPNomad biosensor was transfected with the cDNA of the DRD receptors. Agonism assay: Cells were treated with increasing concentrations of Dopamine diluted in OptiMEM overnight. Antagonism assay: Cells were treated with increasing concentrations of reference antagonist diluted in OptiMEM –Dopamine overnight. Activity measurement: Fluorescent images were acquired in the Cell insight CX7 high content equipment from Thermo Fisher.
Results: Functional assays. Dose-response curves of Dopamine agonist and reference antagonists were obtained using NOMAD technology. A chemical library consisting of 1,200 compounds, sourced from the Prestwick Chemical Library® was used with the objective to identify putative antagonist compounds implicated in the DRD activity regulation. Comparativeof antagonist behaviour of different compounds in cAMPNomad DRD receptors were obtained.
Conclusions: NOMAD® is a genetically encoded fluorescent biosensor platform can be used for the simultaneous measurement of different DRD receptor members. These assays work in living cells and provides accurate quantitative results that are amenable to High Throughput Screening (HTS) and/or High-Content Screening (HCS) with high Z' values.

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SHIFT 02-542

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

REGULATION OF WNT SIGNALING BY LGR5 IN NEURAL AND NEUROGENIC TUMOR STEM CELLS

Hyunhee Park[1], Seong-Ho Koh[2], Hyuk Sung Kwon[2], Hyun-Jung Yu[3], Myung-Hoon Han[4]
[1]Department of Neurology, Guri-si, Korea, Republic of, [2]Department of Neurology, Gyeonggi-do, Korea, Republic of, [3]Department of Neurology, Seongnam, Korea, Republic of, [4]Department of Neurosurgery, Gyeonggi-do, Korea, Republic of

Aims: The role of LGR5, a significant cell surface receptor identified in neural tissues, is pivotal as a stem cell marker and a receptor for R-spondin ligands, facilitating Wnt/β-catenin signaling critical for stem cell proliferation and self-renewal. Understanding the molecular mechanisms driving LGR5-mediated signaling pathways is crucial for insights into tissue homeostasis, regeneration, and disease pathogenesis.
Methods: This study explores LGR5's function in neural stem cells (NSCs) and neural tumor stem cells through genetic modifications, transcriptomic/proteomic analyses, and functional assays. We engineered Lgr5 knock-in NSCs and knock-out neural tumor stem cells from rat and human cell lines, followed by transcriptome and proteome analyses to dissect Lgr5-mediated signaling pathways.
Results: Our research discovered distinct expression patterns of elongation factor Tu (EF-Tu) in neural stem cells versus neural tumor stem cells among 18 analyzed phospho-proteins. Manipulation of EF-Tu expression validated its regulatory influence on LGR5 protein expression. Bioinformatics tools CluGo and String within Cytoscape elucidated the complex interaction between EF-Tu and the Wnt pathway in both cell types.
Conclusions: Our findings underscore the potential of modulating the Wnt signaling pathway to enhance neural stem cell proliferation by targeting LGR5 and Wnt signals. This research opens avenues for developing new therapies for age-related and refractory neurological disorders such as Alzheimer's disease, stroke, and Parkinson's disease. By proposing and validating novel therapeutic strategies, this study offers significant insights for advancing treatments for these conditions.

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SHIFT 02-543

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

WHAT IF DEMENTIA IS DUE TO CALCIUM CARBONATE?

Angela Scibetta
Angela Scibetta, Medicine (MD); Psychotherapy, Ronchis, Italy

Aims: Evaluate the hypothesis and plan a research project
Methods: With new ways to approach neurophysiology and with the use of cerebral tissue prepared specifically for TEM/EELS microscopy we can study an innovative hypothesis. What if it were possible to find a calcium channel incrusted with a calcium salt molecule? What kind of damage could do at a local and adjacent cellular area? $CO_2 + H_2O \Leftrightarrow 2H^+ + CO_3^{2-} + Ca^{+2} > CaCO_3$ However, all these chemicals can be found in the interstitial fluid and neuronal membrane, according to the medical bibliography. Therefore, if the formula above is valid in nature, it can be applied to the neurophysiology field, according to a transitive theory. The combination of TEM and EELS is being applied to the structural and chemical analysis of practical materials down to the atomic scale, able to identify Calcium traces in biological tissues.
Results: It could be expected that: *Micro-regional level* Changes in the membrane next to the calcic channel Slight deformation of the adjacent protein sites Folding and production of beta amyloid protein Activation of the inflammatory process in order to repair the defect *Macro-regional level* Resting potential increase Spike transmission reduced Tao detachment from the axon Reduced consume of energy Reduced activity and local perfusion Water cortical concentration lowering Water falls by gravity into the ventricles Stoke risk increased and more compression next to ventricle As a result: Mechanical resistance would increase Membrane fluidity would not change Pulsatility would decrease
Conclusions: If we can demonstrate that the prefrontal and frontal area are involved in this process, we can explain the symptoms of dementia and the aging of the brain

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SHIFT 02-544

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

IMPACT OF MILD COGNITIVE IMPARIMENT ON LEARNING AND SHORT-TERM MEMORY IN VISUOSPATIAL AND VERBAL MEMORY MODALITIES

Xiangrong Shi, Christopher Cortez, Jewelia Rattanavong, April Wiechmann, Hannah Dyson, Sarah Ross, Robert Mallet
University of North Texas Health Science Center, Fort Worth, United States of America

Aims: To examine short-term memory (STM) and learning ability in subjects with mild cognitive impairment (MCI) in the visuospatial sketchpad and the phonological loop sub-systems.
Methods: Thirty MCI and 28 non-MCI subjects signed the informed consent to participate in the study approved by the North Texas Regional IRB. Diagnostic criteria for MCI included a self- or family member-reported memory complaint; clinical dementia rating ≤0.5; and/or STM testing-score in one or more modalities below the age-/education-adjusted group averages. STM was assessed by immediate and delayed recalls using California-Verbal-Learning-Test-2nd edition (CVLT-II) and Brief-Visuospatial-Memory-Test–Revised (BVMT-R) and learning ability was estimated from the difference between trial 1 raw score and the higher of the raw scores from the last two trials in immediate recall. Values between the groups were compared using t-tests.
Results: There was no difference in age (71.6±1.0 vs 70.6±1.1 years old) or education attainment (15.9±0.2 vs 15.8±0.3 years) between the MCI vs non-MCI subjects. MCI was associated with lower MMSE score (MCI vs non-MCI: 27.9±0.3 vs 28.6±0.2, P=0.058). Both 30-s short-delayed and 10-min long-delayed recall scores in CVLT-II and 30-min delayed recall scores in BVMT-R were significantly lower in the MCI vs non-MCI subjects (CVLT-II short-delayed: 7.2±0.2 vs 8.1±0.2 [P<0.001]; long-delayed: 6.0±0.4 vs 7.9±0.2 [P<0.001], and BVMT-R delayed recall: 5.7±0.6 vs 8.5±0.3, [P<0.001]). Learning scores in the MCI vs non-MCI subjects were lower in BVMT-R (3.2±0.4 vs 4.4±0.3, P=0.016), not in CVLT-II (2.6±0.2 vs 3.0±0.2, P=0.233).
Conclusions: Visuospatial learning is significantly diminished, but verbal learning may be preserved in the subjects with MCI. STM assessed by the verbal memory and visuospatial memory are both impaired with MCI.

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SHIFT 02-545

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS
4-5 April 2025

INTRAVENOUS BIPERIDEN PHARMACOLOGICAL CHALLENGE MODEL IN HEALTHY ELDERLY AS PROOF-OF-MECHANISM TOOL FOR COGNITION: A RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL

Massimo Magliocca[1,2], Eva Thijssen[1], Katelijne Van Der Heijden[1,2], Laura Borghans[1], Philip Kremer[1,2], Gabriel Jacobs[1,2]
[1]Centre for Human Drug Research, Leiden, Netherlands, [2]Leiden University Medical Centre (LUMC), Leiden, Netherlands

Aims: To investigate biperiden administered intravenously (IV) as a cognitive pharmacological challenge model for application in proof-of-mechanism studies involving novel selective muscarinic-1 acetylcholine receptor (M1-AChR) agonists.
Methods: Double-blind, placebo-controlled, randomized, 3-way crossover study including 12 healthy elderly (>65 years) subjects who received biperiden 1.3 mg, 2.6 mg, and placebo IV over 60 minutes. Subjects completed central nervous system test batteries (NeuroCart® and Cogstate®) to assess potential cognitive effects up to 24 hours post-dose. Pharmacokinetic non-compartmental analysis of biperiden was conducted up to 11 hours post-dose.
Results: All 12 subjects completed the study. The variability (CV%) in mean plasma C_{max} and AUC_{inf} of 2.6 mg IV biperiden was 35.1% and 21.9%, respectively, i.e., lower than that of oral biperiden in a previous study [1]. Compared to placebo, 2.6 mg IV biperiden showed robust and reversible pharmacodynamic effects, with statistically significant impairments in, among others, adaptive tracking (-2.36% [-3.65,-1.07], p=0.001), indicating reduced sustained attention and the N-back task, evidenced by both increased reaction time (76.1 msec [46.3, 105.8], p<0.0001) and decreased response accuracy on the 1-back (-0.081 [-0.16, -0.003], p=0.04), indicating decreased working memory. Both effects were associated with changes in EEG theta power.
Conclusions: The findings support that IV biperiden is likely a more reliable pharmacological challenge than oral biperiden for application in proof-of-mechanism studies with novel selective M1-AChR agonists.

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SHIFT 02-546

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / DRUG DEVELOPMENT, CLINICAL TRIALS
4-5 April 2025

IRL757C001 – A FIRST-IN-HUMAN TRIAL ON IRL757, A CORTICAL ENHANCER IN CLINICAL DEVELOPMENT FOR THE TREATMENT OF APATHY IN AD/PD

Joakim Tedroff, Johanna Landström, Clas Sonesson, Lien Nguyen, Susanna Waters, Fredrik Hansson, Boel Löfberg
Integrative Research Laboratories Sweden AB, Gothenburg, Sweden

Aims: IRL757C001 is a Phase 1 trial investigating safety, tolerability and pharmacokinetics of IRL757, a novel compound in development for the treatment of apathy in neurodegenerative disorders including Parkinson's disease (PD) and Alzheimer's disease (PD). Apathy is a clinical feature causing significant suffering and disability in these conditions, and effective treatments are currently lacking. The specific pharmacological mode of action of IRL757, strengthening of cortical catecholaminergic transmission in combination with enhanced cortico-striatal connectivity addresses key aspects of functional aberrations associated with apathy.
Methods: IRL757C001 is a double blind, placebo-controlled, single ascending dose/multiple ascending dose (SAD/MAD) study in male and female healthy volunteers. The dose range investigated is selected to cover pharmacologically relevant exposures, with adequate safety margins in relation to the preclinical toxicology and safety data. The study involves close monitoring of safety parameters, and collection of blood and urine samples for PK and clinical chemistry assessment. The SAD part includes a food-interaction cohort. The MAD part involves 10 days repeated administration of IRL757 BID.
Results: Data from the SAD cohorts shows that IRL757 is safe and well tolerated upon single dosing over a wide dose range. Adverse events are generally sparse and non-specific. MAD data are currently being collected and will be presented at the meeting.
Conclusions: We present data from the first-in-human trial of IRL757 a cortical enhancer in development for treatment of apathy associated with AD and PD. Preliminary results showed that IRL757 is safe and well tolerated over a wide dose range upon single dosing to healthy volunteers. Detailed PK and safety data will be presented at the meeting.

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SHIFT 02-547

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
4-5 April 2025

THE NON-MOTOR CHARACTERISTICS OF PATIENTS WITH IDIOPATHIC PARKINSON'S DISEASE IN THE HAI DISTRICT OF NORTHERN TANZANIA, FOCUSSING ON MOOD AND COGNITION.

Mihika Prakash[1], Catherine Dotchin[2], Elizabeth Scott[1], Kai Harrington[1], Jojet Josephat[3], Marieke Dekker[3], Declare Mushi[3], Richard Walker[2]
[1]Newcastle Medical School, Newcastle Upon Tyne, United Kingdom, [2]Northumbria Healthcare NHS Foundation Trust, Newcastle upon Tyne, United Kingdom, [3]Kilimanjaro Christian Medical Centre, Moshi, Tanzania

Aims: This is an observational study set in the Hai district of Northern Tanzania. It aims to describe the non-motor symptom (NMS) profile of idiopathic Parkinson's disease (PD) in a rural setting in Sub-Saharan Africa, with a focus on the domains of mood and cognition. The global PD burden is rising, with over 8.5 million individuals affected worldwide.
Methods: A door-to-door survey identified PD cases in the district. The following validated assessment tools were used to ascertain the participants' NMS burden: the Non-Motor Symptom Questionnaire (NMSQ), Movement Disorder Society Unified PD Rating Scale (MDS-UPDRS), Identification and Intervention for Dementia in Elderly Africans (IDEA) screening tool for cognitive impairment (CI), and Hospital Anxiety and Depression Scale (HADS). Statistical analysis was done to identify relationships within the dataset.
Results: 100% of the cohort (n=29) experienced NMS. The MDS-UPDRS cohort mean (± SD) for total NMS score was 15.1 (± 1.7) out of 52, and 15 people had CI. MDS-UPDRS data highlighted depressed (n=12), anxious (n=13), and apathetic (n=11) moods amongst participants. The IDEA screen picked up 9 participants with signs of dementia. Participants experienced an average of 10 out of 30 symptoms within the NMSQ. 13 (48%) participants had borderline or abnormal results for both anxiety and depression in the HADS. There was a 100% treatment gap for mood and cognitive symptoms.
Conclusions: The study underscores a high prevalence of NMS in this PD population. PD patients in Tanzania are commonly affected by mood and cognitive disorders and symptoms within these domains are strongly associated with one another. Further research with a larger cohort will strengthen these conclusions and emphasize the need to develop accessible and cost-effective therapies for PD NMS.

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SHIFT 02-548

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / GENETICS, EPIDEMIOLOGY
4-5 April 2025

DEMENTIA AND OPIOID EXPOSURE FOR NON-CANCER PAIN CONTROL: A POPULATION-BASED COHORT STUDY

Hyong Sook Jun[1], Tak Youn[2], Areum Moon[1]
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Aims: We investigated the association between opioid exposure for non-cancer pain control and the development of dementia in patients with chronic non-cancer pain in South Korea.
Methods: This study is a population-based cohort study using big data from the National Health Insurance Service database in South Korea. From 2017 to 2019. Patients diagnosed with musculoskeletal diseases and chronic non-cancer pain including osteoarthritis, lower back and neck pain, and rheumatoid arthritis, were included for control group. Patients with a cancer diagnosis, those who received surgery or those with psychiatric disorders were excluded from the analysis. Patients who had been regularly and continuously prescribed opioids such as morphine, hydromorphone, fentanyl, tramadol, oxycodone, methadone, codeine, and dihydrocodeine for ≥ 90 days were classified as opioid group. The patients who were diagnosed with dementia from 2020 to 2022 over a period of 3 years were included for analysis. Diagnosis of dementia included Alzheimer's dementia, vascular dementia and unspecified dementia.
Results: A total of 850,734 patients with chronic non-cancer pain were included in control group. And 13,867 (1.63% of the control) were opioid users. A total of 23,140 (2.72%) patients with chronic non-cancer pain were newly diagnosed with dementia from 2020 to 2022. The proportions of dementia were Alzheimer's dementia 1.9%, vascular dementia 0.5%, and unspecified dementia 0.7%. In multivariable Cox regression modeling, the opioid group showed a 16% increased likelihood of developing Alzheimer's dementia and unspecified dementia of compared to opioid-naïve patients. There was no statistical difference for vascular dementia. In addition, opioid use was associated with an increased risk in the elderly (≥ 60 years)
Conclusions: Our results suggest that elderly individuals who were prescribed opioids may be at a higher risk for developing dementia.

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SHIFT 02-551

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

FREQUENCY AND LONGITUDINAL COURSE OF BEHAVIORAL AND NEUROPSYCHIATRIC SYMPTOMS IN SPORADIC FRONTOTEMPORAL DEMENTIA

Lena Marth[1,2], Anna Stockbauer[1,2], Alexander Bernhardt[1,2], Olivia Wagemann[1,2], Catharina Prix[1,2], Annika Spottke[3,4], Elisabeth Dinter[5,6], Katharina Buerger[2,7], Günter Höglinger[1,2,8], Sonja Schönecker[1,2], Johannes Levin[1,2,8]

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Aims: Behavioral and neuropsychiatric symptoms are common in frontotemporal dementia (FTD). We therefore aimed to describe behavioral and neuropsychiatric phenotypes in sporadic FTD and quantify their temporal association.
Methods: 312 sporadic FTD patients from the DESCRIBE-FTD cohort were included in the study: 152 behavioral variant FTD (bvFTD), 32 logopenic variant primary progressive aphasia (lvPPA), 61 nonfluent variant PPA (nfvPPA), 31 semantic variant (svPPA) and 36 PPA patients not further classified. Principal component analysis (PCA) was employed to delineate clusters of behavioral and neuropsychiatric symptoms, which were subsequently examined with respect to frequency and severity across groups. We applied linear mixed effects models to describe the evolution of symptoms over time.
Results: PCA revealed four clusters of behavioral and neuropsychiatric symptoms: active behavioral, passive behavioral, affective and psychotic symptoms. Behavioral and neuropsychiatric symptoms were observed across all groups, with psychotic symptoms being least and active behavioral symptoms being most prevalent. While the amount of active behavioral symptoms was influenced by time from symptom onset, gender and phenotypic group, passive behavioral symptoms mainly depended on phenotypic group with bvFTD patients showing the highest amount of symptoms. Affective symptoms were influenced by time from symptom onset, gender and education. None of the investigated variables reached statistical significance when evaluating psychotic symptoms.
Conclusions: Behavioral and neuropsychiatric symptoms are known to be common in bvFTD. Our findings demonstrate that both, behavioral and neuropsychiatric symptoms are also prevalent in PPA. Their severity depends on time from symptom onset, phenotypic group, gender and education. This detailed

understanding of potential symptoms is crucial for optimizing patient care, can guide diagnostic evaluations and the design of clinical trials for novel disease-modifying and preventive therapeutic interventions.

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SHIFT 02-552

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

POPULATION SCREENING WITH XPRESSO: A DIGITAL COGNITIVE SELF-EVALUATION TOOL

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Aims: XpressO is an online self-screening tool developed by Montreal Cognitive Assessment (MoCA) which provides a brief cognitive evaluation to help determine whether users should seek further assessment. XpressO was launched in early 2024 with over 9,000 unique users self-enrolled and more than 24,000 tests were recorded. Here, we evaluate the XpressO test results from online users at baseline.
Methods: We contrasted the XpressO scores with the prevalence of MCI in the US population between ages 60-85, as reported by Petersen et al (2018). In a subset of users (n=500), we gathered additional information using an online user-feedback questionnaire.
Results: We evaluated the baseline results of 9815 users, with a mean age of 56.2 (SD 15.8; see Figure 1), 60.6% female. The mean XpressO score was 72.6 (SD 23.7): 12.2% had a low XpressO score (<= 42), indicating an increased risk for MCI; 21.7% had an intermediate XpressO score, and 66.1% had a high XpressO score (>= 72), indicating normal cognition. The relative proportion of low XpressO scores increases with age, in-line with the prevalence of MCI (see Figure 2). The user-questionnaire indicated that 60% of users worry about their cognitive health and 45% would discuss the result with their healthcare provider.

Figure 1: Histogram of age from the online population. US in dark blue, Non-US locations in light blue

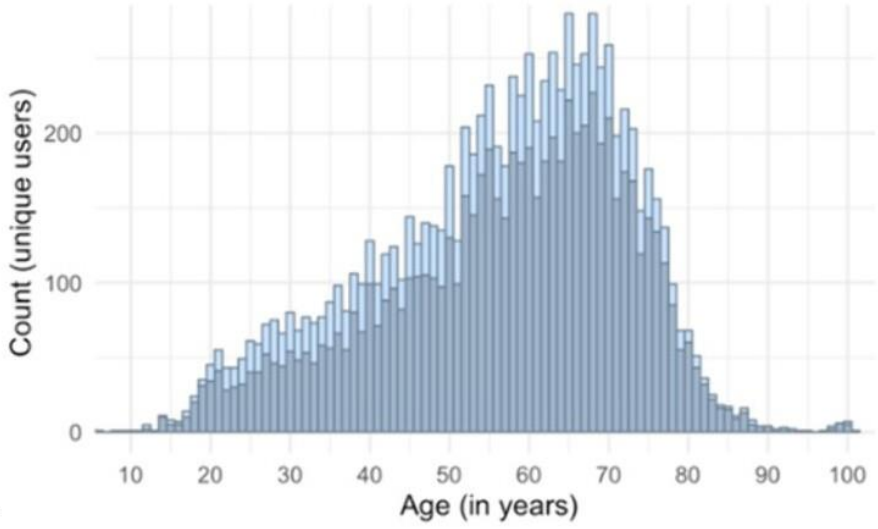
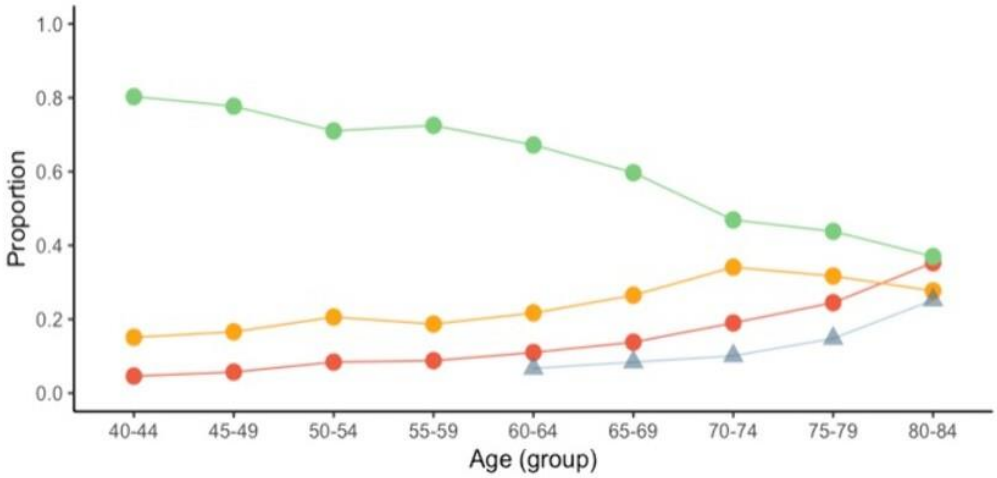


Figure 2: Proportion of users with high (green), intermediate (orange) and low (red) XpressO scores stratified by age. In light blue, the prevalence of MCI in the US based on Petersen et al 2018.



Conclusions: Results demonstrate that the XpressO test score is associated with age-related cognitive decline. The proportion of users with a low XpressO score slightly exceeds the reported prevalence of MCI, suggesting our population is enriched with individuals hwo are concerned about their cognition and may be experiencing age-related cognitive decline. These findings highlight the relevance of the XpressO score in identifying individuals at an increased risk of MCI and support its use for pre-screening in primary care or clinical trials.

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SHIFT 02-553

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

CSF PROTEIN SIGNATURES LINKING DEMENTIA AND DELIRIUM IN OLDER ADULTS WITH HIP FRACTURES: INSIGHTS FROM A NORWEGIAN COHORT

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Aims: Neurodegenerative disorders represent a growing global health challenge, yet the impact of acute neurological complications on disease progression remains inadequately characterized. This study aimed to elucidate cerebrospinal fluid (CSF) proteomic signatures associated with dementia and examine how these molecular profiles are modified by concurrent delirium in a well-characterized Norwegian hip fracture cohort.
Methods: CSF samples from 163 patients (median age: 83±10.64 years) were analyzed using in-solution digestion and LC/MS. Data preprocessing incorporated variance stabilization normalization, XGBoost-based imputation, and batch effect correction. Differential protein expression analysis was performed using LIMMA with empirical Bayes moderation (significance: $|logFC| > 0.5$, adjusted p-value ≤ 0.05).
Results: Analysis identified 1,691 high-quality proteins, with 553 differentially expressed between dementia-positive (n=94) and dementia-negative (n=69) cohorts. Delirium status significantly influenced protein signatures: delirium-negative individuals showed 799 differentially abundant proteins, while delirium-positive individuals exhibited 245. Gene Ontology analysis revealed consistent downregulation of synaptic organization and upregulation of immune responses, while KEGG pathway analysis highlighted alterations in glycosylation and PI3K-Akt signaling.
Conclusions: This comprehensive proteomic profiling reveals distinct molecular signatures associated with dementia, significantly influenced by delirium status. The consistent downregulation of synaptic organization pathways, coupled with the upregulation of immune responses, suggests a complex interplay between neurodegeneration and neuroinflammation. These findings provide novel insights into dementia pathophysiology, potentially informing future therapeutic strategies targeting specific proteomic alterations.

