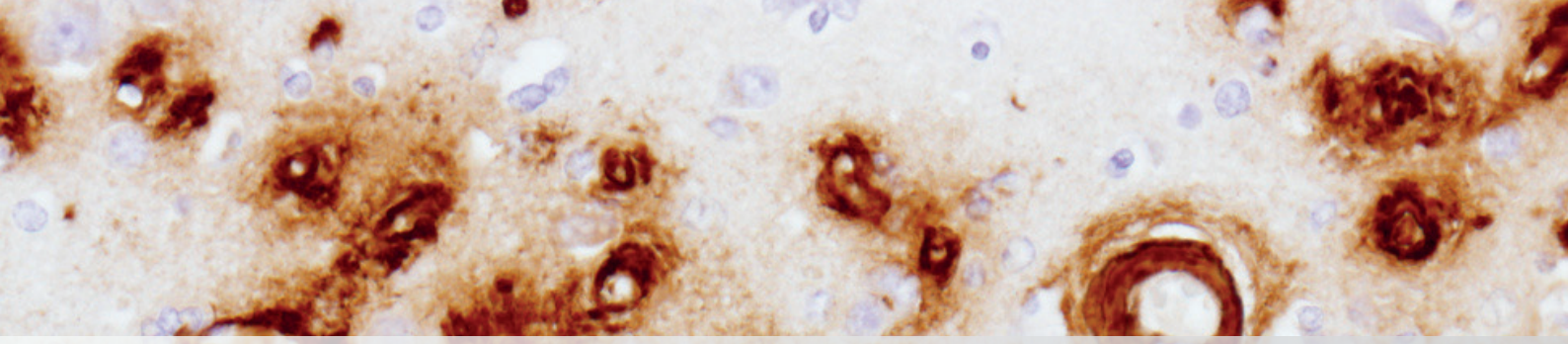

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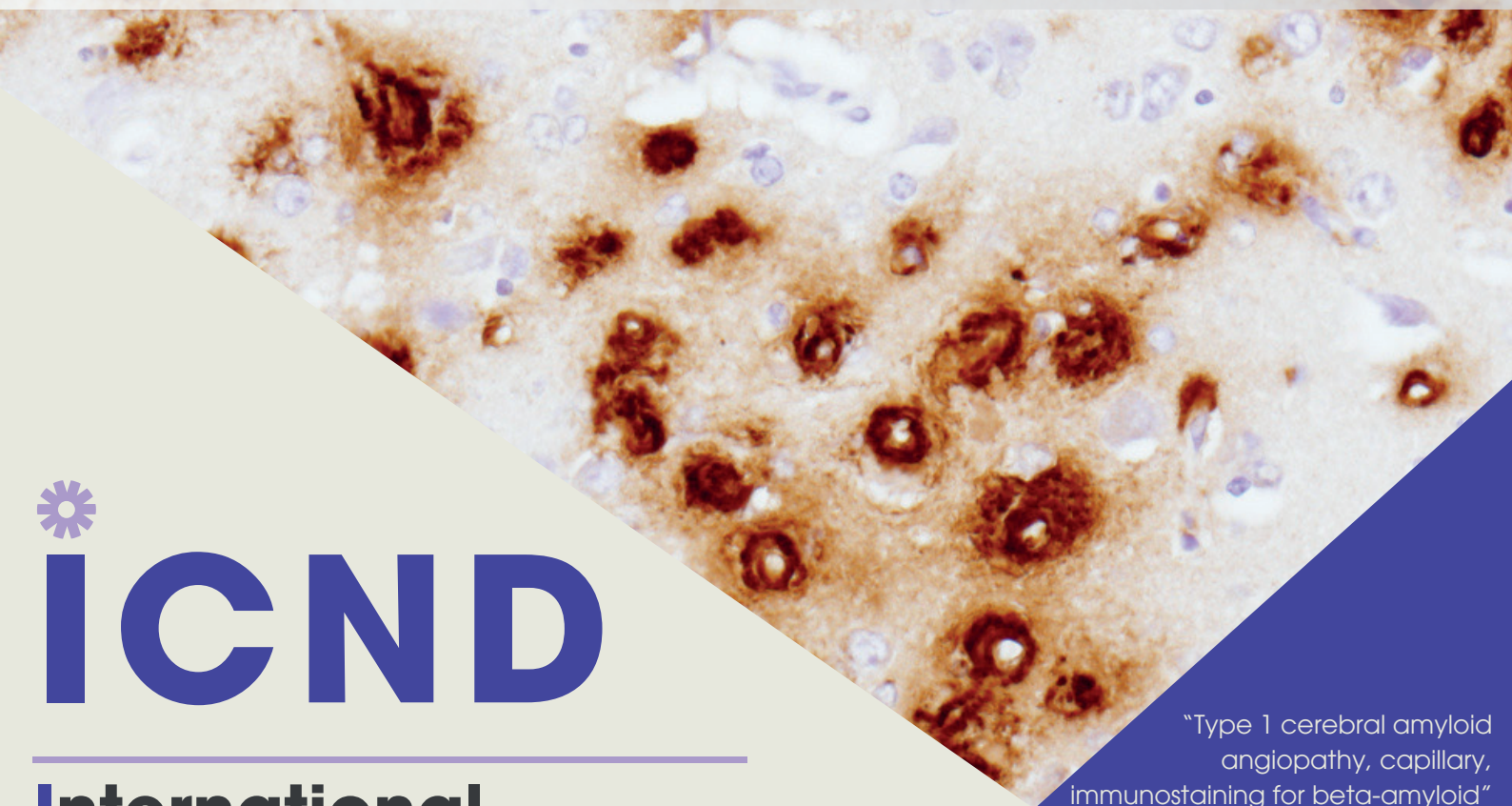