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SHIFT 02-554

Poster on Board - Shift 02
PSYCHIATRIC SYMPTOMS IN NEURODEGENERATIVE DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4-5 April 2025

TREATMENT OF NON-MOTOR SYMPTOMS OF PARKINSONISM USING CLOZAPINE OR ARIPIPRAZOLE WITH ELECTROCONVULSIVE THERAPY: A CASE SERIES

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Aims: During the treatment of Parkinson disease(PD) with L-dopa, non-motor symptoms(NMS) such as dyskinetic movement or psychotic symptoms developed in many patients. For the management of psychiatric NMS, such as visual hallucination, many antipsychotics are used but most antipsychotic medications aggravate PD motor symptoms. Clozapine is not related Dopamine(DA) receptor and aripiprazole is DA stabilizer, not DA antagonist. In addition, electroconvulsive therapy(ECT) has been shown to increase sensitivity in the DA receptors in PD in contrast to L-dopa treatment. The aim of this small case series is to describe cases of psychiatric NMS in PD treated with clozapine, aripiprazole and ECT.
Methods: In this cases series, the treatment effect of clozapine, aripiprazole with ECT was investigated in four PD patients with NMS. Frist patient was diagnosed to PD with severe intractable dyskinetic movement and visual halluicination. Second and third patients were also diagnosed to PD with severe psychotic symptoms such as paranoid delusion and hallucinations. Last patient was also diagnosed to PD with NMS and schizophrenia. Before ECT, clozapine or aripiprazole medications with PD medications were optimally adjusted. After acute phase of ECT, all subjects received maintenance ECT of right unilateral (RUL) or bifrontal (BF) electrodes with ultrabrief stimuli every 1-4 week with medications for PD.
Results: During acute ECT sessions, two or three times of ECT per week was applied for all patients. Psychiatric NMS was improved within 2-4 weeks. All subjects have been treated with maintenance ECT and medication for PD, shows significant improvement of NMS without aggravation of cognitive functioning. Maintenance ECT is applied to all patents.
Conclusions: Cloazapine and aripiprazole with ECT treatment for patients who have severe NMS with PD may be an effective treatment for NMS of PD

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SHIFT 02-555

Poster on Board - Shift 02
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
4-5 April 2025

AAV-TAU INJECTION IN THE SUBSTANTIA NIGRA AS A RAPID AND ROBUST MOUSE MODEL OF TAUOPATHIES WITH PARKINSONIAN FEATURES

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Aims: The objective of this work was to characterize a novel mouse model utilizing adeno-associated virus (AAV)-induced human wild-type tau expression specifically targeting the substantia nigra, designed to study tau-related neurodegeneration in dopaminergic neurons.
Methods: Wild-type C57BL/6 mice underwent unilateral stereotaxic injection of an AAV vector overexpressing wild-type human (2N4R) tau (AAV-Tau) or an empty (control) AAV vector into the substantia nigra pars compacta at 9 (young) or 48 (aged) weeks-of-age. Hindlimb clasping and nesting scores were assessed weekly to monitor the progression of gross motor deficits over time. Asymmetric locomotor behavior was assessed at 6 and 10 weeks post-injection (WPI) of the AAVs via the tail suspension swing test and the cylinder test. The rotarod test was used to evaluate motor coordination and balance at 7 and 11 WPI. Regional neuroanatomical volumes were assessed via automated image analysis of in vivo anatomical MRI scans acquired at 12 WPI using a 7T preclinical MRI scanner.
Results: AAV-Tau-injected mice showed early spontaneous progressive motor dysfunction, including locomotor asymmetry, motor coordination and balance impairments, and hindlimb clasping deficits. The AAV-Tau-induced phenotype was exacerbated in aged mice compared to young animals, and was associated with increased spontaneous contralateral rotations during the cylinder test. Significantly decreased regional neuroanatomical volumes (e.g. midbrain, striatum) were observed in the ipsilateral hemisphere when compared to the contralateral hemisphere in the AAV-Tau animals.
Conclusions: The early development of motor deficits and regional brain atrophy observed in AAV-Tau-injected mice makes this translational model a valuable and reliable tool for preclinical efficacy studies aimed at accelerating the development of disease-modifying therapeutic interventions for tauopathies with Parkinsonian features, such as Progressive Supranuclear Palsy (PSP) and Corticobasal Degeneration (CBD).

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SHIFT 02-556

Poster on Board - Shift 02
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
4-5 April 2025

FROM MOLECULES TO BEHAVIOR: COMPREHENSIVE CHARACTERIZATION OF THE PS19 TAUOPATHY MOUSE MODEL AND ITS PRECLINICAL UTILITY FOR ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease, the leading neurodegenerative disorder, is characterized by the accumulation of Aβ and tau proteins. While most models focus on Aβ pathology, this study aims to characterize the PS19 tauopathy model (B6;C3-Tg(Prnp-MAPT*P301S)PS19Vle/J) to investigate tau's role in AD.
Methods: 36 PS19 and 24 non-carrier mice were monitored from 12 to 50 weeks, with assessments every 4, 8, and 12 weeks, evaluating neurodegeneration, neuroinflammation, BBB integrity, cerebral glucose metabolism, retinal thickness, neurodegenerative biomarkers, as well as behavioral, motor, and memory function.
Results: Neuroimaging revealed reduced cortical (p=0.0023) and hippocampal (p=0.0128) volumes, along with lower water content (cortex: p=0.0003; hippocampus: p=0.0007), suggesting tissue atrophy. Additionally, decreased Fe^{2+} levels (cortex: p=0.0184; hippocampus: p=0.0023) and gadolinium extravasation suggested vascular changes and BBB disruption. PS19 mice also showed reduced glucose metabolism and retinal thinning. Biomarker analysis highlighted elevated circulating $CD34^{+}$ cells (p=0.0122). Plasma biomarkers analysis, assessing using Olink® Target96 Mouse Exploratory, indicated that upregulated proteins are related to signal transduction, cell death, and cytokines pathways, and downregulated proteins with morphogenesis, axonogenesis, neuronal projection, and synapses pathways. Motor deficits were evident, with diminished maximum speed in the open field test (p <0.0001), and reduced rotarod maximum latency time in the continuous speed (p=0.0003) and acceleration (p=0.0378) tests. Behavioral assessments showed hyperactivity, reduced anxiety-like behavior, memory impairment, and altered exploration. Increased neurodegeneration in hind-limb clasping test, and weight loss (both p<0.0001) were observed. Immunofluorescence confirmed increased pTau (hippocampus, p=0.0013), neuroinflammation (hippocampus p=0.0002), microglial activation (hippocampus p=0.0008), synapse and pTau phagocytosis by microglia (cortex p=0.0009, hippocampus p=0.0102 and <0.0001, respectively), and synapse loss (hippocampus p=0.035).

Conclusions: PS19 model serves as a valuable preclinical tool for investigating therapeutic and diagnostic strategies in tau-related AD pathology.

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SHIFT 02-557

Poster on Board - Shift 02
TAUPATHIES / ANIMAL MODELS / TRANSGENIC RODENTS
4-5 April 2025

LONGITUDINAL EVALUATION OF PTHR217 TAU AND OTHER TAU SITES IN IN THE PS19 MOUSE MODEL OF ALZHEIMER'S DISEASE AND OTHER TAUOPATHIES

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Aims: In Alzheimer's disease (AD) and other tauopathies, tau undergoes pathological phosphorylation, leading to its misfolding and aggregation into neurofibrillary tangles. The P301 mutation in the tau protein has been linked to certain tauopathies. We thus longitudinally characterized the PS19 transgenic mouse model that carries the PS301 mutation in the MAPT gene encoding tau protein. The model is used to study tauopathies, downstream effects, and can ultimately be used for the development of new therapeutic strategies.
Methods: Cortical and hippocampal tissue as well as cerebrospinal fluid (CSF) of 2.5, 4.5, 6.5, and 8.5 months old PS19 mice and non-transgenic littermates were analyzed for total and various phosphorylated (p) tau species such as pSer202/Thr205, pThr231 and the highly studied marker pThr217 using biochemical and histological methods. Levels of neurofilament light chain (NF-L) were quantified in CSF using the NF-light® ELISA from UmanDiagnostics. Glial fibrillary acidic protein (GFAP) to evaluate astrogliosis and NeuN to stain neuronal nuclei were subject of histological analyses.
Results: Our findings indicate that total tau and ptau at different residues, such as pThr217, are elevated in the soluble and insoluble fraction of the cortex and hippocampus as early as 2.5 months of age in PS19 mice. An increase in NF-L levels in the CSF of 8-month-old PS19 mice was observed. Ongoing histological analyses of pSer202/Thr205, pThr217, GFAP and NeuN will provide additional insights into the relationship between tau phosphorylation, neuroinflammation, and neuronal integrity in PS19 mice.
Conclusions: Our findings reinforce the usability of PS19 mice as robust model for investigating the effects of elevated levels of mutated tau. This model provides insights into the underlying mechanisms of tau pathology and serves as effective platform for evaluating potential novel therapeutic agents.

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SHIFT 02-560

Poster on Board - Shift 02
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / TAU, TAU ISOFORMS
4-5 April 2025

BRAIN-DERIVED TAU OLIGOMER POLYMORPHS: DISTINCT AGGREGATION AND STABILITY PROFILES

Suhyeorn Park[1,2], Filippa Lo Cascio[1,2], Nikita Shchankin[1,2], Mauro Montalbano[1,2], Rakez Kayed[1,2]
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Aims: Several neurodegenerative disorders are characterized by the aggregation of misfolded proteins, including microtubule-associated tau protein. Although many of the tau polymorphic studies have been performed on tau fibrils, recent evidence has identified the soluble tau oligomers (TauO) as the more relevant and toxic species in the propagation of the disease due to their ability to seed tau misfolding. While methods for isolating and characterizing tau aggregates have been established, there is still a knowledge gap regarding the structural characterization of smaller, more dynamic tau polymorphs.
Methods: We isolated brain-derived tau oligomers (BDTOs) from brain tissues of Alzheimer's disease (AD), dementia with Lewy bodies (DLB), and progressive supranuclear palsy (PSP) patients. We characterized the difference in structures and morphologies of the amplified BDTOs using biochemical assays. We also applied Fluorescent Amyloid Multi Emission Spectra (FLAMES) microscopic analysis that allows us to detect and profile different amyloid structures by using commercially available amyloid fluorescent dyes.
Results: Our results indicate that amplified BDTOs have different morphologies when characterized using AFM and different digestion profiles tested by pronase and Proteinase K digestion, as well as through mass spectrometry. The amplified BDTO polymorphs did not show significant difference in binding to amyloid fluorescent dyes, although they were distinguishable from fibrillar structures using FLMAES. These results revealed different characteristics of tau oligomeric polymorphs.
Conclusions: Our findings suggest that the formation of distinct polymorphic tau oligomers may contribute to the development of multiple tauopathy phenotypes and shape the progression of neurodegenerative diseases. These results may provide insight for developing personalized therapy approaches to specifically target neurotoxic tau species.

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SHIFT 02-561

Poster on Board - Shift 02
TAUPATHIES / CELL, MOLECULAR AND SYSTEMS BIOLOGY / TAU, TAU ISOFORMS
4-5 April 2025

AN INTRANEURONAL TAU AGGREGATION MODEL OF HUMAN IPSC-DERIVED NEURONS WITHOUT TAU SEED ADDITION

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Aims: Tau aggregation models in human neurons are essential to understand the disease biology of tauopathies and develop the therapeutics targeting tau. The models will clarify how tau aggregates in human neurons at cellular and molecular levels, underlying the mechanism of action in anti-tau drugs. It was reported that the tau with double mutations of P301L and S320F (P301L/S320F) exhibits the aggregation by simply forcing its expression in HEK293T cells and mouse brains. In this study, we challenged to generate human iPSC-derived neural stem cells (NSCs) harboring Dox-inducible P301S or P301L/S320F tau to establish the tau aggregation model in human neurons without seeding tau.
Methods: Human iPS (UKBi005-A)-derived NSCs (long-term neuroepithelial-like stem cells (lt-NES cells)) harboring Dox-inducible 0N4R MAPT(P301S) or 0N4R MAPT(P301L/S320F) were generated by piggyBac system. Dox (1 μg/mL) was added from day 10 after the start of neural differentiation to induce tau expression, and 28-day differentiated neurons were analyzed by western blot, immunocytochemistry and proteome analysis.
Results: Dox addition induced the expression of 0N4R tau with P301S or P301L/S320F mutations in the iPSC-derived neurons, among which high-molecular weight (HMW) tau was observed only in the P301L/S320F-expressing neurons. Hyperphosphorylation of tau was observed in HMW tau from the sarkosyl-insoluble fraction of the Dox-treated P301L/S320F neuronal lysates. There was Thioflavin S (ThS)-positivity in the Dox-treated P301L/S320F neurons, which was localized mainly in soma. In addition, we observed AT8- and MC-1-positive neurites as well in this model.
Conclusions: We generated human iPS cell-derived NSCs harboring Dox-inducible mutant tau (P301S, P301L/S320F). In the presence of Dox, sarkosyl-insoluble HMW tau, and ThS+, AT8+, and MC-1+ neurons were differentiated from the double mutant tau NSCs.

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SHIFT 02-563

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4-5 April 2025

INVESTIGATING THE ROLE OF PHOSPHORYLATED TAU IN NEURODEGENERATIVE DISEASE AND GLIOBLASTOMA USING ADULT HUMAN ORGANOTYPIC SLICE CULTURES.

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Aims: The microtubule-associated protein tau plays a critical role in many neurodegenerative diseases, including Alzheimer's disease. Abnormal hyperphosphorylation of tau (pTau), neuroinflammation, and seizures are observed in patients with neurodegenerative disease and glioblastoma (GBM) and recent work suggests pTau may be a potential a link between neurodegenerative changes and glioblastoma. We aimed to develop a platform to study pTau-related changes in human tissue using cultures generated from tissue samples from patients with suspected GBM.
Methods: Using live adult human cortical tissue, obtained from consented patients undergoing neurosurgical tumour resection, we have optimised the development of organotypic brain slice cultures maintained for up to 21/22 days *in vitro* (DIV). Tau preformed fibrils (pff) containing the P301L mutation were added to a proportion of cultures on DIV0/1 and both control and fibril-treated slices were fixed at DIV21/22. Immunohistochemistry was used to detect pTau (PHF-1), neurons (NeuN), and glia (IBA1, GFAP) and sections were imaged using confocal microscopy.
Results: Initial results show that fibril-treated and control slice cultures express pTau in neurons, astrocytes and blood vessels. We found subject and slice variability in the levels of pTau expression as indicated by PHF-1 staining. We additionally see differences in the pattern of glial and neuronal cell labelling between the membrane and surface side of the cultures. We are exploring the links between the culturing process, patient age, disease status, sex, and seizure history to identify the causes of different pTau expression levels.
Conclusions: Our human organotypic cortical brain slice platform expresses both endogenous and fibril-induced pTau and is viable for up to 3 weeks. Ongoing studies are investigating the correlation between glial reactivity, cell death, network excitability and pTau levels.

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SHIFT 02-564

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / ASTROGLIA
4-5 April 2025

FOCAL PERIVASCULAR GLIAL REACTIVITY IS A FEATURE OF TAU LESIONS IN CHRONIC TRAUMATIC ENCEPHALOPATHY

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Aims: To identify pathological features that distinguish Chronic Traumatic Encephalopathy (CTE) hyperphosphorylated tau (p-tau) lesions from Alzheimer's disease (AD) and neurologically normal brains.
Methods: We used multiplex fluorescent immunohistochemistry on superior frontal gyrus tissue from 8 neurologically normal, 9 CTE, and 10 AD cases, applying a 31-antibody panel targeting glial, cytoarchitectural, and pathogenic proteins. Whole-section imaging was performed to identify qualitative distributions of proteins between CTE, AD, and neurologically normal cases. Quantitative measurements of mean grey intensity and area of labelling were also examined between CTE p-tau lesions and comparable regions in AD and neurologically normal cases.
Results: Distinct expression patterns were observed for markers of astrocyte reactivity, microglial reactivity, and L-ferritin. Astrocyte reactivity (NQO1, CHI3L1, GFAP) was significantly increased in CTE lesions, with a focal distribution contrasting with the more widespread grey matter involvement seen in AD. Microglial reactivity markers (HLA-DR, CD68, IBA1) did not significantly differ between CTE and normal cases, however, CTE lesions demonstrated significantly less microglial reactivity compared to AD. L-ferritin levels were significantly elevated in both CTE and AD, but in AD, L-ferritin immunopositivity was confined to microglia and oligodendrocytes, whereas in CTE, L-ferritin-positive astrocytes were present around CTE lesions. These astrocytes in CTE frequently co-labelled with the oxidative stress marker NQO1.
Conclusions: A key feature of CTE lesions is focal perivascular inflammation driven primarily by astrocyte reactivity. Further, the unique presence of L-ferritin and NQO1-positive astrocytes in CTE lesions suggests iron-induced oxidative stress may play a significant role in CTE pathology.

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SHIFT 02-566

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4-5 April 2025

DEVELOPMENT OF CELLULAR MODELS OF TAU INTERNALIZATION AND SEEDING TO ASSESS THE EFFECTS OF TAU BINDERS

John Mcinnis[1], Amarachi Osuji[2], Julia Bonner[1], Kylie Huckleberry[1], Anoushka Lotun[1], Yihang Li[1], Anna Blazier[1], Martin Kramer[1], Yao Chen[1], Iqra Pervaiz[1], S. Pablo Sardi[1], Rajaraman Krishnan[1], Joshua Kritzer[2], Simon Dujardin[1]
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Aims: In Alzheimer's disease, tau becomes hyperphosphorylated, takes on pathological conformations, and aggregates forming neurofibrillary tangles. Pathological tau then propagates in a prion-like manner trans-synaptically from neuron-to-neuron, spreading through neuronal circuits. Cognitive decline parallels the degeneration of each brain area that is newly seeded with tau pathology. Though tau tangles are well characterized in histopathology, the mechanisms of tau spread and the tau species involved are still being elucidated. Here we aimed at understanding how different tau species are 1-uptaken into cells, 2- seed pathology and 3- cause dysfunction. In addition, as prior studies have indicated that the lipoprotein receptor LRP1 could act as a neuronal receptor for the spread of tau pathology, we evaluated how we could use this receptor to modulate tau uptake in our assays.
Methods: We selected several sources of tau fibrillar species (both recombinant or from tissue) and tested their ability to seed and spread in reporter cell lines such as HEK-293T and SHSY-5Y as well as in iPSC-derived neurons and glia cultures.
Results: We monitored tau uptake and seeding in our assays and observed interesting differences between tau species and systems. Additionally, we utilized soluble recombinant LRP1 protein constructs known to bind tau. We showed that LRP1-domain-IV most effectively bound tau and prevented internalization inside cells.
Conclusions: These findings add to our understanding of the current landscape of in vitro tau spreading assays and have important implications for how tau spreads through the brain in Alzheimer's disease and generating drugs that prevent the progression of Alzheimer's pathology.

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SHIFT 02-567

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4-5 April 2025

EX VIVO STUDY OF THE EARLY EVENTS LEADING TO TAU PATHOLOGY IN TRANSGENIC MOUSE HIPPOCAMPUS

Rislane Taouili[1], Camille Lefebvre[1], Thomas Bouillet[1], Marie Oosterlynck[1], Sabiha Eddarkaoui[1], Claude-Alain Maurage[2], Morvane Colin[1], Luc Buee[1], Sophie Halliez[1]
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Aims: Tauopathies are a group of neurodegenerative diseases whose common feature is the progressive accumulation of abnormal tau protein. The spreading of the pathology through the brain is currently assumed to occur via prion-like mechanisms. According to this hypothesis, some pathological species of tau act as seeds leading to *de novo* aggregation of endogenous/physiological tau. These seeds could be transferred from one cell to another and, at least in some tauopathies including Alzheimer's disease (AD), they would spread between different brain regions along the neuroanatomical tracts. However, the underlying mechanisms are not yet well understood. Modelling such processes *in vivo* is quite challenging and more versatile models are required. In recent years, studies based on organotypic slice cultures (OSC) have provided a robust link that integrates the accessibility and versatility of *in vitro* methods while preserving the physiology, cytoarchitecture, and synaptic integrity of the cerebral tissue. Our work aims to use OSC for modeling the uptake and seeding processes, gaining a better understanding of the early events leading to the development of tauopathies, and evaluating potential therapeutic strategies.
Methods: Hippocampal OSC from mice expressing mutated human tau protein are prepared and then treated with human brain homogenates obtained from AD patients or control subjects. We monitored the presence of abnormal tau and in parallel, functional consequences over time.
Results: Our findings show the potentiation of abnormal conformation of the tau protein in OSC treated with different AD brain homogenates, in a robust way and according to the seeding activity of each homogenate.
Conclusions: Our model could be used as a bioassay and we hope to use it to set up a platform for testing therapeutic strategies targeting the initial steps of the spreading process.

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SHIFT 02-568

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / CELL TO CELL TRANSMISSION, SPREADING OF PATHOLOGY, PRION-LIKE
4-5 April 2025

IMPLICATION OF TAU MEDIATED DEGREDATION OF PERINEURONAL NETS IN ALZHEIMER'S DISEASE

Shahid Ullah Zadran, Neha Basheer, Muhammad Khalid Muhammadi, Tomas Smolek, Norbert Zilka
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Aims: The impact of propagating tau pathology on perineuronal nets (PNNs) integrity remains unclear. In this study, we aim to demonstrate that tau pathology mediates the degradation of PNNs and to explore the contribution of neuroinflammation to this process by utilizing a rat model of taupathy.
Methods: Two experimental setups were used to achieve the study's objectives. In the first, terminal-stage tau-transgenic Wistar Kyoto 72 (WK72) rats and age-matched wild-type (WT) controls were utilized. Tau pathology was validated using immunohistochemistry (IHC) with the anti-tau antibody AT8, while PNNs were assessed using antibodies against Wisteria floribunda agglutinin (WFA) and aggrecan. In the second setup, tau propagation was induced by inoculating AD-tau, isolated from human AD brain, into the CA1 region of WK72 rats. IHC was similarly performed to visualize tau pathology and PNN integrity, alongside quantification of neuroinflammation using the microglial marker Iba1 and the astrocyte marker GFAP.
Results: A significant reduction in perineuronal nets (PNNs) was observed in the brainstem of WK72 rats compared to WT controls. In addition, tau propagation was successfully induced in the hippocampus following inoculation with AD-tau. However, no significant reduction in PNNs was detected in the hippocampus after tau propagation. Notably, a marked increase in microglial and astrocytic reactivity was observed, particularly in the CA2 region of the hippocampus.
Conclusions: We conclude that tau accumulation disrupts PNNs in the brainstem, although non significant trend in the reduction of PNNs was observed following AD-tau inoculation. However, the observed glial reactivity, independent of PNN degradation, suggests that glial activation may not directly drive PNN disruption. Further studies are needed to clarify the mechanisms underlying PNN stability in the hippocampus, even in the presence of tau pathology.

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SHIFT 02-569

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / LYSOSOMES, UBIQUITIN, PROTEASOME, ER STRESS
4-5 April 2025

GPNMB IN ALZHEIMER'S DISEASE PATHOGENESIS

Hongsheng Zhang
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Aims: Glycoprotein non-metastatic melanoma protein B (GPNMB), a single-pass transmembrane glycoprotein, is enriched in microglia of the central nervous system and serves as a marker for disease-associated microglia (DAM). Its expression is elevated in Alzheimer's disease (AD) model mice, suggesting a role in AD pathogenesis. This study investigates the mechanistic role of GPNMB in AD using a PS19 model with *Gpnmb* depletion.
Methods: Cognitive function was assessed in AD mice using the Morris water maze and novel object recognition test. Pathological assessments of Tau phosphorylation, hippocampal atrophy, and neuroinflammation were conducted via immunohistochemistry and immunofluorescent staining. To uncover the underlying mechanisms, we utilized snRNA-seq, scRNA-seq, and TMT-protein quantitative mass spectrometry.
Results: Results: (1) *Gpnmb* depletion in PS19 mice exacerbated cognitive impairments.
(2) *Gpnmb* depletion intensified Tau pathology, synaptic and neuronal loss, and hippocampal atrophy. (3) The absence of *Gpnmb* significantly increased neuroinflammation. (4) Depletion of *Gpnmb* facilitated Tau propagation. (5) *Gpnmb* deficiency correlated with impaired microglial lysosomal function.
Conclusions: Conclusion: Our study indicates that GPNMB depletion exacerbates Tau pathology by impairing microglial lysosomal function, potentially contributing to AD progression. These findings offer new insights into the role of GPNMB in AD and suggest its potential as a therapeutic target for further investigation.

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SHIFT 02-570

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

CELL-BASED MODULATION OF THE BRAIN'S IMMUNE RESPONSE

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Aims: Alzheimer's disease (AD) is the most common neurodegenerative disorder, yet current therapies have limited efficacy. Immune responses, primarily from microglia and regulatory adaptive immune cells, are closely linked to the pathological changes in amyloid-beta and tau observed in AD. We previously demonstrated that microglia in adult mice can be replaced through bone marrow transplantation (BMT), leading to improved cognitive and behavioral features in an AD model. However, the conditioning regimen was highly toxic, and single-cell analysis capabilities were limited at the time. Recent advances in reducing BMT toxicity have led us to explore a safer protocol, which has shown strong tolerability in older patients with and without cancer, potentially enabling cell-based modulation of the brain's immune landscape in AD.
Methods: Wild-type recipient mice (C3B6F1) were conditioned with anti-thymocyte serum (ATS), low-dose total lymphoid irradiation (TLI), total body irradiation (TBI), and the CSF1R inhibitor PLX3397 before transplantation with whole bone marrow (BM) from sex- and age-matched Balb/c donors. CD45+ cells from the brain were sorted into donor and recipient populations based on haplotype and analyzed at the single-cell level.
Results: We observed sustained multilineage donor mixed chimerism in peripheral and hematopoietic tissues three months post-transplant, with similar chimerism levels detected in the brain. Single-cell RNA sequencing revealed a comprehensive immune map, capturing diverse microglial populations, including border-associated microglia (BAM) clusters, as well as T cells (CD4+ and CD8+), NK cells, and B cells. BM-derived microglia displayed distinct transcriptional profiles from resident microglia, and ongoing work aims to elucidate their phenotypic and functional differences.
Conclusions: Our results prompt further testing of this approach to modulate the immune environment in neurodegenerative mouse models and assess whether this therapy can delay or prevent neurodegeneration in AD.