# ICND

## International Congress on Neurodegenerative Diseases

"Type 1 cerebral amyloid angiopathy, capillary, immunostaining for beta-amyloid" — Cover Image by CIEN.

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# POSTERS PRE-SELECTED FOR THE ICND 2025 BEST POSTER AWARD

The 10 pre-selected posters will be presented orally before the evaluation committee, according to the assigned dates and times.

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# BOOK OF ABSTRACTS 2025

## POSTER N.º 1

**Introduced by:** Isabel López-Torres

**Title:**

**SCAP-AD CLINICAL COHORT: RESEARCH PROJECT FOR THE EARLY DETECTION OF ALZHEIMER'S DISEASE**

**First Author:** Isabel López-Torres

**Authors:** Isabel López-Torres1, Montse Alegret2, Arcadi Navarro3, Oriol Dols-Icardo4, Mircea Balasa5, Gerard Piñol-Ripoll6, Eloy Rodríguez11, Laura Saiz1, Francisco Javier López-González1, Sonia Wagner1, Teodoro del Ser1, Belén Frades-Payo1, Elizabeth Valeriano-Lorenzo1, María Ascensión Zea-Sevilla1, Meritxell Valentí-Soler1, Mario Ricciardi1, Marta Antón1, Sergi Valero2, Agustín Ruiz2 and Pascual Sánchez-Juan1

**Filiation:** Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain; 2. Ace Alzheimer Center Barcelona (Ace), Barcelona, Spain; 3. Barcelonaβeta Brain Research Center(BBRC), Barcelona, Spain; 4. Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; 5. Hospital Clínic, Barcelona, Spain; 6. Institut de Recerca Biomèdica de Lleida, Lleida, Spain; 11. Instituto de Investigación Sanitaria Valdecilla, Santander, Spain

**Abstract:**

Objectives: Alzheimer's disease (AD) is the most common neurodegenerative disease (60-80% of dementias) that seriously impacts the lives of many patients and their families. There are no curative treatments for AD, but in recent years new drugs are being developed that could modify its course. To apply these new therapies, it is necessary to make an early and accurate diagnosis of the disease. The SCAP-AD project aims to validate precision medicine tools to identify preclinical Alzheimer's disease.

Material and Methods: The SCAP-AD is a multicenter project, coordinated by CIEN, involving 13 Spanish research centers. A clinical validation cohort (n=1,000) of subjects over 60 years of age, without a diagnosis of dementia will be recruited. Neuroimaging, plasma and cerebrospinal fluid markers studies will be performed.

Results: Currently, 681 subjects have been recruited into the clinical validation cohort. 63.7% of the sample are women; the average age is 71.93 years. The educational level is as follows: Basic reading/writing and arithmetic): 1.5%; Less than 6 years of schooling: 5.4%; 6 years of primary education: 12.4%; 8 years of primary education: 13.8%; Upper secondary education: 15.0%; Pre-university studies or professional degrees: 11.9%; University diploma: 10.0%; Bachelor's degree: 21.2%; Master's degree or Doctorate: 8.7%. Marital status is as follows: Single: 7.2%; Married, living with partner: 67.0%; Widowed, 15.6%; Separated or divorced: 10.2%.

Conclusions: This project is funded by the Instituto de Salud Carlos III (ISCIII) under the European NextGenEu funds that finance the actions of the Recovery and Resilience Mechanism and has the approval of its Research Ethics Committee.

Keywords: Alzheimer's disease, precision medicine, biomarkers, early detection.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 2

**Introduced by:** Mario Ricciardi

**Title:**

**NEUROPATHOLOGICAL VALIDATION OF THE BOSTON CRITERIA V2.0 FOR CEREBRAL AMYLOID ANGIOPATHY IN ALZHEIMER'S DISEASE DEMENTIA**

**First Author:** Mario Ricciardi

**Authors:** Mario Ricciardi[a], Iván Burgueño-García[a], Elizabeth Valeriano-Lorenzo[a], María Ascensión Zea-Sevilla[a], Meritxell Valenti[a], Belén Frades[a], Isabel López Torres[a], Marta Anton-Moreno[a], Francisco López-González[a], Paloma Ruiz[a], Laura Saiz[a], Alicia Uceda Heras[a], Linda Zhang[a], Mabel Torres Llacsa[a], Eva Alfayate Sáez[a], Marta Molero Cartón[a], María José López-Martínez[a], Teodoro Del Ser[a], Michel Grothe[a], Alberto Rábano[a], Pascual Sánchez-Juan[a]

**Filiation:** [a]Alzheimer's Centre Reina Sofía - CIEN Foundation – ISCIII

**Abstract:**

BACKGROUND AND OBJECTIVES

Cerebral amyloid angiopathy (CAA) is closely linked to Alzheimer's disease (AD) and increases the risk of Amyloid-Related Imaging Abnormalities (ARIA) in patients receiving anti-amyloid therapies. While brain MRI is the standard for detecting CAA, its effectiveness in this population remains understudied. This study aimed to evaluate the diagnostic performance of the Boston criteria version 2.0 for CAA diagnosis in individuals with advanced AD and neuropathological confirmation.

METHODS

The study included 63 individuals from the VARS cohort of the Alzheimer's Centre Reina Sofía - CIEN Foundation, a clinicopathological cohort of dementia patients, with no history of intracranial haemorrhage. Each underwent antemortem MRI with T2 flair and GRE sequences, and a brain autopsy assessing CAA with the modified Vonsattel scale. The accuracy of the Boston v2.0 criteria was evaluated against neuropathologically confirmed CAA.

RESULTS

The mean age at MRI was 84.7 years, with a median time from MRI to death of 2.5 years. Most participants were women (86%), and 73% had neuropathologically confirmed moderate or severe CAA. Boston v2.0 criteria were not met by 60.3% of subjects, yet 45% of them had moderate or severe CAA. The criteria had a sensitivity of 40.8% and specificity of 64.2% for probable CAA (AUC 0.52), and a sensitivity of 83.7% and specificity of 35.7% for possible CAA (AUC 0.51).

CONCLUSIONS

The Boston v2.0 criteria have low accuracy in patients with AD dementia. New biomarkers are needed to improve the diagnosis of CAA in this population in order to optimize the safety of treatment with anti-amyloid drugs.

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## POSTER N.º 3

**Introduced by:** Francisco J. López-González

**Title:**

**CHOLINERGIC WHITE MATTER PATHWAYS IN ALZHEIMER'S DISEASE, DEMENTIA WITH LEWY BODIES, AND OTHER NEURODEGENERATIVE DISEASES: A POST-MORTEM MRI STUDY**

**First Author:** Francisco J. López-González

**Authors:** Francisco J. López-González[a], Milan Nemy[b], Cene Jerele[bc], Alberto Rábano[a], María José López Martínez[a], Pascual Sánchez-Juan[a], Michel J. Grothe[a], Daniel Ferreira[b]

**Filiation:** [a]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain, [b]Division of Clinical Geriatrics, Center for Alzheimer Research, Department of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm, Sweden, [c]University of Ljubljana, Faculty of Medicine, Ljubljana, Slovenia

**Abstract:**

Background

We propose an imaging-pathologic validation study aimed at investigating cholinergic WM pathways using post-mortem MRI of autopsy-confirmed AD, Lewy body dementia (LBD), mixed pathology (AD+LBD), other neurodegenerative diseases across the frontotemporal lobar degeneration (FTLD) spectrum (OD) and cognitively unimpaired donors (CU).