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SHIFT 02-571

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

NEUROINFLAMMATION AND OXIDATIVE STRESS UNDERLIE SYNAPTIC DYSFUNCTION AND COGNITIVE IMPAIRMENT IN MOUSE MODELS OF SPORADIC AND FAMILIAL ALZHEIMER'S DISEASE

Raimondo Sollazzo, Fabiola Paciello, Marco Rinaudo, Domenica Donatella Li Puma, Sara Autelitano, Claudio Grassi
Università Cattolica del Sacro Cuore, Roma, Department Of Neuroscience, Rome, Italy

Aims: Accumulating evidence suggests that neuroinflammation and oxidative stress are key contributors to Alzheimer's disease (AD) pathophysiology. Specifically, microglial activation and overproduction of reactive oxygen species (ROS) may trigger synaptic dysfunction leading to memory deficits in AD. In order to evaluate the crosstalk among oxidative stress, inflammation and microglia activation at early stages of the disease, we took advantage of two preclinical models, i.e., the triple-transgenic (3×Tg-AD) mice, better reflecting the early-onset familial Alzheimer's disease (EOFAD) caused by genetic alterations, and the herpes simplex virus type 1 (HSV-1) mouse model, that is reminiscent of sporadic AD (sAD), primarily due to environmental factors.
Methods: In the mouse models of EOFAD and sAD the disease phenotype was characterized by molecular, morphological, electrophysiological and behavioral analyses.
Results: At early stages of the AD phenotype, in both experimental models we observed an imbalance between endogenous antioxidant defenses and ROS amount compared to age-matched control mice. In particular, we found increased levels of two antioxidant enzymes, HO-1 and SOD1, accompanied by an upscaled production of ROS and lipid peroxidation. Moreover, elevated NLRP3 inflammasome expression—a key factor in neuroinflammation and cytokine release— was observed. Microglia population analyses revealed heightened phagocytic activity and inflammation, indicated by the prevalence of CD68 expressing cells and reduced branching complexity alongside increased soma area and perimeter, indicating a reactive state. In both 3×Tg-AD and HSV-1 mice the above-described molecular and structural alterations were associated with impaired long-term potentiation at CA3-CA1 synapses and hippocampal-dependent memory deficits.
Conclusions: Collectively, these findings point to a critical role played by oxidative stress and neuroinflammation in synaptic dysfunction and cognitive impairment, thus unveiling potential targets for therapeutic interventions in AD and related neurodegenerative diseases.

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SHIFT 02-572

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

MODELING TAU PATHOLOGY IN VITRO USING HUMAN IPSC NEURONS AND MICROGLIA IN COMPARTMENTALIZED MICROFLUIDIC DEVICES

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Aims: Neuroinflammation occurs in tauopathies, and microglial activation induces tau aggregation in the somatodendritic compartment of CNS neurons. Compartmentalized chips provide a consistent and reliable method to create accessible co-culture models. Three-dimensional cultures recapitulate the complex microenvironment found *in vivo* more than traditional 2D cultures. Aim 1 determined whether human iPSC-derived neurons exhibit more synaptic maturity when cultured within a 3D matrix compared to traditional 2D cultures. Aim 2 developed and validated an *in vitro* compartmentalized model to quantify tau mislocalization in response to a neuroinflammatory microenvironment.
Methods: Human induced pluripotent stem cell (hiPSC) derived neurons (BrainXell) were cultured within a 3D matrix (20% Matrigel®) in two compartment XonaChips® for 35 days. To create an *in vitro* model of tau mislocalization, hiPSC-derived neurons were cultured in 3D within the somatodendritic compartment and hiPSC-derived microglia (BrainXell) were restricted to the axonal compartment. Lipopolysaccharide (LPS), a known inflammatory molecule, was used to selectively activate the compartmentalized microglia.
Results: Confocal imaging revealed healthy neuron growth and development in the 3D matrix, with increased synapse density compared to 2D controls. LPS treatment for four days caused microglial activation observed morphologically and by ELISA analysis for MMP-9. This *in vitro* model was further validated by quantifying neurofilament light chain levels, a current, widely used clinical biomarker for neurological damage. Using this model, we found significant tau-1 accumulation within the somatodendritic compartment and proximal processes.
Conclusions: Our data show significant mislocalization of tau into the somatodendritic compartment, providing evidence of tauopathy-like pathology in hiPSC-derived cortical neurons subjected to axonally restricted activated microglia. In summary, 3D neuron cultures in compartmentalized chips demonstrate increased synapse formation and provide a reliable platform for modeling tau mislocalization and neuroinflammation.

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SHIFT 02-573

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MICROGLIA
4-5 April 2025

COMPLEMENT RECEPTOR 4 MEDIATES THE CLEARANCE OF EXTRACELLULAR TAU FIBRILS BY MICROGLIA

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Aims: Tauopathies exhibit a characteristic accumulation of misfolded tau aggregates in the brain. Tau pathology shows disease-specific spatiotemporal propagation through intercellular transmission, which is closely correlated with the progression of clinical manifestations. Therefore, identifying molecular mechanisms that prevent tau propagation is critical for developing therapeutic strategies for tauopathies. The various innate immune receptors, such as complement receptor 3 (CR3) and complement receptor4 (CR4), have been reported to play a critical role in the clearance of various extracellular toxic molecules by microglia. However, their role in tau clearance has not been studied yet. In the present study, we investigated the role of CR3 and CR4 in regulating extracellular tau clearance.
Methods: Tau Binding (Dot-blot, ICC-IF, IP) Tau Uptake (pHrodo-labelled tau fibrils, High-Content Imaging) Tau Clearance (Western Blot) Tau Seeding (Tau RD FRET biosensor cell)
Results: We found that CR4 selectively binds to tau fibrils but not to tau monomers, whereas CR3 does not bind to either of them. Inhibiting CR4, but not CR3, significantly reduces the uptake of tau fibrils by BV2 cells and primary microglia. By contrast, inhibiting CR4 has no effect on the uptake of tau monomers by BV2 cells. Furthermore, inhibiting CR4 suppresses the clearance of extracellular tau fibrils, leading to more seed-competent tau fibrils remaining in the extracellular space relative to control samples. We also provide evidence that the expression of CR4 is upregulated in the brains of human Alzheimer's disease patients and the PS19 mouse model of tauopathy.
Conclusions: Taken together, our data strongly support that CR4 is a previously undescribed receptor for the clearance of tau fibrils in microglia and may represent a novel therapeutic target for tauopathy.

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SHIFT 02-574

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

TAU PATHOLOGY INDUCES MITOCHONDRIAL DYSFUNCTION IN A RAT MODEL OF TAUOPATHY

Muhammad Khalid Muhammadi, Petra Majerova, Miraj Ud Din Momand, Shahid Ullah Zadran, Neha Basheer, Tomas Smolek, Norbert Zilka
Institute Of Neuroimmunology, Slovak Academy Of Sciences, Bratislava, Slovak Republic

Aims: Mitochondrial dysfunction is widely regarded as a critical factor in the progression of Alzheimer's disease (AD). We aimed to investigate potential defects in various mitochondrial parameters, including metabolism, mitophagy, dynamics, and protein function, in the presence of tau pathology.
Methods: Mitochondrial fractions were isolated from the brainstem (where robust taupathology is developed) and cortex (with tau expression) of transgenic (Tg) along with the age-matched wild-type (WT) rats. The mitochondrial populations were characterized via flow cytometry, utilizing the green Mitotracker dye. Tau pathology was confirmed by using anti-tau antibody, AT8.To investigate mitochondrial dysfunction in the presence of tau pathology, we performed a comparative mitochondrial proteomic analysis using advanced mass spectrometry techniques.
Results: Flow cytometry analysis confirmed the presence of mitochondrial populations in both brainstem and cortex. In brainstem, 153 mitochondrial proteins were significantly dysregulated, while 50 proteins were dysregulated in cortex. Of the affected proteins, 120 in brainstem and 32 in cortex were upregulated, whereas 33 in brainstem and 18 in cortex were downregulated. In brainstem, the dysregulated proteins were primarily associated with mitochondrial metabolism, ATP synthase, respiratory complexes I, III, and V, mitochondrial transport proteins (including the TOMM complex), autophagy, mitochondrial dynamics, and calcium channels. In contrast, the dysregulated proteins in cortex were related to mitochondrial metabolism, respiratory complexes I and III, calcium channels, and outer membrane proteins.
Conclusions: Both truncated tau expression and tau pathology contribute to mitochondrial dysfunction, with tau tangles having a particularly pronounced impact on a wide range of mitochondrial functions including ATP synthase, mitochondrial heomostais, transport system, and mitophagy. These findings underscore the multifaceted nature of tau-induced mitochondrial dysfunction, offering insights into potential pathways through which tau pathology contributes to AD progression. Dockogrant SAS, MultiMemo, WestenND/JPND, APVV grants,

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SHIFT 02-575

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

INVESTIGATING MITOCHONDRIAL DYSFUNCTION IN PROGRESSIVE SUPRANUCLEAR PALSY

Gard Aasmund Skulstad Johanson[1,2], Anna Rubiolo[2], Omnia Shadad[2], Irene Flønes[1,2], Charalampos Tzoulis[1,2]
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Aims: Progressive supranuclear palsy (PSP) is a neurodegenerative disease marked by early postural instability, symmetrical levodopa-resistant parkinsonism, and supranuclear ophthalmoplegia, with a prevalence of 7.7 per 100,000 individuals. PSP has no effective treatments and a survival rate of 3-8 years post-diagnosis. As a tauopathy with an unknown cause, evidence suggests that mitochondrial dysfunction in PSP may be more severe than in Parkinson's disease. Consumption of the complex I inhibitor annonacin has also been linked to a PSP-like syndrome and may induce tau-pathology in neurons, though available data remains limited. This project aims to investigate mitochondrial complex I deficiency in PSP by analyzing formalin-fixed, paraffin-embedded tissue from nine brain regions with varying degrees of PSP pathology, provided by the Barcelona brain bank.
Methods: Samples from 10 confirmed PSP patients and 10 neurologically healthy controls will be stained for VDAC1, a marker of mitochondrial mass, and NDUSF4, a subunit of complex I. By manually analyzing the fraction of VDAC1-positive but NDUSF4-negative neurons, we will assess whether PSP tissue shows complex I deficiency compared to neurologically healthy controls and explore any regional brain differences.
Results: Staining is currently underway, and data will be presented at the conference.
Conclusions: If positive, this project will provide evidence of mitochondrial complex I deficiency in PSP, potentially offering new insights into the role of mitochondrial dysfunction in the disease.

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SHIFT 02-576

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

ELUCIDATING THE SYNERGISTIC ROLE OF TAU AND ALPHA-SYNUCLEIN IN COGNITIVE DECLINE AND NEURODEGENERATION THROUGH THE DISRUPTION OF MITOCHONDRIAL RESPIRATION

Julie Vincent, Danielle Mor
Medical College of Georgia at Augusta University, Neuroscience And Regenerative Medicine, Augusta, United States of America

Aims: The goal of this study is to shed light on the effects and mechanisms of mitochondrial dysfunction and neurodegeneration in AD and PD, and identify potential therapeutic targets to treat the subsequent cognitive decline. Specifically, this study focuses on how tau and alpha-synuclein (a-syn), which often coexist in AD and PD, may act synergistically to enhance neurodegeneration and cognitive decline through the disruption of mitochondrial respiration (MR).
Methods: To model this copathology, I am using C. elegans due to its rapid aging, conserved neurobiology, and ease of genetic manipulation, allowing for highly mechanistic investigations linking molecular mechanisms with behavior. Transgenic strains expressing human tau, human a-syn, or human tau and human a-syn together in all neurons will be used as the disease groups modeling proteotoxicity in AD and PD contexts. Short term associative memory assays have been performed to investigate how tau and/or a-syn impact learning and memory. Confocal imaging is being used to evaluate morphological effects of tau and/or a-syn on learning and memory neurons as well as their morphological effects on the mitochondria of those neurons. Oxygen consumption rate (OCR), a readout of MR, has been measured to evaluate MR when tau and/or a-syn are expressed.
Results: My preliminary data indicates that the tau and a-syn copathology enhances cognitive decline and neurodegeneration of learning and memory neurons, compared to tau or α-syn alone. Significant differences in MR are observed when tau and/or a-syn are expressed compared to the nontransgenic control.
Conclusions: Tau and a-syn co-pathologies display a synergistic, rather than additive, effect enhancing neurodegeneration and cognitive decline through MR disruption. Future work will include single-cell RNA-seq to identify genes altered in MR, providing genetic manipulation targets.

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SHIFT 02-577

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / MITOCHONDRIAL DYSFUNCTION, OXIDATIVE DAMAGE
4-5 April 2025

DIVERGENT CONSEQUENCES OF EXTRACELLULAR TAU ON THE MITOCHONDRIAL FUNCTION OF ASTROCYTES AND NEURONS

Valentin Zufferey[1], Enea Parietti[1], Jeanne Espourteille[1], Yvan Varisco[2], Kerstin Fabbri[2], Pierre Marquet[1], Nicolas Preitner[2], Francesca Capotosti[2], Kevin Richetin[1,3]
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Aims: This study aims to investigate the effects of extracellular tau aggregates (ePHF-tau) on synaptic and mitochondrial integrity in neurons and astrocytes.
Methods: We studied the impact of ePHF-tau (2N4R) on different states and ages of primary cultures of rat neuroglia. Using confocal microscopy and proteomic analysis of synaptosomes, we studied the impact of ePHF-tau on neurite and synapse number. We monitored mitochondrial responses in neurons and astrocytes over 72 hours using advanced fluorescence microscopy for dynamic, high-throughput analysis.
Results: Treatment with ePHF-tau has a strong effect on the neurites of immature neurons, but its toxicity is negligible when the neurons are more mature. At the mature stage of their development, we observed a substantial increase in the density of the PSD-95/vGlut1 zone in neurite, suggesting altered synaptic connectivity and ePHF-tau excitotoxicity. Proteomics revealed significant changes in mitochondrial protein in synaptosomes following exposure to ePHF-tau. In the neuronal compartment, real-time imaging revealed rapid and persistent mitochondrial dysfunction, increased ATP production, and reduced mitochondrial turnover. In contrast, we observed increased mitochondrial turnover and filamentation after treatment in the astrocyte processes, indicating cell-specific adaptive responses to ePHF-tau.
Conclusions: This study sheds light on the intricate effects of extracellular tau aggregates on neuronal and astrocytic mitochondrial populations, highlighting how tau pathology can lead to mitochondrial disturbances and synaptic alterations. By delineating the differential responses of neurons and astrocytes to ePHF-tau, our findings pave the way for developing targeted therapeutic interventions to mitigate the detrimental impacts of tau aggregates in neurodegenerative diseases.

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SHIFT 02-580

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
4-5 April 2025

EXOSOMES DERIVED FROM NEURAL STEM CELLS PREVENT TAU OLIGOMER-INDUCED DISRUPTION OF HIPPOCAMPAL NEUROGENESIS

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Aims: Adult hippocampal neurogenesis (AHN) plays a crucial role in synaptic plasticity, learning, and memory, and it is known to decline during the early stages of cognitive impairment in patients with Alzheimer's disease (AD). We have previously shown that exosomes released by hippocampal neural stem cells (NSCexo) can protect neuronal synapses from the toxic effects of Aβ and Tau oligomers. In this study, we aimed to investigate the impact of Tau oligomers (TauO) and NSCexo on AHN.
Methods: Adult male C57/BL6 mice (6-8 weeks) received intracerebroventricular (ICV) injections of exosomes- isolated from conditioned media of hippocampal neural stem cells (NSCexo) or mature hippocampal neurons (MNexo)- or PBS. Twenty-four hours after exosome injection, the mice received a second ICV injection of TauO (0.5 μM) or artificial cerebrospinal fluid (ACSF). Mice were euthanized 24 hours or 1 week after TauO injection via intracardiac perfusion using 4% paraformaldehyde (PF), and their brains were processed for immunofluorescence analysis of SOX2 (to label neural stem cells) and DCX (to label neuroblasts) in the subgranular zone (SGZ) of the hippocampus dentate gyrus.
Results: ICV delivery of TauO significantly reduced the number of SOX2-positive NSCs in the hippocampus SGZ 24 hours after ICV injection and of DCX-positive neuroblasts one-week post-injection. Moreover, ICV administration of NSCexo, but not of MNexo, prevented TauO-induced decline in SOX2-positive cells in the hippocampus SGZ.
Conclusions: Tau oligomers negatively impact AHN by reducing the population of NSCs and neuroblasts in the hippocampus dentate gyrus. However, NSCexo offers protective effects, mitigating the harmful impact of TauO on AHN. These results highlight the potential of NSCexo as a therapeutic intervention to preserve neurogenesis in conditions associated with Tau pathology, such as AD. Supported by NIH/NIA 1R01AG069433 (GT and MAM)

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SHIFT 02-581

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
4-5 April 2025

VISUALIZATION OF PROTEIN AGGREGATION AND CELLULAR NEURODEGENERATION IN THE POSTMORTEM HUMAN BRAIN

Hana Nedozrálová[1], Pavel Křepelka[1], Jan Van Weering[2], Bonnie Plug[3], Henning Stahlberg[4], Jozef Hritz[1], Wilma Van De Berg[2], Meltem Tatli[2]
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Aims: The accumulation of pathological protein aggregates is a hallmark of numerous neurodegenerative diseases, including Alzheimer's and Parkinson's disease (AD and PD). The accumulation of amyloids in the brain is accompanied by toxicity and disrupted cellular physiology, leading to neuronal death. Pathological effects include disrupted axonal transport, mitochondrial and lysosomal dysfunction, synapse degeneration, and chronic inflammation. Using cryo-correlative light and electron microscopy/tomography, we aim to visualize these pathological protein aggregates and changes in cellular architecture at molecular resolution directly in frozen post-mortem AD and PD brains.
Methods: Our approach enables visualization of pathology in post-mortem (<6 h) human brain tissue with live cell labeling and without heavy metal staining or chemical fixation. We combine cryo-ET imaging on tissue lamella prepared by cryo-plasma-focused ion beam milling with correlative cryo-fluorescent imaging and native bio-contrast volume cryo-imaging.
Results: This poster presents our in-tissue cryo-ET visualization and volume cryo-imaging workflow. It showcases tomograms of human post-mortem AD and PD brains affected by neurodegeneration showing the structure of pathological protein aggregates and ultrastructural features of neurodegeneration on the subcellular level.
Conclusions: We showed that following our protocol, live cell labeling in native tissue is possible and that the neurons are still alive at the time of vitrification. We reconstructed the structure of protein aggregates directly in the tissue and described the sub-cellular environment surrounding the pathology.

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SHIFT 02-582

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
4-5 April 2025

THE INTERACTOME OF TAU AGGREGATES IN MICE AND HUMAN CORTICAL NEURONS

Soki Bradel Ngonza Nito[1], Chloé Baroin[1], Anselme Perrier[1], Ronald Melki[1], Virginie Redeker[1,2]
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Aims: Alzheimer's disease (AD) is characterized by the accumulation of intracellular deposits rich in tau protein aggregates, which are harmful to neurons and induce neuron degeneration. These aggregates are able to propagate from neuron to neuron by exocytosis, internalization in naïve cells, release into the cytosol and amplification by recruitment of the normal endogenous tau protein. The aim of the project was to identify mice and human proteins that interact specifically with tau aggregates, in order to identify new molecular signatures of AD and document the pathophysiological process involved in AD.
Methods: We produced well-charaterized 1N3R and 1N4R tau fibrils and incubated them with proteins extracted from mouse or human neurons. The interactome of tau aggregates was pulled-down, either directly or after stabilization of protein-protein interactions using covalent cross-linking. Mice and human tau protein interactors were identified by mass-spectrometry and bioinformatics analysis.
Results: A total of 1346 mice proteins were identified as interacting with 1N3R and 1N4R tau aggregates (Fc> 10): 1146 proteins are common to both 1N3R and 1N4R tau aggregates; 154 are specific to 1N3R and 46 are specific to 1N4R aggregates. Interestingly, several of the identified interactors were reported previously as interactors of phosphorylated tau. Finally, comparison to monomeric tau interactors and crosslinking experiments contribute to in-depth analysis of these tau aggregates interactomes and to the selection of protein partners of interest (PPOI). Results obtained with human cortical neuronal proteins, and refined interaction and network analyses will be presented.
Conclusions: PPOIs identified by our proteomic analysis will be selected for immunodetection validation in the human brain and further analysis of their functional role, paving the way to the identification of new targets for AD.

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SHIFT 02-583

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / OTHER
4-5 April 2025

INVESTIGATING TAU PATHOLOGY AND COMPLEMENT ACTIVATION IN THE HIPPOCAMPUS TO UNDERSTAND NEURONAL VULNERABILITY IN AGE-RELATED NEURODEGENERATIVE DISEASES

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Aims: Age-related neurodegenerative diseases (NDD), such as Alzheimer's disease (AD), are characterised by intra-neuronal deposition of tau neurofibrillary tangles, with the hippocampus being one of the first regions affected. Neuroinflammation is also a major factor in the progression of AD. We aim to characterise the relationship between tau pathology, the complement immune system and neurodegeneration of the hippocampus in AD patient samples.
Methods: We used single and multiplex chromogenic immunohistochemistry (IHC) with quantitative digital pathology on the hippocampal subfields (DG, CA4, CA3 and CA1/CA2), as well as immunofluorescence combined with 3D confocal imaging on a collection of human *post-mortem* hippocampal tissue from age-matched control (CTL) and AD patients. Various tau antibodies, including AT8 as marker for pre- and mature tangles, were used to assess tau pathology in addition to staining of complement component 1q (C1q), a prominent complement component.
Results: Our analysis shows a general increase in tangle markers in AD compared to CTL. CA1/CA2 region was the most affected by tau pathology in AD, with between 5-fold and 20-fold increase compared to respectively DG, CA4 and CA3. The distribution of C1q showed an inverse trend, with a decrease of C1q-positive stained neurons in the CA1/CA2 area of AD compared to CTL. Additionally, multiplex IHC and confocal imaging revealed distinct neuronal populations in the AD hippocampus, with most neurons showing positivity for either C1q or AT8, while only a few were double-positive for both markers.
Conclusions: Our data suggest a potential molecular interaction between C1q and tau pathology and a role in the regional vulnerability of the hippocampus in AD.

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SHIFT 02-584

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY
4-5 April 2025

EXPRESSING HUMANIZED MUTANT TAU IN THE PRELIMBIC CORTEX DISRUPTS FUNCTIONING OF CORTICAL PROJECTION NEURONS

Emily Nickerson, Erik Bloss
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Aims: Progressive accumulation of tau, a microtubule binding protein, is a defining feature of a group of diverse neurodegenerative diseases known as tauopathies. The cellular and circuit-wide patterns of accumulation, however, are unique to each tauopathy and appear to reflect the clinical symptomology. Furthermore, each contains unique tau proteins suggesting that the structure of tau may dictate disease progression. Yet, exactly how altered forms of tau drive dysfunction is unknown. To address this gap in knowledge, we are employing a viral strategy to examine how mutations in different tau isoforms alter the functioning of prelimbic cortical neurons. Specifically, we aim to 1) assess how introducing these mutations alters the binding partners of human tau (hTau) and 2) evaluate if the accumulation of mutant hTau within dendrites is sufficient to impair synaptic function.
Methods: Our innovative viral approach enables us to limit the expression of hTau to the prelimbic cortex, a region of the brain that is understudied despite its relevance to multiple tauopathies. To interrogate the relationship between hTau primary structure and intracellular function, the binding partners of co-immunoprecipitated flag-tagged protein complexes will be compared using tandem mass spectrometry. By combining our viral approach with neuroanatomical and high-resolution imaging strategies, we can further evaluate how synaptic function might be altered through reconstructing synaptic connections on prelimbic cortical neurons.
Results: Preliminary data has found that, relative to WT hTau, P301L has increased interactions with mitochondrial proteins and those associated with energy and metabolism. Furthermore, expression of P301L led to a significant decrease in spine density on the dendrites of prelimbic cortical neurons.
Conclusions: Together, these findings suggest that altering the primary structure of hTau is sufficient to change its intracellular function and drive synaptic dysfunction.

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SHIFT 02-585

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / SYNAPSE PATHOLOGY
4-5 April 2025

POST-MORTEM VALIDATION OF SYNAPTIC BIOMARKER [11C] UCB-J PET IN PROGRESSIVE SUPRANUCLEAR PALSY.