Methods

We included 55 brain donors (21 AD, 14 AD+LBD, 8 LBD, 7 OD and 5 CU). All donors underwent post-mortem MRI in situ and a neuropathological examination. Mean diffusivity (MD) maps were estimated using the FSL software for each donor and for two cholinergic WM pathways of interest: cingulum and external capsule. Moreover, regional cholinergic WM signal abnormalities were visually scored on FLAIR images using the Cholinergic Pathways HyperIntensities Scale (CHIPS). Differences in MD, CHIPS and in age-adjusted values/scores (after excluding the CU group) between groups were analysed using the Mann-Whitney U-test.

Results

AD donors were older than LBD ($p=0.01$) and than OD ($p=0.02$); and CU donors are significatively younger than all other groups ($p<0.02$). AD and AD+LBD showed higher MD values in cholinergic WM pathways when compared with OD (Cohen's $d\geq0.5$, $p=0.05$) and LBD (Cohen's $d\geq1.3$, $p<0.01$). Qualitatively similar findings were obtained after adjusting for age but at lower effect size and statistical significance

Conclusions

We confirmed the degeneration of cholinergic WM pathways in neuropathologically confirmed dementia groups. This degeneration is more severe in the AD groups than in the LBD group possibly due to differences in the degree of disease/dementia severity. Additionally, DTI-based indices of cholinergic pathway integrity strongly correlate with CHIPS-based visual assessment.

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## POSTER N.º 4

**Introduced by:** Linda Zhang

**Title:**

**INCREASED HIPPOCAMPAL CORTICAL MEAN DIFFUSIVITY IN COGNITIVELY UNIMPAIRED INDIVIDUALS WITH ELEVATED PLASMA %PTAU217**

**First Author:** Linda Zhang

**Authors:** Linda Zhang[a], Jesus Silva Rodriguez[a], Eva Alfayate[a], Sonia Wagner Reguero[a], Pascual Sanchez Juan[a], Michel J Grothe[a]"

**Filiation:** [a]CIEN Foundation, Reina Sofia Foundation Alzheimer Centre, Madrid, Spain

**Abstract:**
Background: Plasma ptau217 has emerged as a reliable early biomarker for Alzheimer's disease pathology. Cortical mean diffusivity (cMD) derived from diffusion-weighted imaging are thought to reflect early microstructural changes before detectable structural atrophy and white matter alterations in neurodegenerative diseases. While ptau217 has been shown to correlate with cortical atrophy in cognitively normal individuals, its relationship with cMD is unclear.
Methods: 924 cognitively unimpaired elderly participants (mean age: 74.8, range: 69-87; 65% female) with 3T MRI and plasma ptau217 measures were selected for baseline cross-sectional analyses from the Vallecas Project cohort, a single-centre 12-year longitudinal study with annual follow-ups. Plasma ptau217 and non-ptau217 levels were measured using mass spectrometry, and the ratio between them (%ptau217) was used to stratify participants into four risk groups: Low, Intermediate, Elevated, and High. Diffusion-weighted images were preprocessed using an in-house pipeline. Hippocampal cMD and hippocampal cingulum white matter MD were extracted and compared between groups, controlling for age, sex, and APOE ε4 carriership.
Results: There was no difference between groups in sex distribution, although individuals with higher %ptau217 levels were significantly older ($p<0.01$). Only those in the High risk group had lower global cognition and memory scores ($p<0.01$). Hippocampal cMD was significantly higher in Intermediate vs. Low and High vs. Low %ptau217 group comparisons, but not in hippocampal cingulum MD.
Conclusions: In our study of a large-scale, well-characterised cognitively unimpaired population, changes in cMD can already be observed in those with elevated plasma %ptau217, and appears to be more sensitive than white matter changes.

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## POSTER N.º 5

**Introduced by:** Cristina Sánchez-Martín

**Title:**

**BASELINE AND LONG-TERM LONGITUDINAL ATROPHY PATTERNS OF COGNITIVELY UNIMPAIRED INDIVIDUALS WITH INTERMEDIATE AND HIGH LEVELS OF PLASMA PTAU-217**

**First Author:** Cristina Sánchez-Martín

**Authors:** Cristina Sánchez-Martín[a], Linda Zhang[a], Jesús Silva-Rodríguez[a], Elizabeth L. Valeriano-Lorenzo[a], Francisco J. López-González[a], Sonia Wagner-Reguero[a], Teodoro del Ser[a], Pascual Sánchez-Juan[a], Michel J. Grothe[a]