George Nolan[1], Negin Holland[1], Shanying Yang[2], Qiyuan Chen[3], Maura Malpetti[1], Kieren Allinson[4], Andras Lakatos[1], Annelies Quaegebeur[2], James Rowe[5]
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Aims: Synapse loss is a candidate biomarker to assess the efficacy of drugs targeting neurodegenerative disorders such as Progressive Supranuclear Palsy (PSP). [^{11}C]-UCB-J, a PET radiotracer for the pre-synaptic protein SV2A, is used in vivo to detect synapse loss in patients, showing correlation with clinical severity and progression in PSP. However, the degree to which [^{11}C]-UCB-J PET signals relate to actual synaptic density remains unclear. Here we developed a method of synapse quantification in post-mortem brain tissue to study synapse density across the brain of PSP donors who underwent [^{11}C]-UCB-J PET during life. Through association studies between PET and post-mortem quantifications, we inform the interpretation of [^{11}C]-UCB-J PET as a synaptic biomarker.
Methods: Frozen brain tissue sections were taken from PSP donors who underwent UCB-J PET during life, and age/gender-matched neurologically healthy controls. Synapses were visualised with triple immunofluorescence staining using presynaptic Bassoon, postsynaptic Homer1 and neuronal/dendritic MAP2. Synaptic puncta were identified by confocal microscopy and segmented via a proximity and colocalisation pipeline to validate intact synapses

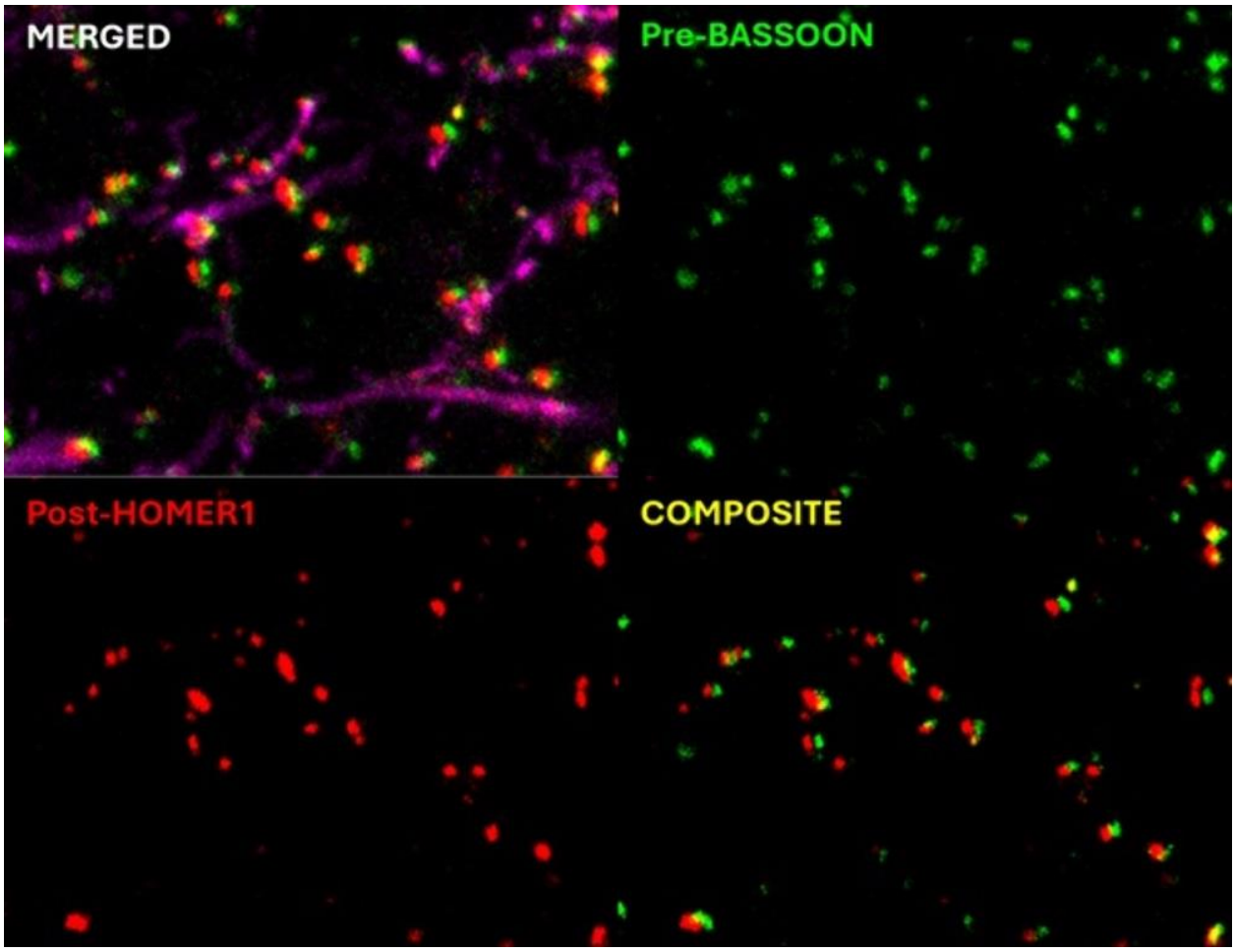

Fig.1. 1. Image from control Cingulate Cortex. Composite displays synapses as pre-synapses juxtaposed to post-synapses indicating intact synapses. Merged shows dendrites with synapses.

Results: Synapse quantification in 3 cortical and 3 subcortical regions found significant loss of synapses in all regions, with more severe synapse loss reported in regions implicated earlier in PSP. Synapse loss varied with Kovacs stage, and occurred in superficial, mid and deep cortical layers.

Conclusions: We present a robust method of synapse quantification in post-mortem brain tissue which identifies patterns of synapse loss predicted by pathology staging in PSP. Correlation analysis with regional *ante-mortem* PSP [^{11}C]-UCB-J PET binding potential and synaptic density *post-mortem* is ongoing.

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SHIFT 02-586

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4-5 April 2025

AAV DRIVEN BRAIN SLICE CULTURE MODEL OF TAU DYNAMICS ENABLES ROBUST TARGET VALIDATION OF TAUOPATHY

Brenda Moore[1], Ali Kaiser[1], Pooneh Amin[1], Annika Sun[1], Justin Guo[1], Alex Roy[1], Danny Ryu[1], Todd Golde[2]
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Aims: Genetic and pathological studies demonstrate that alterations in the tau protein are tightly linked to neurodegeneration in Alzheimer's disease. Tau-inclusion pathology, referred to as tauopathy, correlates with cognitive decline and neuronal loss. Systems level -omic studies have identified hundreds of new factors of interest, however current experimental model systems may not be robust enough to efficiently distinguish between factors that are markers or pathology modulators. Therefore, we expanded our established recombinant adeno-associated virus (rAAV) driven organotypic brain slice culture (BSC) model of tauopathy to enable assessment of both cell-autonomous and non-cell autonomous mechanisms of action.
Methods: To control the extent and kinetics of tau aggregation BSCs were transduced with rAAV encoding novel 0N4R tau mutants, A152T/S320F, P301L/S320L, P301L/S320W, P301L/S324F, and P301L/S320F/I328S under the synapsin promoter (hSyn-hTau24). BSCs expressing mutant tau tagged with photoconvertible Dendra2 were live-imaged, while BSCs expressing untagged versions were harvested and immunohistochemically and biochemically analyzed. To develop paradigms to co-express candidate target genes with various forms of tau BSCs were co-transduced with EGFP tagged wild type tau and a blue fluorescent protein tagged with a nuclear localization signal (hSyn-hTau24-WT-EGFP + hSyn-SBFP2-NLS) at either 0DIV or hSyn-SBFP2-NLS was added 7DIV and live-imaged.
Results: Live-imaging of novel tau mutants resulted in visualization of the progression of tau aggregation. Combined the tau mutants show a gradient of tau pathology. Co-transduction of BSCs at DIV0 resulted in nearly all cells expressing both tau and SBFP2 while addition of SBFP2 at 7DIV resulted in mosaicism of expression.
Conclusions: These paradigms will enable us to assess both cell-autonomous and non-cell autonomous mechanisms of action and perform ex vivo experiments that are analogous to both in vivo prevention studies and therapeutic interventions.

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SHIFT 02-587

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4-5 April 2025

CHARACTERISATION OF TAU IMMUNOPHENOTYPES IN CHRONIC TRAUMATIC ENCEPHALOPATHY LESIONS AND SUBPIAL ASTROGLIOPATHY

Helen Murray[1], Danica Hamlin[1], Chelsie Osterman[1], Richard Faull[1], Andrew Affleck[2], Catherine Suter[2,3], Clinton Turner[1,4], Michael Buckland[2,3], Maurice Curtis[1]
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Aims: Our objective was to compare the tau antibody labelling profile of subpial astrocytic tau pathology seen in Chronic Traumatic Encephalopathy (CTE) with the neurofibrillary tangles seen in the pathognomonic CTE lesions and Alzheimer's disease (AD).
Methods: We used multiplexed fluorescent immunohistochemistry to label superior frontal gyrus tissue from nine CTE and ten Braak stage V-VI AD cases. Sequential rounds of 5-plex labelling were performed using antibodies that bind epitopes associated with early and advanced tangle maturity (hyperphosphorylated tau (p-tau) 202-205 (AT8), p-tau231, cis-p-tau231 4R, 3R, and MN423), neurons (NeuN) and astrocytes (ALDH1L1). Whole-section fluorescent imaging was performed to assess the distribution of labelling for each tau antibody, identify patterns of tau antibody co-labelling and whether the labelling was neuronal or astrocytic.
Results: We found that seven out of nine CTE cases exhibited subpial astrocytic tau pathology, which was predominantly labelled by AT8, p-tau231, and cis-p-tau231. Labelling for 4R was uncommon, and 3R and MN423 labelling was entirely absent in the subpial area. The neurofibrillary tangles within the CTE lesion areas and comparable regions of AD cases were predominantly neuronal (NeuN+) and co-labelled for AT8, p-tau231, cis-p-tau231, and 4R tau. 3R tau and MN423 labelling was only seen within lesion areas in cases classified as high-stage CTE neuropathologic change and in AD cases.
Conclusions: Subpial astrocytic tau was a common comorbid pathology in the CTE cases we examined, and predominantly labelled for p-tau antibodies rather than 4R tau, 3R tau or MN423. Therefore, tau antibody co-labelling profiles may be useful for distinguishing CTE lesions from subpial astrogliopathy. Our findings indicate that neurofibrillary tangles in the CTE lesion areas have similar tau antibody labelling profiles to those seen in comparable regions of AD cases.

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4-5 April 2025

POLY-GLYCINE-ARGININE CONTAINING PROTEINS ARE ASSOCIATED WITH DISTINCT TRANSCRIPTOMIC CHANGES IN AD BRAINS AND AGGREGATE WITH PHOSPHORYLATED TAU IN CELLS

Svitlana Yegorova[1], Rodrigo Tomas[2], Logan Bell[2], Huong Phuong[2], Alexandra Melloni Melloni[3], Theresa Connors[4], Angelica Gaona[3], Jennifer Phillips[5], H. Brent Clark[6], Juan Troncoso[7], Stefan Prokop[5], Bradley Hyman[3], Laura Ranum[2], Lien Nguyen[2]
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Aims: We recently showed poly-glycine-arginine containing (polyGR+) aggregates frequently accumulate and are associated with increased phosphorylated Tau (pTau) levels in postmortem brains from sporadic AD cases. We also identified the GGGAGA repeat expansion in *CASP8* (*CASP8*-GGGGA^{EXP}) that produces polyGR+ proteins and is associated with increased AD risk (odds ratio 2.2, p=3.1x10^{-5}). Here we study transcriptomic signatures linked with polyGR+ aggregates and the effects of polyGR+ proteins expressed from the *CASP8*-GGGGA^{EXP} on Tau phosphorylation in cells.
Methods: We performed RNAseq on frozen frontal cortex tissue from AD cases with high polyGR+ staining (h-polyGR AD), AD cases with no or minimal polyGR+ signal (m-polyGR AD), and control cases (n=3/group) to study transcriptomic changes linked with polyGR+ aggregates. Additionally, we performed cellular experiments using plasmids carrying high-risk or low-risk *CASP8*-GGGAGA^{EXP} (hr-GGGAGA^{EXP} and lr-GGGAGA^{EXP}) sequences cloned from patient DNA to study toxic effects of polyGR+ proteins and the *CASP8*-GGGAGA^{EXP}.
Results: RNAseq analysis identified significant transcriptional changes in h-polyGR AD, which are associated with altered Aβ degradation and clearance, increased pTau formation, disruption of synaptic structure and function. We also detected unique changes in expression levels of myelination-related genes in oligodendrocytes in h-polyGR AD brains compared to controls, which are not detected in m-polyGR AD brains. In HEK293T cells, hr-GGGAGA^{EXP} minigenes expressed 4x higher levels of polyGR+ proteins (p=0.0045), 2x more repeat RNA inclusion (p=0.0085), and are 2x more toxic than lr-GGGAGA^{EXP} minigenes (p=0.029). Consistently, hr-GGGAGA^{EXP} minigenes expressed increased levels of polyGR+ aggregates than lr-

GGGAGA^{EXP} in SH-SH5Y. We detected increased levels of nuclear and cytoplasmic pTau in SHSY-5Y cells positive for polyGR+ staining. Additionally, pTau inclusion co-localizes with polyGR+ aggregates in cells. **Conclusions:** In summary, our results support the pathogenic roles of polyGR+ proteins and the *CASP8*-GGGAGA^{EXP} in AD.

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4-5 April 2025

POST-TRANSLATIONAL MODIFICATION SIGNATURES OF TAU SEEDS WITHOUT ALZHEIMER'S DISEASE NEUROPATHOLOGY

Iris Peng[1], Colin Shin[1], Miguel Avina[2], Danielle Browne[1], Annie Hiniker[2], Allison Kraus[1]
[1]Case Western Reserve University School of Medicine, Department Of Pathology, Cleveland, United States of America, [2]University of Southern California Keck School of Medicine, Department Of Pathology, Los Angeles, United States of America

Aims: To understand the prevalence and age-dependence of tau seeding and associated molecular features in brain tissue from individuals without overt Alzheimer's disease (AD) neuropathology.
Methods: Real-time quaking induced conversion (RT-QuIC) was used as an ultra-sensitive method to estimate tau seeding doses in midfrontal cortex of 19 individuals lacking overt AD neuropathology, with Braak scores between 0-2 and CERAD scores either 0 or 1. Subjects ranged from 35 to 104 years of age. Dot immunoblotting of brain homogenates with antibodies against pSer202/205 (clone AT8), pThr217, pThr231, and C-terminus (Asp430, clone D1M9X) was used to probe the levels of tau modification and normalized against total protein levels as measured by Ponceau stain. We used linear regression to evaluate correlation between seeding activity and presence of PTMs.
Results: Tau seeding ranged between negative ($\leq 10^{2.5}$) up to $10^{5.5}$ seeding doses per milligram tissue, and seeding dose did not correlate with age ($p=0.3038$). Additionally, PTM immunoreactivity did not correlate with age (pS202/205 $p=0.0594$, pT217 $p=0.6657$, pT231 $p=0.0538$, C-term $p=0.2376$). However, pT231 and C-term immunoreactivity exhibited a positive correlation with tau seeding dose ($p=0.0181$ and $p=0.0009$, respectively). In comparison, pS202/205 and pT217 immunoreactivity did not correlate with tau seeding dose ($p=0.5055$ and $p=0.2623$, respectively).
Conclusions: Previous research has shown that tau seeds can be present in brain lacking AD neuropathology. Here, we substantiate prior findings using an ultra-sensitive RT-QuIC seeding assay, without the need for enrichment of tau beforehand, and demonstrate that tau PTMs can contribute to increased seeding capability even in the absence of overt tau neuropathology.

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SHIFT 02-590

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4-5 April 2025

ANATOMY OF TAU AGGREGATION IN SITU USING CORRELATIVE LIGHT AND CRYO-ELECTRON TOMOGRAPHY

Valerie Perez[1], Hung Tri Tran[1], Olive Pedraza[1], Cédric Bouchet-Marquis[2], Mark Mcclendon[2], Victor Cruz-Ruiz[1], Nicholas Sutliff[1], Maliya Nixon[1], Skyler Taylor[1], Sarah Shahmoradian[1]
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Aims: The pathological aggregation of the microtubule associated protein tau is a hallmark of neurodegenerative diseases such as Alzheimer's disease. Previous studies have shown that tau pathology spreads in a prion-like manner in the brain, propagating along synaptically connected brain circuits. Yet it remains unclear how tau begins to template aggregation of the inert endogenous tau in the recipient neuron. This study aims to understand how exogenous tau seeds template aggregation of inert, endogenous tau in cells. Specifically, we investigate the cellular mechanisms and structures involved in tau seeding and aggregation.
Methods: To investigate tau seeding and aggregation in situ, we employ spatiotemporal imaging and cryo-correlative light and electron microscopy (cryo-CLEM), including cryo-electron tomography (cryo-ET) cryo-volume based imaging (cryo-FIBSEM). These methods allow us to pinpoint tau seeding sites and explore the 3D nanoscale architecture of tau fibrils and their associated sub-cellular structures in tau biosensor cells. Using timelapse imaging of seeded tau biosensor cells, we identify key timepoints of tau aggregation for cryo-CLEM investigation.
Results: We observe that exogenous tau seeds are routed to lysosomes, where we visualize both fibrillar and amorphous aggregates. In parallel, we also observe fibrillar-like densities forming close to vesicles within the cells.
Conclusions: We show ultrastructural evidence in near-native conditions regarding the origins of tau aggregation in situ, granting the critical cellular context that is not available through traditional cryo-EM studies of recombinant or ex vivo tau fibrils, while bridging the resolution gap afforded by light microscopy approaches.

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SHIFT 02-591

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4-5 April 2025

GENERATION OF A PATHOLOGICAL TRUNCATED TAU PROTEIN BY ALTERNATIVE TRANSLATION

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Aims: Tau protein is a central actor in Alzheimer's disease (AD). Among pathological Tau species, we found an N-terminal truncated form (Met11-Tau) to be specifically detected in AD brains and involved in Tau pathology development. Regarding the mechanisms leading to Met11-Tau production, we hypothesize that Met11-Tau is generated by alternative translation under stress conditions, especially Integrative Stress Response (ISR). Our work aims to test this hypothesis in appropriate cell models.
Methods: We used Sodium Arsenite (SA) to induce Integrative Stress Response in two cellular models. Met11-Tau production and ISR activation are analyzed by Western Blot and Immunocytochemistry (ICC) using specific antibodies directed against this new N-terminally truncated form of Tau. Tau translation is evidenced by the ribopuromycylation method combined with Proximity Ligation Assay (PLA).
Results: Our results show that when cells are exposed to SA, the ISR is induced and the Met11-Tau is generated. Moreover, we demonstrated that Met11-Tau is indeed produced from an alternative translation initiation event.
Conclusions: Our work establish that Met11-Tau production is related to an alternative translation mechanism occurring under stress conditions that trigger the Integrative Stress Response. More broadly, our work highlights the relevance of Tau translation deregulation in AD physiopathology.

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TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4-5 April 2025

PROBE-DEPENDENT PROXIMITY PROFILING (PROPPR) UNCOVERS SIMILARITIES AND DIFFERENCES IN PHOSPHO-TAU-ASSOCIATED PROTEOMES BETWEEN TAUOPATHIES

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Aims: The diversity of neuronal and glial tau pathology in different tauopathies remains poorly understood on the molecular level. Here we aim to determine the protein composition of tau aggregates in four major tauopathies: Alzheimer's disease (AD), corticobasal degeneration (CBD), Pick's disease (PiD), and progressive supranuclear palsy (PSP).
Methods: Here we present a new approach for *in situ* proximity labeling and isolation of aggregate-associated proteins using formalin-fixed paraffin-embedded (FFPE) human postmortem brain tissue, termed Probe-dependent Proximity Profiling (ProPPr). We used ProPPr for the analysis of proteomes associated with AT8-positive cellular lesions from frontal cortices with data-independent acquisition mass spectrometry. Co-immunofluorescence staining for selected proteins in human brain tissue was performed to further investigate associations with specific tau-related pathologies.
Results: We identified numerous common and tauopathy-specific proteins associated with phospho-tau aggregates. Extensive high-resolution immunofluorescence imaging of distinct aggregates across disease cases reveal the association of retromer complex protein VPS35 and lysosomal protein LAMP2 with specific types of phospho-tau lesions in tauopathies. Furthermore, we discovered disease-specific associations of proteins (e.g., glycogen synthase kinase alpha (GSK3α), ferritin light chain (FTL) the neuropeptide precursor VGF) with distinct pathological lesions. Notably, the identification of FTL-positive microglia in CBD astrocytic plaques indicate their potential role in the pathogenesis of these lesions.
Conclusions: Our findings demonstrate the suitability of the ProPPr approach in FFPE brain tissue for unbiased discovery of local proteomes. Our findings provide valuable insights into the underlying proteomic landscape of tauopathies, shedding light on the molecular mechanisms underlying tau pathology. This first comprehensive characterization of tau-associated proteomes in a range of distinct tauopathies enhances our understanding of disease heterogeneity and mechanisms, informing strategies for the development of diagnostic biomarkers and targeted therapies.

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TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4-5 April 2025

RETINAL TAU POST-TRANSLATIONAL MODIFICATIONS IN AD: A MASS SPECTROMETRY STUDY

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Aims: Our aims with this study are to identify and quantify tau post-translational modifications (PTMs) in the retina of Alzheimer's disease (AD) patients and non-demented controls (NDC), to compare these retinal PTMs with those in the hippocampus of the same individuals, and to correlate the modifications with the neuropathological stages of the disease.
Methods: Retinal and hippocampal samples of 11 AD and 9 NDC were homogenized and trypsinized. The extracted material was subjected to mass spectrometric analysis, and Proteome Discoverer v2.2 (Thermo Fisher Scientific) was used to identify and quantify tau PTMs. Comparative analysis is being conducted to evaluate the PTMs present in the retina of AD and NDC, and to compare the modifications between the retina and hippocampus, as well as to investigate how these modifications correlate with neuropathological assessment, including amyloid-beta and neurofibrillary tangle Braak stages.
Results: Preliminary results indicate that phosphorylation at key sites, including T181, S202, and T231, is consistently observed in both brain and retinal tissues, while the brain exhibits a broader range of modifications. Unique modifications, such as oxidation and methylation, were also identified in both tissues. Our ongoing analysis aims to further characterize the PTMs of tau in the retina, and we will present additional findings at the conference.
Conclusions: We anticipate that our findings will enhance our understanding of tau pathology's role in visual impairment and neurodegeneration, and highlight the potential of retinal PTMs of tau as a non-invasive biomarker for Alzheimer's disease.

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TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4-5 April 2025

A TWO-STEP METHOD FOR ALZHEIMER'S DISEASE PLASMA DIAGNOSIS IN REAL-LIFE SETTING

Chiara Trasciatti[1], Andrea Pilotto[2], Alice Galli[2], Virginia Quaresima[1], Chiara Tolassi[1], Diego Bertoli[2], Andrea Rizzardi[1], Salvatore Caratozzolo[2], Andrea Zancanaro[1], José Contador[3], Henrik Zetterberg[4], Kaj Blennow[5], Duilio Brugnoni[2], Marc Suárez-Calvet[6], Nicholas Ashton[4], Alessandro Padovani[1,2]
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Aims: Blood-based biomarkers have the potential to provide cost-effective and minimally invasive Alzheimer's disease (AD) diagnosis. Plasma p-tau species have demonstrated excellent performance in identifying underlying AD pathology, particularly p-tau 217 and p-tau 181, whereas their applicability and scalability in real-life setting is still debated. [1,2]
Methods: Subjects with AD and age-matched non-AD neurodegenerative disorders (NDD) underwent a standardized cognitive, imaging and biological assessment, including CSF analyses evaluating core AD markers. All subjects underwent blood sampling; p-tau 217 was assessed using Lumipulse, whereas p-tau181, p-tau231, Aβ-42, Aβ-40, NfL and GFAP were assessed using SIMOA analyses. To perform subject AD vs NDD classification, a two-step workflow based on ROC and logistic regression analyses was developed. [3] In the first step, a 95% thresholding method was applied to categorize participants into low-, intermediate-, and high- risk for AD based on the best plasma marker. In the second step, the intermediate-risk group was further classified using an additional plasma biomarker, selected by the ROC analysis.
Results: A total of 160 individuals were included in the analysis, namely 119 AD and 41 NDD, according to CSF classification. AD patients exhibited higher p-tau217, p-tau 181 and Aβ-42/ Aβ-40 ($p<0.001$), being p-tau 217 the one with best discriminative performance (AUC = 0.910). The risk stratification model using 95% of sensitivity and specificity was capable of classifying true positive Alzheimer's cases as high-risk patients with 96% of accuracy and low-risk patients as true negative cases with 85% accuracy. For the intermediate-risk group stratification (n=74), NfL was selected, obtaining 79% of true positive AD and 80% of true negative NDD in this specific subgroup.
Conclusions: A two-step model using p-tau217 reduces the need for confirmatory tests, offering cost-effective approach to Alzheimer's detection.

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RECAPITULATING 4R TAUOPATHY IN AN IPSC DERIVED NEURONAL MODEL

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Aims: Several neurodegenerative diseases including Alzheimer's disease (AD) and those that result in Fronto-Temporal Dementia (FTD) are caused by the accumulation of pathological tau in excitatory neurons. There is intense effort globally to identify drugs that reduce the levels of tau protein or stop it from being toxic to brain cells to prevent or treat these neurodegenerative diseases. Unfortunately, the field has been hampered by the paucity of neuronal cellular models that allow us to measure the build-up of the abnormal 4-repeat (4R) tau isoforms, in an assay system that can be used to screen multiple drugs or identify other gene targets that can regulate the clearance of tau.
Methods: We have bothe engineered an induced pluripotent stem cell (iPSC) line carrying a homozygotes S305N/IVS10+3 *MAPT* mutation as well as obtained pateint-derived iPSC carrying the S305N mutattion which expresses 4R tau when differentiated into cortical i3Neurons. Furthermore, by introducing the HiBiT tag in the C-terminus of *MAPT* gene we can monitor the expression of tau via a luminescence high-throughput assay.
Results: We have thoroughly characterised the derived i3Neurons and found that the S305N/IVS10+3 predominantly express 4R tau, display mis-localization of total tau which is accompanied by increased phosphorylated. The differentiated i3Neurons were able to develop endogenous seed-competent tau after 28 days in culture. The patient-derived i3Neurons presented allele dependent change in 4R tau and phosphorylated tau. Both cell models exhibited synaptic and cytoskeleton changes. Also, by using a range of known tau modulators, we were able to change the levels of HiBiT/tau.
Conclusions: We were able to generate an iPSC derived neuronal model which recapitulate the 4R tauopathy which will also allow us to develop high throughput screening assays to identify new therapeutic targets.

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TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TAU AGGREGATION, PHOPHORYLATION, ACETYLATION & MODIFICATIONS
4-5 April 2025

THE ASSOCIATION BETWEEN TAU AND MITOCHONDRIA IN NEURODEGENERATION

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Aims: Mounting evidence suggests that tau is essential for mitochondrial function, which is compromised in AD. In this study, we aim to dissect the mechanism by which wild-type tau benefits while disease-associated tau variants impair mitochondrial function and therefore lead to neuronal death.
Methods: Different types of tau, including wild-type and several disease-relevant variants, were expressed in mammalian cells to examine tau-mitochondria interaction and associated mitochondrial health. The physical interaction between different tau species with mitochondria was analyzed by mitochondria isolation and fluorescence microscopy. The mitochondrial integrity was assessed by the levels of several mitochondrial components. The mitochondrial function was evaluated by membrane potential and ATP generation.
Results: By mitochondria isolation and fluorescence microscopy, we observed a direct interaction between tau and mitochondria, and wild-type tau is more enriched in mitochondria than the disease-relevant tau variants. In the presence of wild-type tau, the amount of the two key mitochondrial regulators significantly increased compared with disease-relevant tau variants. These regulators play a crucial role in both the electron transport chain and mitochondrial dynamics.
Conclusions: These results suggest that wild-type but not disease-relevant tau may have a beneficial role on mitochondrial function and therefore neuronal health by elevating the key components of mitochondria and sustaining mitochondrial dynamics. In addition, targeting tau variants could suppress neurotoxicity and cognitive decline through mitochondrial regulation in AD and other related dementia.

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4-5 April 2025

SELECTING A SUITABLE IMAGING PLATFORM FOR SINGLE-MOLECULE CHARACTERISATION OF TAU IN CELLULAR MODELS OF ALZHEIMER'S DISEASE

Eva Wong[1,2], Sam Daly[1], Steven Lee[1], David Klenerman[1,2]
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Aims: Tau aggregation is a key hallmark of Alzheimer's disease. The process of aggregation involves the formation of heterogeneous mixtures of soluble oligomeric intermediate species. Tau aggregation strongly correlates with synaptic and neuronal degeneration. While the processes that cause tau aggregation are yet to be elucidated, the different sizes, shapes, and structures of the tau aggregates formed may cause cytotoxicity by different mechanisms. We aim to adapt novel single-molecule imaging techniques to image endogenous tau aggregates in fixed neurons and map which organelles they interact with.
Methods: The localisation-based direct stochastic optical reconstruction microscopy (dSTORM) and DNA points accumulation for imaging in nanoscale topography (DNA-PAINT) were used to image immunolabelled neuronal induced pluripotent stem cells (iPSCs). The fluorescent signals were recorded either in widefield or in 3D using a Fourier light-field generated by insertion of the microlens array in the emission path.
Results: Localisations with precisions of 39 nm (2D lateral), 39.6 nm (3D lateral), and 44.0 nm (3D axial) were achieved using home-built setups. Density-based spatial clustering of the localisations was applied to identify single aggregates and other subcellular components. This has enabled physical characterisation (e.g., length, eccentricity, shape by Hu moments), classification via hierarchical clustering, and spatial correlation in cellular environments.
Conclusions: This work has established an imaging platform, including labelling, optical setup, and post-acquisition processing, for imaging tau aggregates and organelles in cellular models. We envision using this platform to measure the number and shape of the tau aggregates, their cellular location and interaction partners under different conditions to determine the mechanism of aggregation and cytotoxicity.

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4-5 April 2025

SMALL-MOLECULE TRKB/TRKC PARTIAL AGONIST PTX-BD10-3 MITIGATES TAU OLIGOMER TOXICITY AND ACCUMULATION OF PATHOLOGICAL TAU AND ENHANCES SPINE RESILIENCE

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Aims: Tau modifications such as excess phosphorylation and misfolding lead to toxic aggregates that contribute to synaptic failure and degeneration in tauopathies. Suppressing production of these toxic tau species and their synaptic and other downstream effects are key therapeutic goals. Tropomyosin receptor kinase B and C (TrkB, TrkC) modulate signaling networks affecting tau phosphorylation and synapse/spine integrity modules such as RhoA-LIMK1-cofilin. Enhancing TrkB/C signaling may mitigate tauopathy-related degeneration and synaptic dysfunction. We tested the hypothesis that the TrkB/TrkC partial agonist PTX-BD10-3 would reduce tau-related pathology and synaptic degeneration.
Methods: Hippocampal neurons in vitro were exposed to tau oligomers extracted from tauP301S (PS19) mice hippocampi (natural tau oligomer) or to human recombinant 2N4R tau with or without PTX-BD10-3; spine and neurite morphology were then measured using Neurolucida. In addition, PTX-BD10-3 was orally administered to PS19 mice for 3 months, starting at age 6 months, when tau pathology and spine loss are well-established. After treatment, nest-building behavior was assessed, and after sacrifice one-half of the brain was used for Golgi staining and neurite/spine analysis, and the other half for biochemical analyses.
Results: In vitro, PTX-BD10-3 prevented spine loss and reduced the loss of neurites and dendritic complexity induced by natural or recombinant tau oligomers. In PS19 mice, PTX-BD10-3 treatment reversed pyramidal neuron dendritic spine loss, protected against loss of dendritic complexity, and reduced deficient nest-building behavior. PTX-BD10-3 also reduced excessive RhoA activation, excess tau phosphorylation, production of abnormal tau conformers and accumulation of various insoluble tau aggregates, and inhibited alterations in LIMK1 and cofilin phosphorylation.
Conclusions: Modulating TrkB/C with small molecule partial agonists may reduce tau pathology and neurite/synapse degeneration and normalize RhoA-LIMK1-cofilin activity and behavior, offering a potential treatment strategy for tau-related neurodegenerative disorders.

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SHIFT 02-599

Poster on Board - Shift 02
TAUPATHIES / DISEASE MECHANISMS, PATHOPHYSIOLOGY / TRANSCRIPTIONAL & TRANSLATIONAL REGULATION, MICRO RNAS
4-5 April 2025

LEVELS OF M6A RNA METHYLATION REGULATORS IN THE BRAIN OF ALZHEIMER'S DISEASE PATIENTS AND MOUSE MODELS

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Aims: Epitranscriptomic regulation mediated by N6-methyladenosine (m6A) RNA methylation is crucial for the distinct brain functions during development and in the adult, but its role in neurodegeneration, particularly in Alzheimer's disease (AD), is still unclear. The aim of this study was to examine the levels of m6A RNA regulators in the brain of AD patients and transgenic mouse models.
Methods: We performed biochemical, molecular and cell biology approaches to analyze the differential expression of known regulators of m6A RNA methylation at protein and RNA levels in the hippocampus of APP, Tau and double transgenic APP/Tau mice. In addition, transcript levels of m6A RNA methylation regulators were analyzed in published single-cell RNA-seq datasets from the entorhinal cortex of AD patients.
Results: Bioinformatic analysis of single-cell RNA-seq datasets confirmed the dysregulation of multiple key m6A modulators in oligodendrocytes, excitatory neurons, astrocytes and microglia in AD patients. Particularly, reduced levels of HNRNPA2B1, a nuclear m6A reader involved in alternative splicing and the processing of miRNAs, were detected in the hippocampus of AD transgenic mice.
Conclusions: These results indicate that changes in the levels of regulators of the m6A RNA methylation pathway occur in AD, which may be cell-type specific and induce epitranscriptomic alterations leading to gene expression changes during disease progression. Funded by grants PDC2022-133831-I00 and PID2022-137668OB-I00 from MICIU/AEI/ 10.13039/501100011033 and "European Union NextGenerationEU/PRTR, and AGAUR/Generalitat de Catalunya (2021 SGR00142; PIF Predoctoral fellowship 2023FI_1_01104).

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SHIFT 02-600

Poster on Board - Shift 02
TAUPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / AGGREGATION INHIBITORS
4-5 April 2025

DISCOVERY OF LEAD COMPOUNDS FOR THE TREATMENTS OF PROGRESSIVE SPRANUCLEAR PALSY BY CONTROLLING 4R TAUOPATHY

Ae Nim Pae, Yun Kyung Kim, Sungsu Lim
Korea Institute of Science and Technology, Seoul, Korea, Republic of

Aims: Tauopathies are neurodegenerative disorders characterized by accumulation of tau in neurons or glial cells. Several neuropathologic phenotypes are distinguished based on the distinct anatomic areas and specific isoforms of tau (3R/4R) in pathologic deposits. As tauopathies are strongly linked with neurodegenerative disease, there have been a growing interest in tau-targeted drug discovery. Therefore, we studied and developed novel tau-targeted therapeutic drug candidates for the treatment of AD and PSP by inhibition of tau oligomerization in early stage.
Methods: We performed high-contents screening based on Tau Bi-FC cell-based assay platform and identified novel tau-aggregation inhibitors. Lead optimization was subsequently performed to improve potency and ADME/Tox properties, resulting in the production of lead compound. *In vivo* efficacy of the lead compound was validated by demonstration of restoring memory impairment and motor dysfunction in transgenic animal models of P301L Tau-BiFC.
Results: The lead compound, **DTC2162** exhibited excellent 4R tau aggregation inhibitory activities (cell-based IC_{50}, 88 nM, in vitro IC_{50}, 40 nM) with good cell viability (MTS IC_{50}, 105 uM). The **DTC2162** reduced tau oligomerization and protected neuronal cell death. It restored memory impairment and motor dysfunction in P301L Tau-BiFC Tg mouse models (NOR, Y-maze, Barnes-Maze test, Balance beam and Rotarod test) with reduction of tau pathology. The mode of action of **DTC2162** was confirmed by MALDI-TOF Mass Spectrometric Analysis and TR-2 competition study to show reversible covalent inhibition of disulfide dependent oligomer formation.
Conclusions: Highly potent lead compound was identified having selective inhibition of 4R tau aggregation by using 3R and 4R Tau-BiFC, disease-specific cell-based assay platform and in vivo Tau-BiFC P301L Tg mice model that improved significantly cognitive and motor dysfunction, and reduced tau pathology with good pharmacological properties.

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SHIFT 02-602

Poster on Board - Shift 02
TAUPATHIES / DRUG DEVELOPMENT, CLINICAL TRIALS / TAU CLEARANCE
4-5 April 2025

DEVELOPMENT OF TAU-TARGETING PROTEIN DEGRADERS FOR ALZHEIMER DISEASE

Lisha Wang[1], Banesh Sooram[1], Rajnish Kumar[1,2], Sophia Schedin-Weiss[1], Lars Tjernberg[1], Bengt Winblad[1,3]
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Aims: The intraneuronal accumulation of tau aggregates is one of the hallmarks of AD pathology. Lowered efficiency of degradation pathways, such as the ubiquitin-proteasome system, further exacerbates tau pathologies. A new class of molecules, proteolysis-targeting chimeras (PROTACs), can promote the degradation of target proteins. Since 2016, PROTACs have been applied to target tau pathologies, progressing from being based on peptides to fully synthetic small molecules. This exploration is still at an early stage. Here, we aim to develop novel small-molecule PROTACs as tau-targeting protein degraders for AD treatment.
Methods: We generated a library of novel PROTACs and modelled their ability to form the ternary complex (tau-PROTACs-E3 ligase) by the Molecular Operating Environment platform. The stability of top-ranked PROTACs is evaluated by molecular dynamics simulations. We also established different cell models to evaluate their effects on tau pathology: human neuroblastoma SH-SY5Y cells with human tau overexpression and mouse embryonic primary neurons under amyloid-β peptide (Aβ) treatment. The reported tau-targeting PROTACs QC-01-175 and C004019 have been evaluated in these cell models by western blot and immunofluorescence staining. The proteasome inhibitor is applied to test if it could abolish their effects. Co-immunoprecipitation will be performed to test the ternary complex.
Results: After Aβ treatment, the levels of phosphorylated tau (p-tau) are elevated in primary neurons. Reported PROTACs QC-01-175 and C004019 can reduce p-tau levels back to normal but have no effects on total tau levels. Our potent designed PROTACs will be synthesized and evaluated in our cell models according to the methods listed above.
Conclusions: The most potent PROTACs with least off-target effects will move on to *in vivo* study in the future. It provides pre-clinical evidence for novel treatment of AD tauopathies.

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SHIFT 02-603

Poster on Board - Shift 02
TAUPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
4-5 April 2025

CLINICAL PRESENTATION OF FRONTOTEMPORAL DEMENTIA WITH PARKINSONISM LINKED TO THE N279K MUTATION

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Aims: Tauopathies are proteinopathies that contribute to both sporadic and inherited neurodegenerative diseases. The tau protein involved in these disorders is encoded by the MAPT gene. Mutations in the MAPT gene can cause inherited forms of frontotemporal dementia (FTD) with parkinsonism. Aim of this study is to compare the clinical manifestation of largest clinically and pathologicaly studied kindred with MAPT N279K mutation known as Pallidopontonigral degeneration (PPND) Family with progressive supranuclear palsy (PSP) cases.
Methods: This study includes 17 patients from PPND Family, 18 patients with early-onset PSP, and 19 patients with clasical onset PSP. In each case, the diagnosis was confirmed by brain autopsy. We performed a retrospective analysis of clinical data, including age at symptom onset, disease duration, age at death, symptom profile, and timing of each symptom.
Results: Balance disturbances occurred later in PPND than in late-onset PSP 2.7±1.6 vs. 1.5±1.3 years after symptom onset (p=0.0200) and less frequently as the first symptom 5.9% vs. 50.0% and 47.7% in early-onset and classic-onset PSP, respectively. Unprovoked falls occurred later than in EPSP and LPSP (4.1±1. vs. 2.7±1.2 vs. 1.5±0.7; p<0.0001) and PPND patients were wheelchair bound later (6.0±1.9 vs. 4.9±1.3 vs. 4.1±1.0; p=0.0080). In addition, patients with PPND were more likely to have pyramidal signs (47.1 vs. 5.6 vs. 0%; p=0.0002), sleep (47.1 vs. 16.7 vs. 5.3%, p=0.0084) and smell (41.2 vs. 11.1 vs. 5.3%, p=0.0132) disturbances. Benefits of dopaminergic treatment were more frequently reported in PPND (56.9 vs. 16.7 vs. 5.3%; p=0.0015).
Conclusions: PPND shares a similar phenotype with PSP; however, in the early stages of the disease it may present with symptoms more indicative of Parkinson's disease, including tremor, sleep disturbances, olfactory problems, and a positive response to dopaminergic treatment.

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SHIFT 02-604

Poster on Board - Shift 02
TAUPATHIES / GENETICS, EPIDEMIOLOGY / OTHER
4-5 April 2025

SHARED GENETIC ARCHITECTURE AND NOVEL LOCI IN ALZHEIMER'S DISEASE, AMYOTROPHIC LATERAL SCLEROSIS, LEWY BODY DEMENTIA, AND PARKINSON'S DISEASE: A MULTI-TRAIT GENOME-WIDE ASSOCIATION STUDY

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Aims: Neurodegenerative disorders such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Lewy body dementia (LBD), and Parkinson's disease (PD) often show overlapping pathophysiological processes suggesting potential shared molecular mechanisms. We aimed to study the shared and distinct genetic architecture of these diseases and identify novel as well as pleiotropic genetic loci.
Methods: We applied Multi-Trait Analysis of GWAS (MTAG) on AD, ALS, LBD, and PD. Functional mapping and annotation were performed to detect independent signals and annotate loci. Moreover, we conducted a colocalisation analysis on the top MTAG signals to detect potential pleiotropic loci and a subsequent eQTL-colocalisation analysis on loci showing pleiotropy to prioritise shared genes and tissues of expression.
Results: The MTAG analysis identified 4 novel loci for AD, 3 for ALS, 4 for LBD, and 1 for PD. Colocalisation analysis indicated 12 loci that colocalised with two or more traits, of which, 6 shared a candidate causal variant: rs35749011 (colocalised with LBD and PD), rs34311866 (ALS, LBD, and PD), and rs6733839 (AD and LBD). A subsequent eQTL-colocalisation analysis showed 3 loci with possible shared genes expressed in disease-relevant tissues. Specifically, rs34311866 (colocalised with ALS, LBD, and PD) was an eQTL for DGHQ (brain cerebellum) and PCGF3 (brain hippocampus); rs2526378 (AD and ALS) was an eQTL for BZRAP1-AS1 (nerve tibial); and rs769449 (AD and LBD) was an eQTL for ZNF230 (artery aorta).
Conclusions: Our study uncovers novel insights into the shared genetic architecture of neurodegenerative diseases and highlights candidate genes and tissues that may play a pivotal role in disease pathogenesis. Overall, our results provide a foundation for further exploration into shared disease mechanisms, potentially guiding the development of therapeutic strategies that target converging genetic pathways.

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SHIFT 02-605

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
4-5 April 2025

EXPLORING METACOGNITIVE JUDGEMENTS IN BEHAVIORAL VARIANT FRONTO-TEMPORAL DEMENTIA: PRELIMINARY DATA FROM VERBAL FLUENCY TASKS

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Aims: Patients with dementia are often unable to understand the severity of their cognitive and functional deficits. This anosognosia is a cause of frustration for caregivers. Although being common to neurodegenerative disorders, it is thought to be particularly prominent in behavioral variant Frontotemporal dementia (bvFTD). Metacognitive paradigms provide a methodology for understanding anosognosia. We explored metacognition by asking people to predict their performance on two verbal fluency tasks. We compared patients with bvFTD, Alzheimer's disease (AD) and controls.
Methods: We included 44 participants (61 years median age, 8 years median education) with a comprehensive customized neuropsychological assessment protocol. Clinical groups were diagnosed according to the most recent international criteria and underwent cerebrospinal fluid (CSF)-AD biomarker analysis.
Results: Significant group differences were found for MMSE, MoCA and verbal fluence (all $p<.001$): bvFTD<AD<Controls. For predictions prior to the task, controls underestimate themselves more than AD and bvFTD, with performance being higher than predictions. After completing the task, predictions are more accurate, but AD and bvFTD still underestimating, whereas controls now overestimate. Concerning discrepancy scores (difference between performance and prediction), controls showed higher differences than AD and bvFTD ($p=.002$ and $p<.001$), and AD showed higher differences than bvFTD (p=.008).
Conclusions: Patient groups underestimate their verbal fluency performance. After experiencing the task, they continue to underestimate, despite adjusting their prediction. In contrast, controls significantly increase their prediction and overestimate performance. Surprisingly, AD patients seemed to be less accurate than the bvFTD group, and this task did not reveal a particular metacognitive difficulty in bvFTD.

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SHIFT 02-606

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / COGNITIVE, PSYCHOMETRIC & BEHAVIORAL TESTS, DIGITAL ENDPOINTS, REMOTE TESTING
4-5 April 2025

ASSESSING LONGITUDINAL PROGRESSION IN SPORADIC AND GENETIC FORMS OF FRONTOTEMPORAL DEMENTIA

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Aims: Behavioral variant of frontotemporal dementia (bvFTD) is a devastating and eventually genetically-determined neurodegenerative disease. Reliable predictors progression comparing sporadic and genetic forms have not been sufficiently identified. We investigated baseline and longitudinal neuropsychological profiles of sporadic-bvFTD, GRN-bvFTD and C9orf72-bvFTD for their ability to distinguish between groups and track disease progression.
Methods: Patients were recruited between December 2019 and December 2021 and longitudinally assessed. Clinical, genetic, neuropsychological data were analysed.
Results: Twenty-nine patients, 11 females, mean age 62.38 years (SD=5.88) were included. Eight carried a C9orf72 expansion and 6 have a GRN-associated mutation. At baseline there were no differences between groups in FTLD-CDR global score and SB scores, but GRN-bvFTD patients were more impaired on verbal comprehension (than C9orf72-bvFTD; p=.016) and visuoconstruction (compared to both groups; p=.023). After 12-months there were no significant differences between sporadic and genetic forms, but GRN-bvFTD compared to C9orf72-bvFTD patients showed worse results in learning (p=.021), facial emotion recognition (p=.014) and FBI (p=.037). We then explored which tests could track progression between baseline and 12-months. Repeated measures analysis showed that MMSE, verbal initiative and orientation (all p<.05) could detect disease progression in sporadic-bvFTD. In genetic groups, the digit span was able to track progression (p<.05). Only the FTLD-CDR SB achieved statistical significance for all groups.
Conclusions: Our results are in agreement with previous studies where measures of attention, executive function and language showed significant differences between groups at baseline and follow-up, confirming the value of neuropsychological assessment in tracking progression. We found measurable group differences at baseline and follow-up, highlighting different phenotypes in bvFTD among genetic and sporadic forms. Despite the small sample size, particular neuropsychological tests as well as FTLD-CDR SB were able to track disease progression.

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SHIFT 02-613

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF- AND BLOOD-BASED BIOMARKERS
4-5 April 2025

PLASMA DENATURATION PROFILES USING NANODSF COUPLED WITH MACHINE LEARNING FOR ALZHEIMER'S DISEASE DETECTION

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Aims: This study aims to evaluate the potential of nano-Differential Scanning Fluorimetry (nanoDSF) as a diagnostic tool for Alzheimer's disease (AD). nanoDSF has previously demonstrated high-throughput diagnostic capacity in cancer when integrated with machine learning algorithms. Its use in AD detection remains unexplored, but this method could serve as a rapid, non-invasive initial screening tool. We aim to conduct a preclinical study using plasma samples from wild-type (WT) mice and AD model mice developing either amyloid pathology (5XFAD) or Tau pathology (P301S). This will help us evaluate the initial potential of the method and determine whether Tau and amyloid pathologies exhibit distinct plasma denaturation profiles.
Methods: Plasma samples from 9 month-old WT, 5XFAD and P301S mice will be analyzed using a nanoDSF Prometheus NT.plex instrument to capture plasma denaturation profiles. Machine learning algorithms will then classify these profiles to distinguish WT from AD models with high accuracy.
Results: Our preliminary results indicate differences in the plasma denaturation profiles between young and aged mice. We are currently collecting the plasma samples in young vs. aged 5XFAD and P301S mice in order to apply machine learning algorithms and classify these profiles.
Conclusions: The findings of our study will determine whether nanoDSF holds promise as a high-throughput, non-invasive diagnostic tool for Alzheimer's disease. This method could offer the possibility of large-scale initial screening using simple blood samples. Future studies in human plasma will be essential to confirm its diagnostic value in clinical settings.

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SHIFT 02-618

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

A NOVEL TECHNIQUE FOR ANALYSING WASTEOSOMES OBTAINED FROM CEREBROSPINAL FLUID AND POTENTIAL DIAGNOSTIC TOOL FOR FRONTOTEMPORAL LOBAR DEGENERATION

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Aims: Wasteosomes, also known as corpora amylacea, are structures which act as waste containers and appear in the human brain with aging and certain neurodegenerative diseases. Generated in astrocytes, they contain waste products and are released from the brain to the cerebrospinal fluid (CSF). Consequently, the study of wasteosomes obtained from the CSF can provide information regarding the brain function or dysfunction. This study explores a new approach to improve the characterization of wasteosomes contained in CSF.
Methods: Post-mortem intraventricular CSF samples were used. The samples were centrifuged to obtain the pellets, and pellets were then fixed with paraformaldehyde and embedded in resin. From each sample, 300 semi-thin sections (500 nm thick) were prepared. Given that the diameter of the wasteosomes can attain more than 40 µm, each wasteosome is thus sliced in different sections. Then, in order to label and characterize the wasteosomes, consecutive sections were used to perform the PAS staining and to apply immunofluorescence techniques with specific antibodies.
Results: Analysis of the semi-thin sections revealed the presence of wasteosomes. Notably, and due to the presence of each one of these bodies in some consecutive sections, this method allows the observation of the different components within each wasteosome.
Conclusions: This new technique enhances the study of wasteosomes in human CSF by optimizing sample use and permits to test the presence of different components in each wasteosome. Moreover, since there is currently no established biomarker for the diagnosis of frontotemporal lobar degeneration, we propose to study the presence of tau, TDP-43, or FUS in wasteosomes obtained from the CSF as a potential diagnostic tool for frontotemporal lobar degeneration.

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SHIFT 02-619

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

PROTEOMIC BIOMARKER PROFILING IN ALZHEIMER'S DISEASE AND RELATED DEMENTIAS USING NULISA

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Aims: Evaluate the performance and potential utility of the Nucleic Acid-Linked Immuno-Sandwich Assay (NULISA) central nervous system (CNS) disease panel for characterizing AD pathology and detecting non-AD proteinopathies.
Methods: Retrospective cross-sectional EDTA plasma samples from 239 WRAP and WADRC participants were analyzed using the Alamar NULISA CNS disease panel(195(81.6%) cognitively unimpaired (CU); 35(14.6%) MCI; 9(3.8%) dementia). Amyloid and tau positivity were determined by visual read of PiB and MK-6240 PET scans, respectively. We used ROC analyses to characterize how well NULISA pTau217 detected amyloid or tau PET positivity. Differential biomarker expression across A/T and cognitive groups was compared using volcano plots. Exploratory analyses of longitudinal hippocampal volume change and cognitive decline were completed using mixed linear models.
Results: Comparing pTau217 from the CNS panel to amyloid positivity by PET yielded an AUC of 0.92. No significant difference was found between NULISA and Simoa pTau217 AUCs for amyloid positivity. Proteomics analysis showed five proteins up-regulated and one down-regulated in the amyloid positive group, with APOE4 and pTau217 showing the largest fold changes (5.76 and 1.21, respectively). pTau217 and S100A12 were up-regulated in T+ participants (0.57 and 0.65, respectively). Nineteen proteins, including pTau217, and pTDP43 were upregulated in MCI compared to CU, with no differences between MCI and dementia. In exploratory analysis we found that higher pTDP43 levels were associated with accelerated hippocampal volume decline and worse cognitive trajectories.
Conclusions: These data demonstrate the utility of applying proteomic approaches to well-characterized cohorts for identification of novel biomarker candidates for neurodegenerative proteinopathies. The high

sensitivity and multiplexing capabilities of the NULISA Argo platform provide a wealth of CNS biomarker data from low sample volumes, suggesting this technology could be especially useful in volume-limited applications.