**Filiation:** [a]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Madrid, Spain

**Abstract:**
Background: Plasma p-tau217 exhibits a strong association with AD pathological changes. However, little is known about how baseline p-tau217 predicts neurodegeneration. This study aims to characterize cross-sectional and longitudinal patterns of gray matter atrophy in cognitively unimpaired (CU) individuals with intermediate and high baseline plasma p-tau217 levels.
Methods: 924 CU older individuals (74.7±3.9 yrs; 65.8% female) from the Vallecas Project cohort at the CIEN Foundation (Madrid) were included in this study. All participants underwent blood sampling, clinical and neuropsychological evaluations, and 3T-MRI scanning at baseline, and 824 individuals had annual longitudinal follow-up assessments for up to ten years (average follow-up: 6.3±3.5 yrs; for a total of 4464 MRI acquisitions). Baseline plasma %p-tau217 was measured using mass spectrometry, and individuals were classified into three risk categories based on a pre-established two-cut-off model. T1 MRI images were processed in CAT12 to obtain segmented gray matter maps, which were analyzed using both ROI-based and voxel-wise approaches. Cross-sectional analyses employed ANCOVA models and longitudinal analyses employed linear mixed effects models. Finally, a mediation analysis was performed to determine whether plasma p-tau217 affects cognitive decline through its impact on longitudinal hippocampal atrophy.
Results: Participants were classified as having Low (n=636, 68.8%), Intermediate (n=138, 14.9%), and High (n=150, 16.2%) %p-tau217. At baseline, the High group showed significantly more atrophy compared to the Low group in the medial temporal lobe (MTL), specifically in the hippocampus and the amygdala (Fig 1). Longitudinally, atrophy trajectories in the Intermediate and High groups were significantly different compared to the Low group (Fig 2, Fig 3), showing faster atrophy, particularly, in the MTL, temporo-parietal and medial frontal regions. Additionally, the hippocampus partially mediated the effect (30.8%) of plasma p-tau217 on cognitive decline.
Conclusions: At baseline, higher levels of p-tau217 were associated with a greater degeneration, as well as with a faster atrophy progression. In addition, the effect of p-tau217 on cognitive decline was, partially, mediated by the longitudinal hippocampal atrophy.

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## POSTER N.º 6

**Introduced by:** Anabela Câmara

**Title:**

**AMYLOID BETA-RELATED ANGIITIS PRESENTING WITH RECURRENT FOCAL DEFICITS AND COGNITIVE DECLINE: A CASE REPORT**

**First Author:** Anabela Câmara

**Authors:** Anabela Câmara[ab], Joana Milhazes Pinto[c], Aurora Costa[c], Setfanie Moreira[c], Eduardo Freitas[c], Carla Ferreira[c], Sofia Rocha[c]

**Filiation:** [a]- Serviço de Neurologia do Centro Hospitalar do Funchal, Portugal, [b] - Serviço de Neurologia da ULS Braga, Portugal, [c]Serviço de Neurologia da ULS Braga, Portugal

**Abstract:**
Amyloid beta-related angiitis (ABRA) is a rare inflammatory response to beta-amyloid deposition in cerebral vessel walls. It may present with cognitive decline, seizures, or focal neurological deficits and can mimic other central nervous system pathologies.
We report the case of a 78-year-old woman with atrial fibrillation on anticoagulation, who presented via stroke fast-track with sudden-onset left brachiofacial paresis. Non-contrast CT revealed focal cortical hyperdensities in the right frontal convexity, suggestive of petechial hemorrhage. In the preceding months, she had progressive disorientation, memory impairment, and behavioral changes. MRI findings included haemosiderin deposition and superficial haemosiderosis in the right frontolateral region. Concurrently, she developed an acute confusional state, resolving within five days. Extensive blood tests were unremarkable. CSF showed mild hyperproteinorrhachia, reduced Aβ42/Aβ40 ratio, and elevated p-tau. Autoimmune and infectious panels were negative.
One month later, she re-presented with transient focal symptoms and confusion. Imaging showed new right frontal juxtacortical hyperdensities with edema. EEG was normal; MRI revealed diffusion restriction in the right centrum semiovale and T2/FLAIR hyperintensity. A diagnosis of possible ABRA was considered.
She was treated with intravenous methylprednisolone followed by oral prednisolone, with radiological improvement. Mycophenolate mofetil was added, and anticoagulation was discontinued with left atrial appendage closure. She remained clinically stable with no further deficits or cognitive decline.
ABRA is a potentially reversible cause of subacute cognitive decline and focal deficits. Early recognition and immunosuppressive therapy may prevent irreversible damage and improve outcomes.

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## POSTER N.º 7

**Introduced by:** Felipe Hernández-Villamizar

**Title:**

### AGE-RELATED BLOOD PROTEINS DISPLAY SEX-SPECIFIC ASSOCIATIONS WITH COGNITION AND ALZHEIMER'S BIOMARKERS

**First Author:** Felipe Hernández-Villamizar

**Authors:** Felipe Hernández-Villamizar[afb], Luisa Braun-Wohlfahrt[h], Greta García-Escobar[fg], Marina de Diego[af], Helena Blasco[af], Paula Ortiz-Romero[af], Esther Jiménez-Moyano[af], Rosa María Manero-Borràs[g], José Contador[afg], Isabel Estragués[afge], Irene Navalpotro-Gómez[afg], Oriol Grau-Rivera[afgd], Aida Fernández-Lebrero[afge], Marta del Campo[af], Albert Puig-Pijoan[afg], Federica Anastasi[afc], Marc Suárez-Calvet[afg]

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**Abstract:**

Peripheral blood factors influence brain aging in animal models, but their role in humans, especially in Alzheimer's disease (AD), remains unclear. We investigated whether these proteins are associated with AD biomarkers and cognition in cognitively impaired patients.

This cross-sectional study analyzed 10 age-related blood proteins in 366 cognitively impaired participants from the BIODEGMAR cohort (Hospital del Mar, Barcelona; median age: 74.4 years; 57% women; 44% APOE-ε4 carriers; 62.8% CSF amyloid-positive). Proteins and AD biomarkers were measured using ELISA, MSD, Simoa, or Lumipulse. Linear regressions assessed associations with age and cognition, with sex and amyloid status as modifiers. False discovery rate (FDR) correction was applied to the linear regressions.

Osteocalcin and Klotho levels were higher in women, while β2-microglobulin levels were higher in men. Older age was linked to higher β2-microglobulin (β=+0.189, FDR-p=0.002), TIMP2 (β=+0.240, FDR-p<0.001), and sVCAM1 (β=+0.160, FDR-p=0.008). Sex modified associations of CCL19, Klotho, and TIMP2 with age: in men, age was linked to lower CCL19 (β=-0.204, FDR-p=0.027), lower Klotho (β=-0.168, p=0.040), and higher TIMP2 (β=+0.382, FDR-p<0.001). Higher CCL2 and β2-microglobulin were associated with worse cognition overall. In women, higher CCL11 correlated with poorer executive function (β=+0.321, FDR-p=0.030). Finally, higher α-Klotho correlated with lower plasma p-tau217, NfL, and higher CSF Aβ42/p-tau181, only in men.

Sex modulates the relationship between age-related blood factors, age, cognition, and AD biomarkers. Klotho was protective in men, whereas CCL11 was associated with poorer cognition in women. These findings support sex-specific biological pathways in aging and neurodegeneration.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 8

**Introduced by:** Alfredo J. Miñano-Molina

**Title:**

**VALIDATION OF A SYNAPTIC-RELATED BLOOD-BASED BIOMARKER FOR EARLY DIAGNOSIS OF ALZHEIMER'S DISEASE**

**First Author:** Alfredo J. Miñano-Molina

**Authors:** Alfredo J. Miñano-Molina[ca], Débora Ricciarelli[d], Olivia Belbin[ea], Daniel Alcolea[ea], Juan Fortea[ea], Alberto Lleó[ea], José Rodríguez-Álvarez[cab]

**Filiation:** [a]Institut de Neurociències i Departament de Bioquímica i Biologia Molecular. Universitat Autònoma de Barcelona, Spain, [b]Centro de Investigación Biomédica en Red en Enfermedades Neurodegenerativas (CIBERNED), Madrid, Spain, [c]Institut de Neurociències i Departament de Bioquímica i Biologia Molecular. Universitat Autònoma de Barcelona, Spain, [d]Sant Pau Memory Unit, IR SANT PAU, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [e]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, New York, USA

**Abstract:**

Synaptic dysfunction is believed to occur during the preclinical stages of Alzheimer's disease (AD), before neuronal loss and classical pathological hallmarks. microRNAs (miRNAs) are promising candidates for non-invasive biomarkers due to their stability in biofluids like plasma. We previously proposed a synaptic-related miRNA signature (miR-92a-3p, miR-181c-5p, miR-210-3p) as a potential early biomarker for AD. This study aimed to evaluate its diagnostic performance, measured by RT-qPCR, in a new patient cohort across AD clinical stages.