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SHIFT 02-620

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

DIFFERENTIAL DIAGNOSIS OF MILD COGNITIVE IMPAIRMENT AND ALZHEIMER'S DISEASE BY SILK FIBROIN-BASED SERS PLATFORM USING HUMAN PLASMA

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Aims: Early diagnosis of the Alzheimer's disease (AD) before symptoms is in high demand for providing appropriate treatment to delay disease progression. To diagnose AD in the prodromal stage, we developed a silk fibroin (SF)-based surface-enhanced Raman scattering (SERS) platform by analyzing four AD-related biomarkers (total tau, p-tau181, beta-amyloid 42, and brain-derived neurotrophic factor (BDNF)).
Methods: The SF-based substrate was developed by maskless plasma etching and metal deposition on the SF film to have unique structural features, resulting in the maximum field intensity of about 358, and thereby, the theoretical enhancement factor of SF-based SERS substrates was estimated to be 1.64×10^{10}. Additionally, by introducing optimal SERS probe on the substrate, four biomarkers were detected with high sensitivity of sub-femtomolar level (0.872 fM to 1.032 fM).
Results: As a result, healthy controls, mild cognitive impairment (MCI), and AD groups were successfully discriminated with high accuracy using plasma samples.
Conclusions: Therefore, our proposed SF-based SERS platform can be a robust alternative to traditional sensing platforms for predicting the onset of AD in the asymptomatic phase.

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SHIFT 02-621

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

WASTEOSOMES FROM ALZHEIMER'S DISEASE AND FRONTOTEMPORAL LOBAR DEGENERATION CAN CONTAIN TAU, TDP-43, OR FUS DEPENDING ON THE UNDERLYING PROTEINOPATHY

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Aims: Wasteosomes (or *corpora amylacea*) appear in the human brain with advancing age and in some neurodegenerative diseases and it has been proposed that they act as waste containers. In this context, wasteosomes have the potential to entrap some of the proteins that misfold, aggregate and accumulate in these diseases. In this work, we scrutinized the presence of some of these proteins in wasteosomes from Alzheimer's disease (AD) and from frontotemporal lobar degeneration (FTLD).
Methods: Cryopreserved human hippocampal sections were obtained from 3 cases of AD; 4 cases of FTLD with tau pathology (FTLD-tau), 3 cases of FTLD-TDP, and 3 cases of FTLD-FUS. Immunofluorescence methods with prior antigen retrieval were applied to detect tau, phosphorylated-TDP-43 (pTDP-43) and FUS in wasteosomes.
Results: Our results revealed the presence of tau in some wasteosomes from AD, and the presence of tau, pTDP-43 and FUS in some wasteosomes from FTLD-tau, FTLD-TDP, and FTLD-FUS, respectively. Considering that all of these proteins are highly or specifically ubiquitinated in these diseases, the results also suggest that the presence of p62 in wasteosomes can be relevant because of its capacity to entrap and retain ubiquitinated substances. These results corroborate that wasteosomes may entrap misfolded proteins and indicate that the composition of wasteosomes differs depending on the proteinopathy.
Conclusions: Wasteosomes in AD can contain tau and those from FTLD can contain tau, TDP-43 or FUS in concordance with the affected protein. Moreover, since there is currently no established biomarker for the diagnosis of FTLD, we propose to study the presence of these proteins in wasteosomes obtained from the cerebrospinal fluid as a potential diagnostic tool for FTLD.

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SHIFT 02-622

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

WHITE MATTER HYPERINTENSITY SHAPE IS ASSOCIATED WITH CSF BIOMARKERS AND MEMORY FUNCTION IN MILD COGNITIVE IMPAIRMENT PATIENTS.

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Aims: White matter hyperintensity (WMH) are features of cerebral small vessel disease (SVD) that are associated with cognitive performance in mild cognitive impairment (MCI). However, the association of WMH shape markers and cognitive measures in MCI remains unclear. We explored the association between WMH shape and volume and cognitive measures and cerebrospinal fluid (CSF) Alzheimer's disease (AD) biomarkers in mild cognitive impairment (MCI).
Methods: Three hundred and sixteen MCI patients of the Alzheimer's Disease Neuroimaging Initiative (ADNI) study underwent 3.0T brain magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) examination, and neuropsychological assessment. WMH features (volume, subtype and shape) were automatically determined.
Results: Increased shape complexity of the periventricular WMH, higher total WMH volume, and higher periventricular WMH volume were associated with memory function in MCI patients (all $p < 0.05$). Similar associations were seen between WMH volume and shape markers and CSF AD biomarkers were seen in MCI patients ($p < 0.05$).
Conclusions: Our results suggest that WMH shape markers may provide additional information about WMH burden.

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SHIFT 02-623

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / CSF, BLOOD, BODY FLUID BIOMARKERS
4-5 April 2025

CLINICAL VALIDATION OF LUCENTAD COMPLETE, AN ALGORITHMIC LAB DEVELOPED TEST (LDT) FOR AMYLOID DETECTION IN PLASMA

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Aims: Objectives: To clinically validate the LucentAD Complete, a multi-biomarker algorithmic test that includes p-Tau 217, across diverse clinical cohorts as a CLIA LDT.
Methods: Methods: Upper and lower diagnostic thresholds for the Simoa LucentAD 217 plasma test were optimized to achieve ≥90% accuracy for objective symptomatic patients across a training sample set of randomized samples from 2 independent cohorts (Bio-Hermes, Amsterdam Dementia Cohort) representing divergent clinical settings, comparator methods, and geographic/ethnic/racial/mean age samplings. Across these diverse cohorts, the intermediate zone was 32.9%. All samples were also tested for amyloid ratio, NfL, and GFAP using the Simoa N4PE kit. Multivariate logistic regression modeling was performed on all biomarker results to arrive at a probability scale. Samples with uncertain p-Tau 217 results were re-classified based on their probabilities being outside 90% lower and upper boundaries of the multi-marker intermediate zone optimized with the same training set. The resulting two sets of thresholds (p-Tau 217 and logistic probability) were validated with a validation set of 545 randomized samples from the BioHermes and Amsterdam cohorts. A third set of 537 longitudinal samples from the ADNI cohort was also tested to further validate the optimized thresholds.
Results: Results: The clinical performance parameters depicted in Table 1 were obtained:
Conclusions: Conclusions: Across these diverse sample sets, the LucentAD Complete blood test achieved consistent results and the intermediate zone from p-Tau 217 was reduced approximately three-fold. Clinical accuracy and specificity was maintained at 90% (weighted mean across all three sample sets), with an overall mean positive predictive value of 93.3%. The LucentAD Complete test provides a blood-based method for accurate amyloid risk stratification of patients with objective cognitive symptoms while minimizing the intermediate zone with associated inconclusive results.

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SHIFT 02-625

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4-5 April 2025

STRUCTURAL DIVERSITY OF TAU AGGREGATES IN PICK'S DISEASE

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Aims: The role of tau protein is central to the progressive neuropathological changes in neuropathies. The trajectory by which tau spreads through neural networks is specific to each disease but the sequence of events by which aggregates of tau drive disease progression is unknown due to the challenge of detecting specific aggregate forms *in situ*.
Methods: Here we examine the molecular organization of tau-containing lesions in the dentate gyrus of a 79-year-old male subject of frontotemporal dementia. Neuropathological examination revealed extensive Pick bodies in the granular layer and modest amounts of neurofibrillary tangles and dystrophic neurites in the Cornu Ammonis region 4 (CA4) and hilus. Synchrotron-based *In situ* micro X-ray diffraction (μXRD) was used at the ID13 beamline to assess the abundance and distribution of fibrillar tau. Local accumulation of specific metals was imaged using micro X-ray fluorescence (μXRF) imaging at the ID21 beamline.
Results: μXRD data indicated that tau within the Pick bodies of the granular layer is largely low in fibril content, whereas neurofibrillary lesions within the CA4 and hilus regions of the hippocampus exhibit a far greater density of fibrillar tau. μXRF data show elevated levels of zinc, calcium and phosphorous relative to the surrounding tissue in essentially all tau-containing lesions. In many cases, sulfur deposition appeared greater in lesions exhibiting high fibrillar content.
Conclusions: These observations demonstrate a correlation of lesion morphology with anatomical localization, degree of tau fibrillation and differential accumulation of metals. Lesions containing different levels of tau fibrils may harbor biochemically distinct microenvironments that influence both lesion morphology and tau seed formation and spreading.

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SHIFT 02-626

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / MULTIMODAL IMAGING
4-5 April 2025

DIABETES MELLITUS EXACERBATES CHANGES IN WHITE MATTER HYPERINTENSITY SHAPES AND VOLUME: A LONGITUDINAL STUDY.

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Aims: Although white matter hyperintensity (WMH) can progress over time, little is known about the underlying mechanisms. Besides, type 2 diabetes mellitus (T2DM) exacerbates the accumulation of WMH. Here, we aimed to investigate longitudinal changes in WMH shapes and volume in older adults with and without T2DM.
Methods: Participants underwent baseline and follow-up magnetic resonance imaging (MRI). WMH volume and shape markers were automatically assessed. We compared WMH volume and shape markers at baseline and follow-up.
Results: 200 participants were included at baseline and 181 at follow-up. The mean age of our study participants was 69.86 ± 6.03 years; 79 (39.90 %) had a history of diabetes mellitus (T2DM) and 73 (36.50 %) were males. For shape markers, participants with T2DM showed more complex periventricular (eccentricity, $p = 0.027$) and deep WMH shape markers (fractal dimension, $p = 0.002$) than participants without T2DM. At baseline, there were no significant differences ($p > 0.05$) in WMH volume when participants with T2DM were compared to participants without T2DM. At follow-up, a more complex shape of periventricular/confluent WMH on follow-up (concavity index, $p = 0.005$; inverse sphericity index, $p = 0.001$). Also, total ($p < 0.001$), periventricular ($p < 0.001$), and deep ($p = 0.001$) WMH volumes increased significantly.
Conclusions: A more irregular shape of periventricular and deep WMH and higher WMH volumes were associated with T2DM participants. These findings suggest that WMH shape markers may be useful in determining SVD prognosis and aid in future preventive treatments.

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SHIFT 02-627

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / PET - TAU
4-5 April 2025

SYNTHESIS OF NOVEL COPPER COMPLEXES FOR POTENTIAL USE IN THE DIAGNOSIS OF ALZHEIMER'S DISEASE

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Université Sorbonne Paris Nord, Bobigny, France

Aims: Predicting Alzheimer's disease is the focus of many research projects. In the literature, the potential of PET-tau to predict cognitive decline and the development of brain atrophy in Alzheimer's patients has been proposed. In our laboratory, we are developing new copper complexes for PET-tau imaging in the diagnosis of this disease. With a longer lifetime than radiotracers already in use, copper complexes appear to be an innovative solution.
Methods: Previous work in our laboratory led to the synthesis of new copper complexes targeting amyloid plaques, yielding promising results. The aim of the present study is to synthesize a series of new copper complexes designed for tau protein aggregates. These complexes will be derived from [18F]-Flortaucipir and [18F]-RO948, two molecules able to recognise tau. The key step in this synthetic strategy is a reductive amination between a diamine and a molecule capable of targeting tau. The synthesis of the ligand that will allow the preparation of the first complex involves Suzuki couplings followed by reductive cyclisation.
Results: Due to solubility problems, the ligand synthesis pathway had to be adapted by adding a pyrido-indole ring protection/deprotection step. As a result, one of the ligands was successfully synthesized in 6 steps. The other ligands are still being synthesized using the same strategy.
Conclusions: We have synthesized a new ligand designed to develop a novel copper complex that may be able to specifically target tau protein aggregates and contribute to the development of new strategies in the diagnosis of Alzheimer's disease.

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SHIFT 02-630

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4-5 April 2025

BRAIN NETWORK TOPOLOGY ROUTES THE PATTERNS OF NEURODEGENERATION IN PATIENTS WITH PROGRESSIVE SUPRANUCLEAR PALSY

Carla Palleis[1,2], Andrea Quattrone[1], Amir Dehsarvi[3], Sebastian Roemer-Cassiano[1,3], Hans-Jürgen Huppertz[4], Adam Boxer[5], Matthias Brendel[6], Johannes Levin[1,2], Günter Höglinger[1], Nicolai Franzmeier[3]
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Aims: 4-repeat (4R) tau pathology is presumed to spread across interconnected neurons, which may therefore give rise to network-like neurodegeneration in Progressive Supranuclear Palsy (PSP). We hypothesized that interconnected brain regions show correlated brain atrophy in PSP and that brain atrophy propagates from local epicenters across connected regions.
Methods: We included 2 independent datasets of 12-month longitudinal 3T structural MRI of patients with PSP-Richardson Syndrome (PSP-RS, $n_{discovery}/n_{validation}$=114/90) from the placebo arms of PASSPORT and AL-108-231 trials. Cross-sectional MRI-based grey matter volumes were assessed for 246 regions of the Brainnetome atlas and converted to w-scores indicating local atrophy (i.e., volumes adjusted for age, sex and intracranial volume-adjusted compared to a sample of 377 healthy amyloid- and tau-negative controls from the ADNI cohort). Similarly, annual grey matter volume changes were determined for each Brainnetome ROI using longitudinal structural MRI. 3T resting-state fMRI from 69 ADNI healthy controls was used to determine a connectivity template across which we modelled spread of grey matter atrophy.
Results: Strongest grey matter atrophy and longitudinal volume change was found bilaterally in the frontal lobe and subcortical regions. Interconnected brain regions showed correlated brain atrophy and correlated volume change over time. Regions with strong atrophy/fast volume decline were strongly connected to other atrophic/fast declining regions, whereas regions with little atrophy/volume change were connected to regions with similarly little atrophy/volume changes. Moreover, the seed-based connectivity patterns of epicenters with highest baseline atrophy or fastest volume change predicted brain-wide atrophy or volume change patterns on the subject level. All results were fully replicated across both samples.
Conclusions: Our findings suggest that grey matter atrophy expands across interconnected brain regions in PSP-RS patients, supporting the view that atrophy may follow transneuronal tau propagation in PSP.

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SHIFT 02-631

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4-5 April 2025

ROBUST LONGITUDINAL MRI ATROPHY ANALYSIS REDUCES SAMPLE SIZE REQUIREMENTS FOR PROGRESSIVE SUPRANUCLEAR PALSY (PSP) CLINICAL TRIALS

Simone Zehntner, Felix Carbonell, Jean-Philippe Coutu, Alex Zijdenbos, Barry Bedell
Biospective Inc, Montreal, Canada

Aims: Given that PSP is a rare disease, minimizing the number of participants in clinical trials is critical. The aim of this work is to identify the brain regions-of-interest that require the lowest sample sizes to detect potential therapeutic effects for PSP clinical trials.
Methods: 3D T1-weighted MRI images from PSP subjects (148 scans) and cognitively normal healthy controls (188 scans) were obtained from the 4-Repeat Neuroimaging Initiative (4RTNI) and Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI). We performed fully-automated image processing and analysis using our in-house PIANO software platform to obtain regional brain volumes.
Results: Rapid progression of brain atrophy in PSP subjects was detectable over a 12 month period. Up to approximately 4% decrease in volume was apparent in the superior cerebellar peduncles, pallidum, midbrain, and brainstem. Sample size calculations showed requirements of 15-40 subjects per arm to detect a 60% reduction in observed brain atrophy. While statistically significant atrophy was also observed in the cerebral cortex, these changes were on the order of approximately 1.5-2% with higher sample size requirements (>90 subjects per arm). In comparison, other processing and analysis methods, including FreeSurfer, MRPI, and MRPI2.0, typically resulted in even larger sample size requirements, with MRPI requiring 51 subjects, MRPI2.0 requiring 34 subjects, and FreeSurfer over 192 subjects per arm to detect an 60% reduction in observed brain atrophy.
Conclusions: By identifying specific brain regions with high rates of atrophy and minimizing methodological variability using a robust image processing platform, sample size requirements for tracking disease progression and potential disease modification via therapeutic intervention can be reduced. This work highlights the importance of selecting the most sensitive processing and analysis approaches to minimize sample size while maintaining statistical power in clinical trials.

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SHIFT 02-632

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4-5 April 2025

MRI GRAY MATTER DENSITY ANALYSIS IDENTIFIES BRAIN REGIONS THAT REDUCE THE SAMPLE SIZE REQUIRED FOR CORTICOBASAL DEGENERATION (CBD) CLINICAL TRIALS

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Biospective Inc, Montreal, Canada

Aims: Due to the rarity of CBD, minimizing the number of participants in clinical trials is essential. This research focuses on identifying cortical brain regions that enable the detection of potential therapeutic effects with the smallest possible sample sizes in CBD clinical trials.
Methods: 3D T1-weighted MRI images from CBD subjects (117 scans) and healthy controls (188 scans) were obtained from the 4-Repeat Neuroimaging Initiative (4RTNI) and Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI). We performed fully-automated image processing using our in-house PIANO software platform to obtain gray matter density and regional brain volumes.
Results: significant decreases in gray matter density observed in focal brain regions. Thresholding the voxelwise t-statistic revealed the most rapidly changing regions. Utilizing this exploratory approach, we identified areas within the sensorimotor, parietal, and temporal cortices as having the greatest loss of gray matter density over 12 months in CBD subjects. Statistical analysis of the regional volumes illustrated between a 2.5% and 4.8% decrease in volume in these regions. Sample size calculations indicated that 30-44 subjects per arm would be required to detect a 60% reduction of the observed brain atrophy. Subcortical regions, such as thalamus and hippocampus, also showed statistically significant atrophy and moderate sample sizes (23 and 29 subjects per arm, respectively) to achieve similar power.
Conclusions: By accurately identifying brain regions with significant atrophy and reducing methodological variability using a robust image processing platform, the sample size requirements for clinical trials can be minimized. This approach enhances our ability to track disease progression and evaluate therapeutic interventions, making it possible to detect potential disease modification cost-effectively and efficiently.

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SHIFT 02-633

Poster on Board - Shift 02
TAUPATHIES / IMAGING, BIOMARKERS, DIAGNOSTICS / STRUCTURAL MRI, MR SPECTROSCOPY
4-5 April 2025

PROGRESSION OF BRAIN ATROPHY IN FRONTOTEMPORAL DEMENTIA (FTD) VARIANTS OVER 24 MONTHS AND IMPLICATION FOR CLINICAL TRIALS

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Aims: The objective of this work was to utilize neuroimaging to assess the natural history of brain atrophy in FTD variants and generate sample size estimates for detecting potential therapeutic effects in clinical trials.
Methods: 3D T1-weighted MR images from FTD subjects [behavioral variant FTD (bvFTD), semantic dementia (svFTD), progressive nonfluent aphasia (PNFA)] and healthy controls were obtained from the Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI). We performed fully-automated image processing using our in-house PIANO software platform to obtain regional brain volumes. Given that the hippocampus is a particularly challenging structure to segment, our hippocampal segmentation was performed using a deep learning approach, in which a previously trained 3D U-net was applied to the FTLDNI data.
Results: Statistically significant brain atrophy was observed in numerous regions over the 24 months assessed. When evaluating the FTD subgroups, distinct patterns of atrophic changes were apparent as early as 6 months. The PNFA variant was clearly distinguished from svFTD by both the pattern and rate of regional atrophy progression, with significant atrophy initially observed in the temporal cortex and hippocampus, followed by additional deep brain structures, such as the striatum and thalamus. Our deep learning segmentation approach reduced both longitudinal variability and quality control failure rates, thereby substantially reducing the estimated sample size requirements. For example, a sample size estimate of ~35 subjects per arm was found to be sufficient to detect an 80% reduction in the observed atrophy in the hippocampus over a 6-month time frame in the svFTD group.
Conclusions: By leveraging robust volumetric segmentation methods that accurately and reproducibly segment brain regions which undergo significant atrophy in FTD (e.g. hippocampus), reasonable sample sizes can be realized for clinical trials.

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SHIFT 02-634

Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / ANTI-INFLAMMATORY
4-5 April 2025

FURTHER INVESTIGATION ON THE IMMUNOMODULATORY AND ANTI-INFLAMMATORY EFFECTS OF NEURORESTORE ACD856, A TRK-PAM IN CLINICAL DEVELOPMENT FOR THE TREATMENT OF ALZHEIMER'S DISEASE

Cristina Parrado-Fernández[1,2], Ruchi Gera[3], Veronica Lidell[2], Azita Rasti[2], Sumonto Mitra[3], Maria Backlund[2], Gunnar Nordvall[1,2], Johan Sandin[1,2], Maria Eriksdotter[3,4], Pontus Forsell[1,2]
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Aims: BDNF and NGF, acting through Trk receptors, mediate neuronal survival, plasticity, and cognition in neurological disorders like Alzheimer's Disease (AD). NeuroRestore ACD856, a positive allosteric modulator of Trk receptors, passed phase-I trials with good safety, pharmacokinetics, and signs of CNS efficacy. In vivo, ACD856 increases BDNF, improves cognition, and has long-term antidepressant effects. In vitro, it enhances neurite outgrowth and protects against Aβ toxicity. Recent findings showed that ACD856 decreases IL-6, IL-1b, and IgG release in aging and APP^{NLGF} models, prompting us to investigate its immunomodulatory activity in an in vivo tauopathy model characterized by progressive microglial activation preceding tangle formation and in an in vitro LPS-induced neuroinflammation model.
Methods: Anti-inflammatory effects were examined in microglial BV2 cells stimulated 6 days with 20 ng/ml PMA, pre-treated with ACD856 or BDNF for 3h, and co-incubated with LPS for 21 h. The supernatant was tested for IL-6 using ELISA. ACD856 (3 mg/kg, p.o.) was given to ten Tau PS19 transgenic mice (P301S mice) twice daily for 30 days (from 5 to 6 months old). Ten P301S mice and wild-type littermates received vehicle as controls. Additional ten P301S mice were sacrificed as baseline control.
Results: In vitro experiments in BV2 cells showed that ACD856 reduced the release of IL-6 levels triggered by LPS-mediated inflammation. Results from the in vivo P301S mouse model will be presented. The data will include global hippocampus proteomic profiling, and peripheral and central inflammatory markers.
Conclusions: Consistent with the anti-inflammatory effects of ACD856 in old and APP^{NLGF} mouse models, we found that ACD856 significantly reduced the release of IL-6 in BV2 cells after LPS-induced inflammation suggesting that ACD856 may modulate brain immune cells and possibly delaying neurodegeneration in neuroinflammatory diseases like AD.

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SHIFT 02-635

Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
4-5 April 2025

DISCRIMINATION OF ANTI-TAU ANTIBODIES TARGETING DIFFERENT TAU EPITOPES BY A P301S MOUSE HIPPOCAMPAL SEEDING MODEL OF TAUOPATHY

Wencheng Liu, Maneesha Paranjpe, Shiron Lee, Hechen Bao, Ching-Lien Fang, Joydip Kundu, Charlotte Chung, Chanchal Sadhu, Rajeev Sivasankaran, Todd Carter, Dinah Sah
Voyager Therapeutics, Neuroscience, Lexington, United States of America

Aims: VY7523 is a recombinant humanized IgG4 monoclonal version of murine Ab-01 designed to inhibit the spread of pathological tau in Alzheimer's disease (AD). Ab-01 targets an epitope in the C-terminus of tau, binds to pathological tau (p-tau) with high affinity and selectivity over wild-type tau, and blocks paired helical filaments (PHF) seed-induced tau aggregates in the P301S mouse hippocampal seeding model. Here, we compared Ab-01 to murine surrogates of antibodies in clinical development targeting different tau epitopes for reduction of p-tau levels in this seeding model, including murine surrogates of anti-tau antibodies that failed to meet primary endpoints in the clinic. In addition, we quantified tau species containing the epitope targeted by Ab-01 in PHF from hippocampi of AD Braak stages II, III, IV and V.
Methods: Evaluating anti-tau antibodies for p-tau lowering in our seeding model Quantifying levels of tau species containing the target of Ab-01 in PHF from AD hippocampus, using LC-MS/MS
Results: Murine surrogates of anti-tau antibodies that failed to meet primary efficacy endpoints in clinical trials showed no efficacy in our seeding model. Ab-01 exhibits efficacy and tolerability similar to murine surrogates of other anti-tau antibodies in clinical development evaluated in our seeding model. Unlike these other antibodies, Ab-01 is highly selective for pathological over wild-type tau Tau species targeted by Ab-01 are present in PHF isolated from hippocampus of AD Braak stages II, III, IV and V.
Conclusions: Our P301S mouse hippocampal seeding model may serve as a negative predictor for clinical outcomes of anti-tau antibodies. Antibodies targeting the mid-domain and C-terminus of tau, including Ab-01 and murine surrogates of other antibodies in clinical development, have similar efficacy in reducing p-tau levels in this model.

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SHIFT 02-636

Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / IMMUNOTHERAPY
4-5 April 2025

IMMUNIZATION WITH JNJ-64042056 GENERATES ANTIBODIES IN NON-HUMAN PRIMATES THAT INHIBIT TAU AGGREGATION IN A NEURONAL TAU SEEDING MODEL

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[1]Johnson & Johnson Innovative Medicine, Neuroscience Discovery, Beerse, Belgium, [2]Johnson & Johnson Innovative Medicine, Statistics & Decision Sciences, Beerse, Belgium, [3]AC Immune, Research, Lausanne, Switzerland

Aims: JNJ-64042056 is an active immunotherapy targeting phosphorylated Tau (pTau), currently in a Phase 2b clinical trial (ReTain), which induces a strong and sustained pTau antibody response in preclinical models and Alzheimer's disease (AD) patients. To continue and further elaborate on the work of AC Immune regarding the evaluation of the functional characteristics of the JNJ-64042056 induced polyclonal antibodies, an in vitro model in rat primary neurons was set up that mimics Tau seeding, and post-immune serum from non-human primates (NHP) was evaluated in this assay.
Methods: AD patient-derived Tau aggregates (AD-Tau seeds) were used to induce the aggregation of endogenous rat Tau in primary cortical neurons. Pre- and post-immune serum from NHP immunized with JNJ-64042056 were co-incubated with AD-Tau seeds, added to primary rat cortical neurons, and the levels of induced Tau aggregation were evaluated using specific immunoassays.
Results: The results demonstrate that pre-incubation of AD-Tau seeds with anti-pTau antibodies present in polyclonal serum after JNJ-64042056 immunization (2 or 4 doses) significantly inhibited the induction of Tau aggregation in rat cortical neurons. Most consistent inhibition was obtained at lower serum dilutions (higher antibody concentrations), with higher dilutions showing progressively lower effects.
Conclusions: JNJ-64042056, an active immunotherapy currently in clinical trials for the treatment of AD, induces the generation of polyclonal antibodies in NHP which displayed the functional capacity of inhibiting Tau aggregation in a rodent neuronal model.