We analyzed plasma samples from participants at the Sant Pau Memory Unit, classified as controls, mild cognitive impairment (MCI) not due to AD, MCI due to AD (prodromal AD), or AD dementia based on CSF pathology (p-tau181/Aβ1-42 ratio). Primary outcomes included cognitive decline (MMSE score change) and progression to dementia. miRNA levels were compared between groups using significance threshold of $p < 0.05$. ROC curves and logistic regression were used to assess sensitivity, specificity, and diagnostic value of individual and combined miRNAs.

From 200 participants (mean age 69.7 ± 4.1 years; 51.5% female), 36.3% of plasma samples were hemolyzed. miRNA levels increased with AD progression, consistent with previous findings. However, all AUC values were below 0.70 indicating limited diagnostic accuracy in this cohort. Despite this, miRNA levels remained significantly associated with AD progression.

These findings suggest that although this miRNA signature shows limited diagnostic performance, it may still hold potential as marker of disease stage, and further validation in larger and diverse cohorts is needed to confirm its utility in early-stage AD detection.

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## POSTER N.º 9

**Introduced by:** Adriana Gea González

**Title:**

**SOCS PROTEINS IN MICROGLIA FROM ALZHEIMER'S DISEASE**

**First Author:** Adriana Gea González

**Authors:** Adriana Gea González[eca], María Ángeles Cortés Gómez [eca], Dimitri Budinger [f], Sergio Fuster Picher[c], Víctor Manuel Barberá Juan [d], Javier Sáez Valero[cab], María Salud García Ayllón[eca]

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**Abstract:**

Alterations in the expression of suppressor of cytokine signaling proteins (SOCS) have been demonstrated in a variety of diseases, including cancer and autoimmune disorders. The dysregulation of cytokine signaling pathways may play a critical role in the pathogenesis of Alzheimer's disease (AD). However, there is little information regarding regulatory functions of SOCS proteins in AD.

Levels of SOCS1 and SOCS3 were analyzed in brain samples of control subjects and AD patients via western blot and qPCR. Microglial cells were obtained from AD patient-derived induced pluripotent stem cells (iPSCs) and treated with lipopolysaccharide and amyloid-beta to induce the immune response. SOCS1 and SOCS3 were also knocked-out from iPSCs from AD patients and isogenic controls via CRISPR/Cas9.

Different SOCS proteins presented contrasting patterns of expression, as SOCS3 was increased in AD patients' brains, whilst SOCS1 remained unchanged. There was a similar pattern in microglia derived from AD patients after their exposure to pro-inflammatory agents as LPS and Aβ. SOCS1 and SOCS3 genes were targeted in different iPS cell lines, resulting in the suppression of their expression. Cells were also free from any genomic footprint and demonstrated normal pluripotency. These cells will be used to further characterize the SOCS response in the context of AD.

Our results suggest that the SOCS response could be altered in the AD brain, thus failing to participate correctly in the anti-inflammatory system. This study provides novel insights into the role of anti-inflammatory regulators SOCS proteins in AD pathogenesis, highlighting their potential as therapeutic targets for the disease.

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## POSTER N.º 10

**Introduced by:** Isabel Liste

**Title:**

**MODELLING ALZHEIMER'S DISEASE USING HUMAN CEREBRAL ORGANOIDS AT THE CELLULAR AND MOLECULAR LEVEL**

**First Author:** Patricia Mateos Martínez

**Authors:** Isabel Liste[c], Patricia Mateos Martínez[ca], Raquel Coronel[c], Rosa González Sastre[ca], Sabela Martín Benito[ca], Cristina Soriano[ca], Victoria López Alonso[b]

**Filiation:** [a]Unidad de Regeneración Neural, Unidad Funcional de Investigación de Enfermedades Crónicas, Instituto de Salud Carlos III, Majadahonda, 28220 Madrid, Spain, [b] Unidad de Biología Computacional, Unidad Funcional de Investigación de Enfermedades Crónicas, Instituto de Salud Carlos III, Majadahonda, 28220 Madrid, Spain, [c]Unidad de Regeneración Neural, Unidad Funcional de Investigación de Enferm Unidad de Biología Computacional, Unidad Funcional de Investigación de Enfermedades Crónicas, Instituto de Salud Carlos III, Majadahonda, 28220 Madrid, Spain

**Abstract:**

Alzheimer's disease (AD) is the leading cause of dementia in the elderly. AD brains are characterized by the presence of neurofibrillary tangles and amyloid plaques, caused by an increase in hyperphosphorylated Tau protein and amyloid beta (Aβ) peptide, respectively.