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SHIFT 02-638

Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / OTHER
4-5 April 2025

ON THE EFFICACY OF THE TAU AGGREGATION INHIBITOR HYDROMETHYLTHIONINE: DIFFERENT DOSING REGIMENS AND SYMPTOMATIC ACTIONS

Lianne Robinson[1], Jack Bray[1], Valeria Melis[1], Charles Harrington[1], Claude Wischik[2], Gernot Riedel[1]
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Aims: We have previously reported that hydromethylthionine (HMT) dissolves tau protein aggregates and corrects memory decline in tau transgenic mice. Here we explored whether (i) the treatment regime affects efficacy of HMT, and (ii) whether it is also effective in a symptomatic model of Alzheimer's disease.
Methods: (i) The treatment regime of HMT (15 mg/kg) was administered for 4 weeks via oral gavage either 1, 3 or 5 days per week for 7 weeks in 6-month-old female Line 1 and NMRI mice. Then, mice were tested for spatial learning in a problem-solving task in the water maze for up to 3 weeks. (ii) Scopolamine (0.5mg/kg, ip.) induced memory deficits were used as a symptomatic model in 3-month-old female NMRI mice. HMT (5mg/kg or 15mg/kg) was co-administered daily followed by spatial learning and memory performance in a reference memory task in the water maze.
Results: (i) Line 1 mice presented with significantly impaired performance in the problem-solving task compared to NMRI controls. Treatment with HMT for either 1, 3 or 5 days per week was able to ameliorate the deficit observed in Line 1 mice. (ii) Systemic administration of scopolamine induced significant impairments in spatial learning and memory of the mice compared to vehicle controls. These deficits in performance were reversed by treatment with HMT at both doses of 5 and 15 mg/kg. Furthermore, co-administration of rivastigmine also ameliorated the scopolamine deficit.
Conclusions: Beneficial effects of HMT on cognitive performance were observed following intermittent and shorter treatment regimens of only one administration per week. Furthermore, like previous observations from our group with methylthioninium chloride, HMT was effective in a symptomatic model of AD confirming multiple mechanisms of action.

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Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES
4-5 April 2025

FIBRILPAINT TARGETS TAU OLIGOMERS AND FIBRILS FOR UBIQUITINATION

Stefan Rüdiger
Utrecht University, Protein Chemistry Of Disease, Utrecht, Netherlands

Aims: Neurodegenerative diseases are characterised by the progressive loss of neuronal tissue, and the accumulation of amyloid fibrils. Currently, there are no therapeutics that remove these amyloids. Targeted protein degradation could be a promising strategy to remove fibrils or oligomeric precursors. This approach requires degraders that specifically recognise amyloid fibrils, preferentially in early stages. Thus, the aim is to develop a degrader that is selective in recognising amyloid fibrils and their oligomeric precursors and initiate their ubiquitination.
Methods: Here we introduce FibrilPaint20, a peptide that acts as PROTAC compound for targeted protein degradation, for the ubiquitination of various protein fibrils and their short precursors through the E3-ligase CHIP. To study ubiquitination, we developed an application of Flow Induced Dispersion Analysis (FIDA) to monitor fibril length. FIDA determines the size of the fluorescently labelled particles giving as a readout of the apparent size in nm. The advantage of FIDA measurements is that they are solvent-independent, which allows precise measurements in cell lysates or blood.
Results: The peptide FibrilPaint20 specifically mediates the ubiquitination of amyloid fibrils. It is a PROTAC, containing both of a fibril recognition module and a recruitment motif for the E3 ubiquitin ligase CHIP. Importantly, FibrilPaint20 does not bind to the functional monomer but exclusively to fibrils and oligomeric percursors. Remarkably, FibrilPaint20 ubiquitinates chemically diverse fibrils, unrelated in sequence and morphology. This includes fibrils of the disease-related proteins of a-synuclein, Abeta, Huntingtin and various Tau species, such as patient-derived fibrils from Alzheimer, Frontotemporal Dementia and Corticobasal Degeneration. Binding of FibrilPaints remains selective in blood.
Conclusions: FibrilPaint20 is an exciting lead for targeted protein degradation of amyloid fibrils and their oligomeric precursors.

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TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / PROTEIN AGGREGATION, NFT, MISFOLDING, CHAPERONES
4-5 April 2025

TARGETED PROTAIN DEGRADATION OF TAU FOR THE TREATMENT OF ALZHEIMER'S DISEASE AND PRIMARY TAUOPATHIES

Lili Zhang, Yunhong Huang, Steve Paget, Yen-Ting Lai, Yuan Chai, Xiang Gu, Xiaojuan Wang, Jie Hong, Wen Gao, Zhenyu Li, Xujin Zhan, Chenhua Zhang, Ming-Kuei Jang, Mark Shearman
APRINOIA Therapeutics, Cambridge, United States of America

Aims: Misfolded tau aggregates play a crucial pathogenic role in Alzheimer's (3R/4R tau) and primary tauopathies such as progressive supranuclear palsy (PSP) (4R tau) and frontotemporal dementia (FTD) (3R tau) but have been considered undruggable for traditional small molecule approach. Targeted protein degradation (TPD) is a promising therapeutic platform with multiple drugs in clinical development for oncology indications. Our objective is to leverage the emerging TPD technology to develop degraders selectively removing tau aggregates as a novel treatment for tauopathies.
Methods: APRINOIA's tau binders from the APN-1607 tau PET tracer program have been validated for selective binding to pathological tau including 3R, 4R, and 3R/4R tau aggregates in a broad range of tauopathies. A tau degrader library was generated by combining a diverse collection of tau binders from the APRINOIA tau PET tracer program with different linkers and ligands of CRBN E3 ligase. The compounds were screened in cellular tau aggregation assay followed by confirmation of E3 ligase dependent mechanism of action. In vivo drug efficacy was determined by IV injection in tauopathy mouse model rTg4510.
Results: Potent degraders were identified from the proprietary degrader library with selective reduction of tau aggregates without affecting the large pool of soluble tau. Preliminary study demonstrated a reduction of pathological tau in rTg4510 mice following IV injection with tau degraders in 24 to 48 hours.
Conclusions: We have established a platform to identify novel tau aggregate degraders by taking advantage of APRINOIA's rich collection of well-characterized tau binders from its tau PET tracer program. Current effort is focused on further optimization of the drug properties of top tau degrader series as a promising therapy for AD and related tauopathies.

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SHIFT 02-643

Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TAU, PHOSPHORYLATION, TRUNCATION
4-5 April 2025

FUNCTIONAL GENOMICS TO IDENTIFY NOVEL, GENETICALLY-VALIDATED, DISEASE-MODIFYING THERAPEUTIC TARGETS IN NEURODEGENERATIVE DISEASE

Hannah Maxwell, Sarah Burley, Tom Campbell, Jason Clark, Emily Coode, Rosanna La Rocca, Pedro Garção, Aitor Martinez-Zarate, James Smith, Rick Livesey
Talisman Therapeutics Limited, Cambridge, United Kingdom

Aims: A key bottleneck for the development of disease-modifying therapeutics for neurodegenerative diseases is a lack of credible, genetically-validated targets. Human genetics has identified mutations causal for monogenic forms of Alzheimer's, Parkinson's and other neurodegenerative diseases, as well as genomic variants that increase relative risk of developing each disease. However, exploiting these insights for target identification has proven challenging. Functional genomics data have the potential to provide critical data for identifying novel, genetically-validated targets. To test this, we combined human stem cell models of Alzheimer's disease and frontotemporal dementia with whole-genome, loss of function CRISPR screening to develop a functional genomics platform for novel target identification.
Methods: Human iPSCs constitutively expressing Cas9 were generated in non-demented control, APP, and MAPT mutant backgrounds. Whole genome CRISPR knockout screens were carried out by lentiviral transduction of human iPSC-derived progenitor cells with a library of 100,000 sgRNA pairs (VectorBuilder), which were then matured to excitatory, cortical neurons. A FACS-based assay for neuronal tau (MAPT) protein levels was optimised, enabling comparison of total tau protein with MAP2, an unrelated microtubule-binding protein. Screen outcomes were assessed by sgRNA sequencing from genomic DNA neuronal populations, and analysed with MAGeCK.
Results: Human iPSC lines with constitutive Cas9 expression were established in iPSCs with different mutations causal for neurodegenerative disease. A whole genome CRISPR knockout library was introduced to human iPSC-derived neural progenitor cells, which were then differentiated to excitatory neurons. Survival and FACS-based screens were performed to enable identification of genes regulating each phenotype analysed.
Conclusions: CRISPR-based functional genomics in human stem cell models of neurodegenerative disease successfully identified genes that modify key aspects of disease pathogenesis. Validation of a subset of these genes is currently ongoing.

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SHIFT 02-644

Poster on Board - Shift 02
TAUPATHIES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT / TAU, PHOSPHORYLATION, TRUNCATION
4-5 April 2025

P-TAU ANTIBODY AS A NOVEL THERAGNOSTIC APPROACH FOR ALZHEIMER'S DISEASE

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Aims: Alzheimer's disease (AD) and other tauopathies are leading causes of dementia and loss of autonomy in the elderly, implying a progressive cognitive decline and limitation of social activities. This study suggests a theragnostic approach based on the importance of phosphorylated tau protein (p-Tau) in the early pathophysiological processes of AD. We have developed a theragnostic monoclonal antibody (mAb), to provide *in situ* diagnostic and therapeutic effects.
Methods: We have developed a novel p-Tau mAb. Doped with deferoxamine for radiolabeling with Zirconium-89 (Zr-89) for positron emission tomography (PET) imaging and fluorescence dies for immunofluorescence assays. The mAb (B6) was evaluated i*n vitro* for toxicity; by MTT assay, LDH activity, propidium iodide/Annexin V assay, and mitochondrial membrane potential (MMP) assay. Treatment with osmotic pumps at two different times, at 4 and 7 months, was developed with the B6 antibody or the IgG1 control antibody.
Results: *In vivo* experiments of tauopathy model mice (PS19) with radiolabeled p-Tau mAb with ^{89}Zr show that the ^{89}Zr-pTau-mAb and ^{89}Zr-Fg-pTau-mAb are stable in circulation for up to 10 days. In addition, non-toxic effects were found. However, only less than 0.2% reached the brain. In addition, we demonstrated that B6-treated mice maintained their motor and memory abilities significantly compared with IgG1 treatment. In addition, we observed a significant reduction in p-Tau levels in different parts of the brain.
Conclusions: We demonstrated that our mAb recognizes very early pathology forms of pTau by non-invasive techniques, such as ELISA and PET. In addition, mAb has non-toxic effects, both *in vitro* and *in vivo*. Although they are stable in circulation, only 0.2% reach the brain. However, direct intraventricular treatment significantly reduces cognitive impairment in Alzheimer's animal models and the accumulation of toxic p-Tau species.

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SHIFT 02-645

Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4-5 April 2025

FLUORESCENT CELLULAR MODEL FOR ALS/FTD DRUG SCREENING TARGETING TDP-25 AGGREGATES

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Aims: TDP-43 (TAR DNA-binding protein 43) plays a significant role in RNA metabolism. In neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), a specific fragment of TDP-43, known as the 25 kDa C-terminal fragment, is frequently found in pathological inclusions within neurons and glial cells.Under pathological conditions, TDP-43 and its 25 kDa fragment often mislocalize from the nucleus to the cytoplasm, disrupting normal cellular functions and promoting the formation of toxic aggregates. Here, we present a fluorescent TDP-25 aggregation cellular model to study ALS and FTD, providing a valuable tool to accelerate drug discovery.
Methods: U2OS cell line stably expressing TDP-25 tagged with the turboGreen fluorescent were treated with 50 mM sodium arsenite for 24 hours, cells were dyed with 0.5 mg/ml hoechst the last 30 ´of the sodium arsenite treatment. Fluorescent images were acquired in the Cell insight CX7 high content equipment from Thermo Fisher. The proteins aggregation was quantified with the "spot detector" application from the HCS Studio Cellomics software.
Results: 1.Live-Cell Imaging: Observe the dynamic behavior of TDP-25 in live cells to study its real-time localization and any potential aggregate formation. 2. The expression and cellular localisation of the aggregates corresponding to endogenous TDP-43 and recombinant TDP-25 have been analysed in western-blot and immunofluorescence assays before and after arsenite intoxication.
Conclusions: Treatment with 50 mM sodium arsenite induces the formation of aggregates in the TDP-25 cell line that persist even after the removal of arsenite exposure. The formation of TDP-25 aggregates does not colocalise with TDP43 stress granules. None of the reference compounds that inhibit TDP-43 aggregation have shown effectiveness in reducing TDP-25 aggregation. This cellular model is suitable for evaluating potential compounds with anti-aggregation effects.

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SHIFT 02-646

Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4-5 April 2025

ESTABLISH NEURAL CELL CULTURE FROM OLFACTORY SWABS OF HEALTHY SUBJECT

Francesco Silvestri[1], Erika Bronzato[1], Valerio Arietti[2], Elisa Marazzi[2], Ilaria Scambi[1], Michele Fiorini[1], Elena Fontana[1], Luca Sacchetto[2], Raffaella Mariotti[1], Gianluigi Zanusso[1], Matilde Bongianni[1], Ermanna Turano[1]
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Aims: The olfactory neuroepithelium (ON) is a region close to the brain that has gained increased interest as a research tool for the study of neurodegenerative diseases (NDs). It comprises olfactory sensory neurons and glial-like cells such as supporting, microvillar, and stem cells. Some pathological proteins involved in NDs have been found in olfactory neurons and supporting glial-like cells derived from nasal swabs (NS) of affected patients, suggesting complex mechanisms of protein misfolding in the ON. The study aims to isolate and characterize cells derived from the ON of healthy subjects collected by NS.
Methods: The ON was obtained from healthy controls by NS procedure performed at the level of medium and upper turbinate in both nostrils. Cells from NS were manually disaggregated and seeded in a 25 cm^2 flask or P24 wells coverslips and placed in Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12 culture medium, added by 20% fetal bovine serum, 1% penicillin/streptomycin and B27 supplement to support neuronal survival. Characterization of cells with immunocytochemistry and flow cytometry was carried out at different days of cultures.
Results: Immunofluorescence staining showed the presence of a mixed cells populations, including olfactory neurons and glial-like sustentacular cells, characterized for immunophenotypic markers and morphology. The positivity against NeuN, neurofilament, β3-tubulin, and PCK antibodies confirmed the presence of mature, immature, neuronal and sustentacular cells; furthermore, this result was confirmed also by flow cytometry.
Conclusions: The complexity of the ON provides a unique cellular resource for investigating the expression of pathological proteins associated with NDs. This approach could represent a suitable experimental model for further studies on biomarkers, neural development, and cellular alterations in the pathogenesis of human NDs.

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Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4-5 April 2025

ADP-RIBOSYLATION OF FUS IN THE DNA DAMAGE REPAIR RESPONSE

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Aims: FUS (Fused in Sarcoma) is a DNA/RNA-binding protein that is genetically linked to the neurodegenerative disorders ALS and FTD and forms aggregates in these disorders. In healthy cells, FUS primarily localizes to the nucleus where it regulates multiple DNA/RNA-related processes such as DNA damage repair, transcription, splicing, and mRNA transport. It can undergo liquid-liquid phase separation and localize to nuclear and cytosolic condensates, including sites of DNA damage and stress granules.
Methods: Published proteomics and in vitro studies suggest that FUS is ADP-ribosylated by the enzyme PARP1, and that both FUS and PARP1 are important for DNA damage response. However, it is still unknown whether and when in the DNA-damage-response FUS gets ADP-ribosylated and how FUS ADP-ribosylation affects FUS phase separation and its functions in the DNA-damage-response. We are investigating these questions using a variety of biochemical and imaging approaches *in vitro* and in cells.
Results: Our data suggest that FUS gets poly-ADP-ribosylated by recombinant PARP1 *in vitro*, suppressing FUS phase separation. Using an *in vitro* reconstituted repair foci system, we could recapitulate PARP1-dependent recruitment of FUS to damage sites and release of FUS from damage sites upon ADP-ribosylation. Additionally, we found that FUS gets ADP-ribosylated by PARP1 upon H2O2 treatment in cells. Using published proteomics datasets, we identified 4 potential ADP-ribosylation sites and mutagenesis of these sites resulted in a decrease in DNA-damage-induced ADP-ribosylation of FUS. Currently, we are investigating the impact of ADP-ribosylation of FUS on the formation/stability of DNA damage foci in cells.
Conclusions: Our research shows that FUS ADP-ribosylation contributes to regulating the DNA damage response. This highlights a new post-translational modification of FUS that could play an important functional role and a potential pathological role in FUS-associated ALS/FTD.

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4-5 April 2025

ASSESSMENT OF THE NEURODEGENERATION-ASSOCIATED GRN RISK VARIANT IN IPSC-DERIVED MICROGLIA

Roosa-Maria Willman[1], Elena Ppali[2], Heli Jeskanen[1], Raisa Giniatullina[2], Sami Heikkinen[1], Rosa Sinisalo[1], Sini-Pauliina Juopperi[1], Paula Korhonen[2], Annakaisa Haapasalo[2], Susanna Kemppainen[1], Mari Takalo[1], Henna Martiskainen[1], Ville Leinonen[3,4], Tarja Malm[5], Mikko Hiltunen[1]
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Aims: Progranulin is a lysosomal protein expressed in neurons and microglia in the brain tissue. A common variant rs5848 (C>T) in the progranulin gene (*GRN*) associates with increased risk for neurodegenerative diseases, such as limbic-predominant age-related TDP-43 encephalopathy (LATE), frontotemporal dementia and Alzheimer's disease. However, the cellular mechanisms underlying the risk-modifying effect remain elusive. Here, the functional and expressional effects of the *GRN* rs5848 risk variant were studied in human induced pluripotent stem cell (iPSC) -derived microglia (iMG).
Methods: iPSCs were generated from the skin fibroblasts of individuals who are homozygous carriers of the risk allele (TT) (n=5) and non-carriers (CC) (n=4). The iPSCs were differentiated into iMG and the cells were subsequently treated with lipopolysaccharide (LPS) followed by functional and omics-based assays.
Results: Bulk RNA-sequencing and the subsequent pathway enrichment analyses revealed that pathways related to immunometabolism (e.g., oxidative phosphorylation and fatty acid metabolism) were upregulated in the *GRN* rs5848 TT iMG when compared to CC iMG upon LPS treatment.
Conclusions: The forthcoming assays will further uncover the mechanisms underlying the *GRN* rs5848 risk variant in neurodegeneration.

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Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / CELL, MOLECULAR AND SYSTEMS BIOLOGY
4-5 April 2025

TUNING TDP-43 CONDENSATION BEHAVIOR TO UNDERSTAND THE PHYSIOLOGICAL RELEVANCE OF TDP-43 PHASE TRANSITIONS

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Aims: TDP-43 is an RNA-binding protein with important roles in RNA metabolism. It is commonly found in inclusions in patients affected by ALS, FTD, and AD. TDP-43 can undergo phase separation (PS), and partition into biomolecular condensates in cells. Dysregulation of this process is believed to favor the formation of pathological aggregates, and potentially contribute to disease progression. PS of TDP-43 most likely has physiological importance; however, it remains unclear which RNA regulatory functions of TDP-43 might require its ability to form condensates. We aim to elucidate the link between TDP-43 condensation status and its roles in RNA processing, to better understand which molecular functions of TDP-43 are dysregulated in disease.
Methods: We generated a panel of TDP-43 PS mutants with varying abilities to undergo phase separation. We characterized them in *in vitro* PS assays, e.g. using confocal microscopy, FRAP, DLS, aggregation and sedimentation assays. By stably expressing these mutant TDP-43 variants in HeLa cells in an inducible manner in the absence of endogenous TDP-43, we aim to analyze the effect of PS-altering mutations on the TDP-43-interacting proteome using mass spectroscopy and on TDP-43-dependent splicing using mRNA-sequencing.
Results: Mutations in different parts of the largely disordered C-terminal region of TDP-43 affect the protein's ability to phase separate *in vitro*, modifying the dynamics of resulting condensates and influencing TDP-43's ability to form nanoscale assemblies. In line with these *in vitro* experiments, TDP-43 PS mutants differ in their propensity to form nuclear foci in unstressed or heat stress-exposed cells.
Conclusions: TDP-43 PS behavior can be tuned *in vitro* and in cells by specific mutations, and this toolkit can be used to further investigate the relevance of TDP-43 PS for its functionality using proteomics and genomics approaches.

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Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

IPSC-BASED NEURON-MICROGLIA CO-CULTURES FOR MODELING SYNAPTIC DYSFUNCTION IN FRONTOTEMPORAL DEMENTIA

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Aims: Frontotemporal dementia (FTD) is a common cause of early-onset dementia.
The *C9orf72* hexanucleotide repeat expansion (C9-HRE) is the most common genetic cause of FTD, but there are also many sporadic FTD patients. These facts warrant the need for studies elucidating the underlying mechanisms of different forms of FTD. Our previous studies suggest changes in neurons, including synaptic morphology and function, as well as altered microglial phagocytic activity. Our aim is to utilize human induced pluripotent stem cells (iPSCs) obtained from C9-HRE-carrying and sporadic FTD patients and healthy control individuals and differentiate them to cortical neurons and microglial cells (iMGs) to reveal mechanisms of synaptic dysfunction in different forms of FTD.
Methods: Neurons are differentiated from the iPSCs using lentivirus-mediated overexpression of *NGN2*. iMGs are differentiated using a protocol mimicking primitive hematopoiesis. Neuronal cultures are used for examining synaptic alterations, such as those in gene expression and at the pre- and post-synapses. Co-cultures of neurons and iMG are utilized to assess changes in microglial activity and synaptic pruning. Both cultures are also used for microelectrode array studies measuring the neuronal network activity.
Results: The *NGN2* neuronal differentiation method has been validated and optimized for all the three study groups. C9-HRE-carrying neurons were confirmed to express typical pathological hallmarks e.g., RNA foci and DPR proteins. The neurons also expressed pre- (Syn1) and post-synaptic proteins (PSD95). Currently, we are setting up and validating the neuron-iMG co-cultures.
Conclusions: Our studies indicate that the *NGN2* differentiation method is suitable for studying molecular mechanisms related to C9-HRE and synaptic function in FTD neurons. Experiments in the neuron-iMG co-cultures are expected to uncover underlying mechanisms and contribution of microglia in synaptic dysfunction in different forms of FTD.

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SHIFT 02-654

Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

INVESTIGATING TDP-43 STRAIN VARIABILITY: IMPLICATIONS FOR TAU AGGREGATION AND NEUROTOXICITY

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Aims: The pathological aggregation of transactive response DNA-binding protein 43kDa (TDP-43) is a defining feature of frontotemporal lobar degeneration with TDP-43 (FTLD-TDP) and amyotrophic lateral sclerosis (ALS). Misfolded TDP-43 has also been implicated in limbic-predominant age-related TDP-43 encephalopathy, including up to 57% of Alzheimer's disease (AD) patients, where it correlates with cognitive decline and more severe neuropathology. Notably, TDP-43 has been shown to colocalize with neurofibrillary tangles, suggesting a pathological synergy with tau. We aim to characterize distinct TDP-43 strains and investigate their functional diversity in driving neuronal dysfunction in the context of tau co-pathology, to better understand TDP-43 and tau combined impact on neurodegeneration and their potential role in shaping clinical outcomes.
Methods: Pathological TDP-43 was isolated from the frontal cortex of AD, ALS and FTD patients and subsequently amplified using recombinant TDP-43 monomers. Tau-overexpressing primary neurons were exposed to these distinct TDP-43 variants and neurotoxicity was assessed using cell viability assays. TDP-43 and tau pathologies, synaptic function and neuroinflammation were investigated using protein blotting, ELISA and imaging techniques.
Results: Pathological TDP-43 treatment potentiated tau pathology, leading to elevated phosphorylated-tau levels. TDP-43-treated neurons exhibited synaptic deficits and morphological changes, along with an increased release of pro-inflammatory cytokines and a reduction of anti-inflammatory markers. Moreover, differences were noted between TDP strains in driving neuronal damage.
Conclusions: Preliminary data highlight the interaction between pathological TDP-43 and tau in driving neurodegeneration, emphasizing the impact of strain-specific variations on the progression and severity of neuropathology. Additionally, the heightened release of anti-inflammatory cytokines suggests that TDP-43 pathology also intensifies neuroinflammation, further amplifying neuronal vulnerability. These observations highlight the importance of considering strain heterogeneity in neurodegenerative research, as it might influence disease progression and the efficacy of therapeutic interventions.

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TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

MAPPING THE CELL TYPE-SPECIFIC MOLECULAR CHANGES ASSOCIATED WITH LATE BY SINGLE CELL TRANSCRIPTOMICS ANALYSIS

Shih-Hsiu Wang[1], Madigan Reid[2], Bella Ding[2], John Ervin[1], Tammie Tam[3], Brittany Davidson[3], Jessica Tsui[3], Alexis Combes[3], Andrew Yang[2]
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Aims: Limbic-predominant age-related TDP-43 encephalopathy (LATE) is characterized by TDP-43 inclusions predominantly in the limbic system and causes an amnestic dementia resembling Alzheimer's disease (AD). Despite the severe burden of dementia attributable to LATE, the mechanisms that lead to LATE neuropathological change (LATE-NC) is unknown. Recently, we performed bulk RNA sequencing (RNA-seq) on a cohort of subjects with LATE and controls and showed significant upregulation of inflammatory signaling (TNF-α, IFN-γ, and TGF-β) and hypoxia/angiogenesis pathways in the amygdala of subjects with LATE. To understand the cellular context of altered inflammatory and hypoxic signaling in LATE, we performed single nuclei RNA-seq to examine the cell type-specific molecular changes in all major cell types in the brain.
Methods: We used vessel isolation and nuclei extraction for sequencing (VINE-seq), a recently developed method that efficiently captures brain vascular-associated cell types for single nuclei RNA-seq, to profile the brains of 8 subjects with LATE and 8 age- and sex-matched controls. We examined the cell type proportional changes, cell type-specific pathway alterations, and differences in cell-cell interactions associated with LATE.
Results: We profiled over 70,000 nuclei and captured all of the major cell types in the human brain, including several vascular associated cell types. We observed significant differences in the percentage of oligodendrocytes, astrocytes, vascular endothelial cells (EC), and vascular smooth muscle cells (SMC) in LATE compared to controls. Similar to our bulk RNA-seq results, there was significant upregulation of inflammatory and hypoxic signaling in EC's and SMC's in LATE.
Conclusions: Our single nuclei RNA-seq results identified cell type-specific molecular changes in several vascular-associated cell types, highlighting a potential role for vascular dysfunction in the pathogenesis of LATE.

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SHIFT 02-657

Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / GENETICS, EPIDEMIOLOGY
4-5 April 2025

MUTATION IN PROGRANULIN: A WHOLE FAMILY WITH EXTRAORDINARY PHENOTYPIC VARIABILITY

Anxo Minguillón Pereiro[1], Jéssica Pouso Diz[1], Jesús García De Soto[1], Isabel Jiménez Martín[2], Alberto Ouro Villasante[3], Tomás Sobrino Moreiras[3], Beatriz Quintáns Castro[4], José Manuel Aldrey Vázquez[1], Juan Manuel Pías Peleteiro[1]
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Aims: Progranulin is codified by the GRN gene and has relevant biological functions, such as being a trophic factor and regulator of neuroinflammation and autophagy. When its levels decrease, a wide spectrum of diseases may occur, ranging from frontotemporal dementia (both its behavioral variant and primary aphasia), to Parkinson and Alzheimer diseases and also corticobasal syndrome. The purpose of our work is to report the first case in the literature of primary alexia due to a GRN mutation and the further study of the rest of his family.
Methods: We present a three-generation family in which there are two patients with a pathogenic mutation in GRN, in addition to four others with suspicion. The two index cases present primary alexia and non-fluent primary progressive aphasia (PPA). In addition, another one has PPA, two have Parkinson's disease and one has heart disease. Several tests are performed in the living subjects, such as structural and functional neuroimaging, genetics and CSF biomarkers. In addition, all available information about the deceased cases is collected.
Results: Despite phenotypic differences, the same pathogenic mutation in GRN: *NM_002087.4:c.415T>C;NP_0020078.1:pCys139Arg* , is found in heterozygosis in the cases studied. A systematic review of the literature supports the association of progranulin mutations with the spectrum of disease in patients, although there is much less data on its involvement in PD and heart disease.
Conclusions: This work presents a family with an extraordinary phenotypic variability due to the same mutation in progranulin and includes a case of exceptional presentation, such as primary alexia, in addition to the whole phenotypic spectrum with which GRN mutations have been linked.

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Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

NEUROCOGNITIVE EVALUATION FROM THE HOME: VALIDATION OF THE CUMULUS PLATFORM IN FTD AND ALS POPULATIONS

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Aims: People living with ALS (plwALS) and/or FTD (plwFTD) often experience cognitive change. However, detection can be confounded in one-off clinical/research visits due to factors including fatigue and testing anxiety. The Cumulus platform (Fig 1), consisting of a hand-held tablet with gamified cognitive tasks, and a portable dry electroencephalography (EEG) device, enables ecologically valid data collection from the home and better estimates of true performance. We assess here platform feasibility and compare the Cumulus digital tasks against traditional pen and paper neuropsychological tests.
Methods: Participants completed neuropsychological assessments in the clinic at baseline, 4 months, and 8 months. In their homes, they completed three 25-minute Cumulus sessions every 2 weeks. The gamified tasks targeted emotion recognition, working and visuospatial memory, and language while also providing EEG measures (not presented here). We analyzed usability using the System Usability Scale (SUS), adherence rate, and percentage of successful sessions. Linear mixed effects models were used to examine longitudinal cognitive performance. Case study analyses for individual participants and group-level results

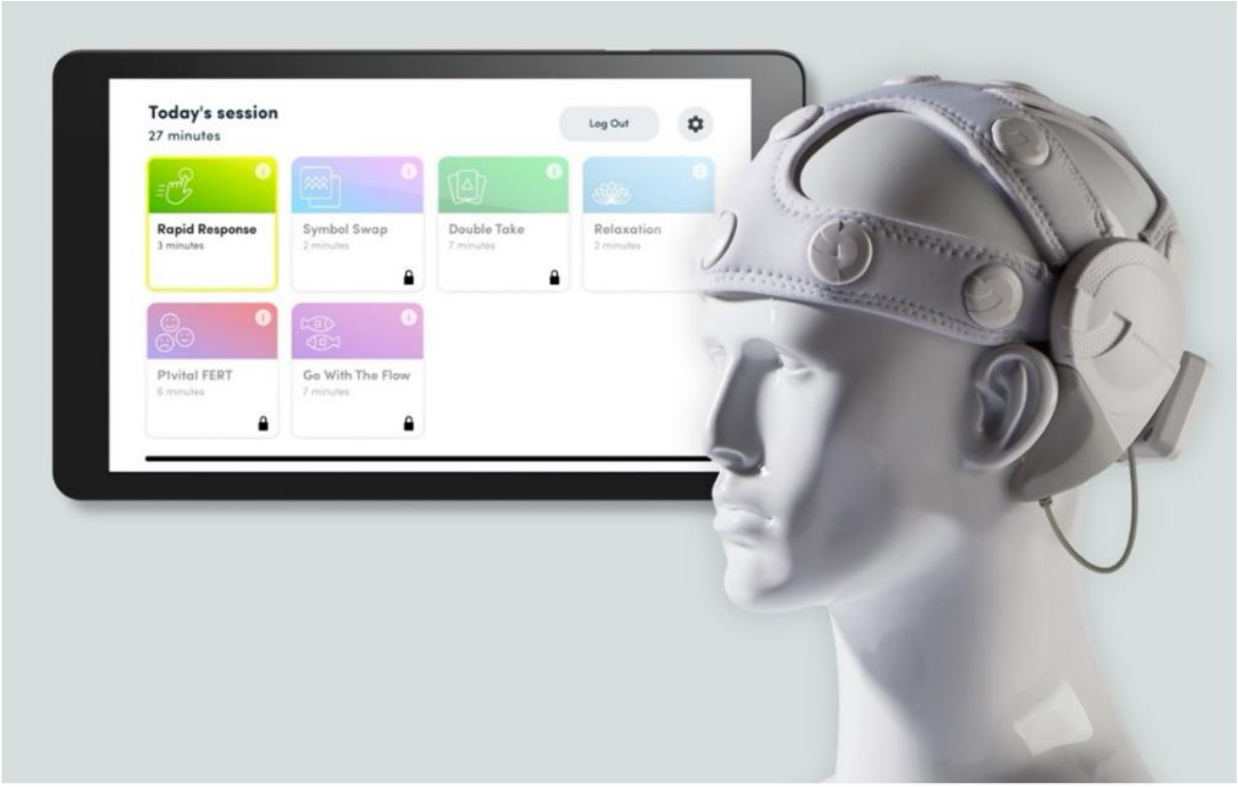

Figure 1: Cumulus Neuroscience 16-channel dry EEG headset and tablet mobile app.

are presented.

Results: Eleven plwALS, 7 plwFTD and 10 age- and education-matched controls were recruited. Adherence to the study protocol was 41% for plwALS, 59% for plwFTD and 76% for controls (Fig 2). All groups had >85% of successfully completed sessions and SUS scores >70. Longitudinal decline was not observed on benchmark cognitive tests. However, the ALS group showed significant decline on the digital emotion recognition task ($\chi2(2)=11$, $p=0.004$), and speech fluency task ($\chi2(2)=8.12$,

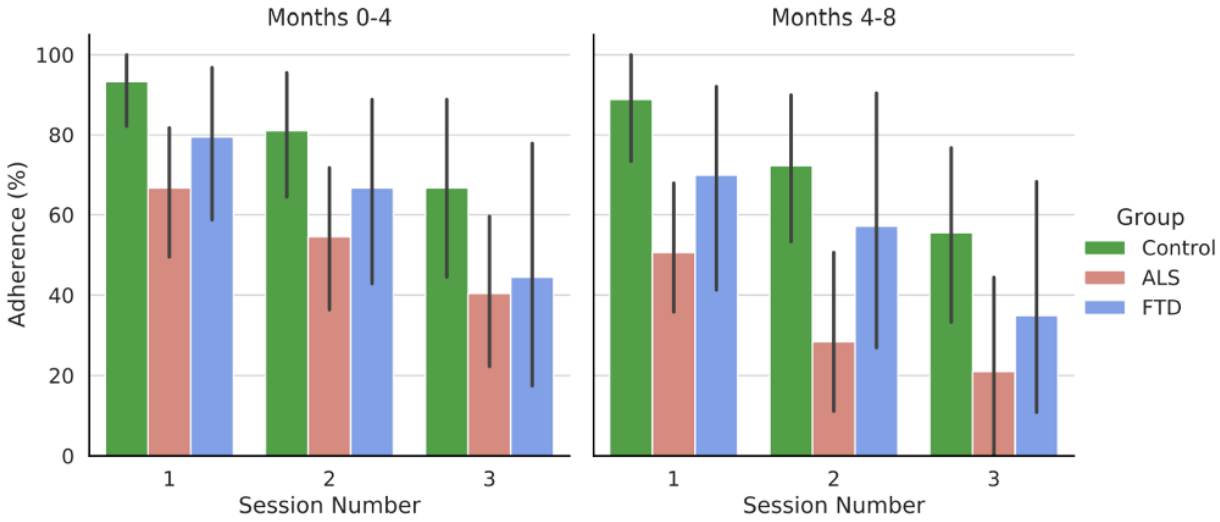

Figure 2: Adherence to the schedule of Cumulus sessions in the first and second stage of the study and within each 2-week cycle. Session 1 included Rapid Response (Psychomotor speed task), Relaxation (EEG Resting State), Sonic Cinema (Mismatch Negativity), Symbol Swap (Digit Symbol Substitution Task), and Lingo (Language Task); Session 2 included Rapid Response (Psychomotor speed task), Relaxation (EEG Resting State), Astrotap (Visual Oddball) and Double Take (N-back); Session 3 included Rapid Rapid Response (Psychomotor speed task), Relaxation (EEG Resting State), Memory Match (Associative Memory Task), Go with the flow (Flanker) and P1vital FERT (Face Emotion Recognition Task).

p=0.02).

Conclusions: These findings suggest that the Cumulus platform is feasible and usable for plwALS and plwFTD, can identify cognitive deficits to a similar extent as benchmark tests and possibly capture emotional recognition and speech fluency decline in plwALS.

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SHIFT 02-659

Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

CEREBROSPINAL FLUID NPTX2 IS SIGNIFICANTLY ALTERED IN PATIENTS WITH AMYOTROPHIC LATERAL SCLEROSIS

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Aims: Neuronal pentraxin 2 (NPTX2) has been shown to be a reliable marker for detecting synaptic dysfunction in various neurodegenerative diseases, showing reduced levels in *e.g.*, Alzheimer's Disease, dementia with Lewy bodies and Frontotemporal lobar degeneration (FTLD), among others. Recent data implicate NPTX2 in amyotrophic lateral sclerosis (ALS), where NPTX2 is aberrantly accumulated in neurons with TDP-43 pathology [Hruska-Plochan *et.al* Nature 2024]. Therefore, the aim of this project was to assess the biomarker potential of cerebrospinal fluid (CSF) NPTX2 in patients with ALS.
Methods: We included patients with ALS (n=368), aged-matched controls (n=63) and patients with other pathologies (OP) such as neuropathies and non-ALS motor neuron diseases (n=69) from two independent sources (University Hospital of Umeå; CReATe Consortium). We quantified NPTX2 using a novel ultra-sensitive in-house single molecule array (Simoa) assay developed by Gothenburg University. Group differences were examined by the Kruskal-Wallis test (with Dunn's test for multiple comparisons).
Results: There was significant difference in CSF NPTX2 levels across the diagnostic groups ($p<0.001$).

NPTX2 levels was significantly lower in both ALS (median fold change [FC]=0.73, p<0.001), and OP (FC=0.71, p<0.001) compared to controls. However, there was no significant difference between ALS and OP (p=0.22). NPTX2 distinguished ALS from controls with an AUC of 0.65 ($CI_{95\%}$=0.57-0.73). This is in line with previous NPTX2 results in neurodegenerative disorders, where CSF NPTX2 was significantly decreased compared to controls, especially in FTLD patients [Sauer et al., unpublished].

Conclusions: NPTX2 has been recently implicated in the pathophysiology of ALS. Using our novel ultra-sensitive immunoassay, we demonstrated lower levels of CSF NPTX2 in both ALS and OP patients. This approach could streamline and increase the assessment of synaptic dysfunction in ALS, providing valuable insights for disease management and treatment strategies.

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SHIFT 02-660

Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

DEVELOPING SINGLE MOLECULE MICROSCOPIC METHODS TO CHARACTERISE TDP-43 AGGREGATES IN DISEASE MODELS

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Aims: TAR DNA-binding protein-43 (TDP-43) was identified as the major disease protein in Amyotrophic Lateral Sclerosis in 2006. Aberrant disordered aggregates of TDP-43 can induce cell toxicity in various mouse and neuronal models, resulting in neuronal loss and neurite degeneration. Changes in the biophysical and biochemical properties of TDP-43 caused by oligomerisation can disrupt its physiological function, leading to loss of function. Additionally, TDP-43 proteinopathy is detected in the brains of up to 50% of AD cases across all subtypes and was shown to be associated with increased cognitive impairment and greater brain atrophy. The aim of the study is to develop single-molecule microscopy methods to characterise TDP-43 aggregates in different disease models.
Methods: In this study, two novel methods were developed to characterise TDP-43 aggregates. The first method leverages the concept of single-molecule pulldown, specifically capturing TDP-43 aggregates in a sandwich complex by using the same antibody for capture and detection. Super-resolution microscopy was integrated into this approach to further explore the size and shape of aggregates. The second method adapts the single molecule array platform developed by Quanterix for aggregates. This technique allows the detection of TDP-43 aggregates at extremely low concentrations.
Results: These two methods provide powerful tools for further investigation of TDP-43 proteinopathy in neurodegenerative disease. By monitoring closely the aggregate formation, the methods can validate the accuracy and relevance of disease models. Furthermore, these techniques enable the exploration of key biological processes in the brain , including autophagy and cellular stress response, and their effects on the pathogenesis of TDP-43 proteinopathy, enhancing our understanding of disease progression.
Conclusions: In conclusion, the feasibility of using single-molecule microscopy to specifically capture and characterise TDP-43 aggregates in various disease models was established.

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SHIFT 02-661

Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4-5 April 2025

INVESTIGATING THE PHARMACOLOGICAL ACTIVITY OF NUZ-001 ON AUTOPHAGY IN THE NSC-34 MOTOR NEURON CELL LINE

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Aims: Autophagy is a critical cellular process for maintaining neuronal homeostasis and is increasingly recognised as a key therapeutic target in neurodegenerative diseases such as MND. NUZ-001, initially developed for its anthelminthic properties, has shown promise as a therapeutic candidate for motor neuron disease (MND) due to its potential to modulate autophagy. The NSC-34 motor neuron cell line, derived from a fusion of neuroblastoma and spinal cord cells, provides a valuable in vitro model for studying MND. TDP-43 proteinopathies, including the Q331K mutation, have been strongly implicated in MND pathology, highlighting the importance of investigating autophagy in this context. This study aims to evaluate the pharmacological activity of NUZ-001 in regulating autophagy in the NSC-34 motor neuron cell line, particularly in response to exogenous TDP-43^{Q331K} aggregates. By assessing NUZ-001's effects on autophagic flux, we seek to determine its potential therapeutic relevance for MND.
Methods: NSC-34 cells will be treated with various concentrations of NUZ-001 (1 µM, 10 µM, 50 µM), and an autophagy activator Rapamycin for different time points (6, 12, and 24 hours). Autophagy assessment will be via western blotting of key markers such as LC3, p62, and Beclin-1. Cell viability assays will further determine the cytotoxic effects of NUZ-001.
Results: This study will provide valuable insights into the dose- and time-dependent effects of NUZ-001 on autophagy modulation in motor neurons. Additionally, the correlation between autophagy regulation and cellular viability will be explored, with potential implications for NUZ-001's use as a therapeutic in MND.
Conclusions: NUZ-001 may represent a novel therapeutic approach for MND by modulating autophagy in motor neurons, particularly in TDP-43-related pathology. This study will lay the groundwork for further investigation of NUZ-001's therapeutic potential in preclinical models of MND.

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Poster on Board - Shift 02
TDP43, TMEM106B AND C9ORF72-RELATED DISEASES / THERAPEUTIC TARGETS, MECHANISMS FOR TREATMENT
4-5 April 2025

SMALL MOLECULE TARGETING OF CHAPERONE {IP} PREVENTS AND REVERSES TDP-43 AGGREGATION IN VITRO AND IN VIVO

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Aims: Nuclear depletion and neuronal cytoplasmic aggregation of the transactive response DNA-binding protein 43 (TDP-43) is the most characteristic pathology of amyotrophic lateral sclerosis (ALS) and coincident frontotemporal dementia (FTD). The cytoplasmic aggregation of TDP-43 has been correlated with inducing neuronal loss. As such, preventing TDP-43 aggregation could have therapeutic potential for ALS/FTD and associated diseases. It has been shown that aggregation of TDP-43 can be attenuated by chaperone proteins. Herein, we identified small molecule JRMS as potent binder of {IP-protein} which upregulates its non-canonical chaperone function to prevent/reverse TDP-43 aggregation.
Methods: We developed high throughput models of TDP-43 aggregation by expressing the highly aggregation prone C-terminal fragment TDP-25 in cells through transient expression, mouse primary cortical neurons through lentiviral expression, and organotypic slices and mouse model through AAV9 expression.
Results: Acute and chronic treatment of JRMS reduced TDP-25 aggregation in a dose-dependent manner by ~75% in cells. This reduction of TDP-25 aggregates was validated to be dependent on {IP-protein}, and that JRMS elevates activity of the target {IP-protein}. Similarly, in mouse primary cortical neurons transduced with TDP-25 lentivirus, JRMS reduced TDP-25 aggregates by ~50% reduction. We screened JRMS on organotypic slices from 10 day-old mice inoculated with AAV9-TDP-25. Over 7-days, DMSO treated slices showed ~60% increase, while JRMS treatment showed a ~20% reduction in number of TDP-25 aggregates observed prior to treatment. Finally, two weeks treatments of AAV9-TDP-25 expressing mice at 6 weeks of age with JRMS exhibited ~30% reduction in number of aggregates compared to DMSO control.
Conclusions: We have validated JRMS as a preclinical therapeutic candidate for the treatment of TDP-43 proteinopathy. We are currently working on building a Target Product Profile (TPP) with the goal of providing a drug(s) for clinical testing.

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SHIFT 02-665

Poster on Board - Shift 02
VASCULAR DISEASES / DISEASE MECHANISMS, PATHOPHYSIOLOGY
4-5 April 2025

CEREBROVASCULAR DYSARCHITECTURE AND NEUROVASCULAR DYSFUNCTION IN AN ALZHEIMER'S DISEASE MOUSE MODEL.

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[1]Sanders-Brown Center on Aging, Lexington, United States of America, [2]University of Kentucky, Sanders-brown Center On Aging, Lexington, United States of America, [3]IU School of Medicine Neurology & Stark Neurosciences Research Institute, Neurology, Indianapolis, United States of America, [4]Walailuk University, School Of Allied Health Science, Thasala, Thailand, [5]Indiana University, Stark Neuroscience Research Institute, Indianapolis, United States of America

Aims: Several forms of cerebrovascular pathology are highly comorbid with the clinical hallmarks of Alzheimer's disease. These understudied pathological lesions could accelerate aging and disease progression. Here, we aim to investigate whether aging and a genetic predisposition to Alzheimer's disease can worsen cerebrovascular architecture and function.
Methods: Cranial window surgery was performed for intravital two-photon imaging to investigate vascular architecture, pathology, and function in the brains of young (3-5 months) and old (24 months) wild-type and Alzheimer's mouse model (Tg2576). Methoxy-X04 was used to identify Aβ plaques and cerebral amyloid angiopathy (CAA), while rhodamine dextran was used to visualize the bloodstream. Air-puff stimulation of contralateral whiskers was applied to induce penetrating arteriole dilation as a measure of neurovascular coupling in awake mice. Human brain sections were used as reference pathology. Immunochemistry and immunofluorescence were employed to confirm vascular pathology and abnormalities.
Results: A reduction in neurovascular function was observed in aged wild-type mice, and more severe impairment was found in vessels with CAA pathology in Tg2576 brains. Beta amyloid predisposition increased cortical leptomeningeal and penetrating vessel aneurysms, both blebbing and saccular. Microvessel tortuosity characteristics, including curved, looped, and folded vessels, were increased in aged wild-type mice and extensively increased in Tg2576 mice. Cerebrovascular integrity, indicated by lectin staining, was reduced, and the astrocyte marker GFAP was increased in Tg2576 compared to wild-type mice. These results highlight that the vascular pathology found in Tg2576 brains recapitulates the vascular pathology found in human brains.
Conclusions: The results suggest that aging and beta-amyloid predisposition are factors that worsen cerebrovascular function associated with vascular abnormalities. Reducing vascular risk factors and implementing additional vascular treatments may provide better outcomes for AD patients.

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Poster on Board - Shift 02
VASCULAR DISEASES / GENETICS, EPIDEMIOLOGY
4-5 April 2025

MULTI-RESPONSE MENDELIAN RANDOMISATION REVEALS CONDITIONAL EFFECTS OF CARDIOMETABOLIC RISK FACTORS ON DEMENTIA SUBTYPES

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Aims: Several cardiometabolic risk factors (RFs) have been associated not only with vascular dementia (VaD), but also with Alzheimer Disease (AD), where they may accelerate neurodegeneration. We aimed to investigate the conditional effects of cardiometabolic RFs on AD and VaD endophenotypes using a multi-response Mendelian randomisation (MR2) approach.
Methods: MR2 is designed for multiple outcomes to identify exposures that cause more than one outcome or, conversely, exert their effect on distinct responses. The studied exposures included body mass index (BMI), low-density lipoprotein (LDL), systolic blood pressure (SBP), type 2 diabetes (T2D), smoking and education, while the outcomes included Alzheimer's disease (AD), white matter hyperintensities (WMH) and small vessel stroke (SVS). We estimated the genetic correlations between the outcomes and assessed the conditional effects of the exposures on the outcomes using the false discovery rate (FDR) correction method.
Results: Genetic correlations between the outcomes were moderate for AD-WMH (r=0.25), AD-SVS (r=0.04) and WMH-SVS (r=0.168). Genetically predicted SBP was the only RF associated with two outcomes with a direct causal effect of 0.08 (P=3.7×10^{-4}) for WMH and 0.36 (2.6×10^{-14}) for SVS. Genetically predicted T2D, smoking and education showed a direct causal effect (0.11, 0.02, -0.12 respectively) with SVS only. BMI and LDL were not significant for any of the examined outcomes, conditionally on the other cardiometabolic RFs.
Conclusions: Our results suggest direct causal effects of SBP, T2D, smoking and education on SVS, a hallmark of VaD. These cardiometabolic RFs did not show associations with AD when examined jointly and conditionally on all outcomes, suggesting that their effect on AD may be mediated by their effects on SVS. Similarly, the effect of LDL on AD, WMH and SVS is likely mediated by other cardiometabolic RFs.

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SHIFT 02-672

Poster on Board - Shift 02
VASCULAR DISEASES / IMAGING, BIOMARKERS, DIAGNOSTICS
4-5 April 2025

DURAL ARTERIOVENOUS FISTULA PRESENTING AS INITIALLY REVERSIBLE ASYMMETRIC PARKINSONISM AND IMPROVEMENT OF DOPAMINE TRANSPORTER IMAGING (F-18 FP-CIT PET) AFTER ENDOVASCULAR EMBOLIZATION TREATMENT

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Aims: Dural arteriovenous fistula (DAVF) is a rare type of cerebral arteriovenous malformation, which refers to an abnormal direct connection between an intracranial artery and a dural venous sinus. A DAVF initially presenting with parkinsonism is extremely rare, and improvement of dopamine transporter imaging after embolization treatment have not been reported. Our aim is to report a case of unusual manifestation of dural arteriovenous fistula (DAVF) which showed initially reversible asymmetric parkinsonism as like Parkinson's disease and improvement of dopamine transporter imaging (F-18 FP-CIT PET) after embolization treatment.
Methods: A case study, discussing the reversible dopamine transporter functional neuroimaging, in a 58-year-old man with asymmetric parkinsonism associated with DAVF resembling Parkinson's disease is presented.
Results: A 58-year-old man referred to us due to bradykinesia and gait disturbance. His neurological examination revealed not only asymmetric parkinsonism, but also vertical gaze limitation. Brain magnetic resonance image (MRI) and cerebral artery angiography show high signal lesions in the right temporo-occipital area with obstructed right transverse and sigmoid sinus, and so he was diagnosed as DAVF. After successfully complete embolization of the right transverse and sigmoid sinus DAVF with Onyx, parkinsonism and vertical gaze limitation symptoms fully recovered and dopamine transporter functional neuroimaging also improved markedly for a long time over eight years.
Conclusions: For now, we report for the first time a rare manifestation of DAVF presenting initially reversible asymmetric parkinsonism and vertical gaze limitation and confirmed improvement of dopamine transporter imaging after rapid embolization treatment. As like this case, if there are abnormal parkinsonism and vertical gaze limitation, it should be considered diagnosis of DAVF as well as atypical parkinsonism including progressive supranuclear palsy (PSP), and treatment for neurological symptoms by DAVF with rapid endovascular embolization.