Cellular and molecular alterations in AD are known to begin decades before the appearance of the first clinical symptoms. In addition, there is an urgent need to develop new and more translational human models to understand the molecular mechanisms of AD evolution.

We have used the protocol previously established in our laboratory to generate and characterize human cerebral organoids (hCOs) with mutations associated with familial AD (PSEN1 mutation G206D or APP duplication) and controls.

We observed an increase of p-Tau as well as the Aβ42/40 ratio in hCOs with AD mutations compared to controls. After proteomics studies, several of the proteins used in clinical practice as AD biomarkers were detected in hCOs with the PSEN1 mutation: proteins associated with axon development (GAP43), microtubule stabilization (NEFL, MAPT, DCX, MAP6), involved in oxidative stress processes (SOD1, CAT, TXN), astrogliosis (GFAP, S100β), calcium signaling in neurons (VSNL1, STX1B), and APP processing pathway (BACE1, APP).

Since there is currently no effective treatment to stop or slow the neurodegeneration that occurs in AD, hCOs with AD mutations may be a useful tool to investigate the mechanisms that trigger AD, analyze the effects of various drugs and to advance the development of future new therapies for AD.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 11

**Introduced by:** Silvia de Santis

**Title:**

**DISSECTING THE ASSOCIATION BETWEEN MRI MICROSTRUCTURAL EARLY ALTERATIONS AND PLAQUE-ASSOCIATED MICROGLIA REACTIVITY IN ALZHEIMER'S DISEASE MOUSE MODEL**

**First Author:** Patricia Martínez-Tazo

**Authors:** Patricia Martínez-Tazo[a], Antonio Cerdán-Cerdá[a], Emma Mcnulty Saxton[a], Aroa S.Maroto[a], Jose Vicente Sánchez Mut [a], Silvia De Santis[a]

**Filiation:** [a]Institute of Neuroscience of Alicante UMH-CSIC

**Abstract:**

Microstructural damage in Alzheimer's disease begins years before cognitive symptoms appear [1]. Non-invasive tools to detect early Alzheimer-specific patterns, like early neuroinflammation that later turns chronic, are urgently needed. Advanced diffusion-weighted (dw) MRI biomarkers capturing microglia morphology changes have become available [2], making inflammation a potential early target. Here, we tested the association between dwMRI inflammation markers and glia changes over time in APP/PS1 mice and controls.

METHODS: APP/PS1 mice and controls (15/20, 50%f) were scanned at 3, 4.5, 6, 9, and 12 months (7T Bruker). Conventional and advanced dwMRI were used to extract DTI markers (MD) and inflammation-sensitive metrics (FR, KW). MRI parcellation used the MouseX-DW-ALLEN Atlas [3]. A subset (4/4) was perfused and stained for plaques (6E10), nuclei (DAPI) and microglia (Iba-1), segmented with QUINT [4] (Figure1a). Z-score highlighted regions and MRI markers discriminating groups. Pearson correlation assessed MRI–histology associations at each stage.

RESULTS AND DISCUSSION: Histology showed early amyloid deposition and periplaque microglia in APP/PS1 (Figure1b) and allowed segmenting clustered microglia (Figure1c). MRI revealed sensitivity to group differences starting at 3 months and increasing in time (Figure1d). Correlation between histology and MRI revealed stage-specific associations (Figure 1e-f). Process dispersion (KW) and mean diffusivity (MD) showed progressively stronger negative correlations with microglia at mid (6) and late (9–12) stages, reflecting progressive pathology (*p < 0.05, **p < 0.01, ***p < 0.001). Interestingly, at early stages (3–4.5), restricted fraction (FR) showed a positive correlation, suggesting increased diffusion restriction near early deposits. These preliminary results point at FR as a non-invasive marker sensitive to early-stage Alzheimer-specific microstructure.

[1] Sochocka, 2019 [2] Garcia-Hernandez, 2022 [3] Martínez-Tazo, 2024 [4] Yates, 2019.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 12

**Introduced by:** Andrea Alonso Gómez

**Title:**

**ALZHEIMER'S DISEASE IN THE HUMAN OLFACTORY BULB: A STEREOLOGICAL AND MOLECULAR ANALYSIS FROM A SEX-BASED PERSPECTIVE**

**First Author:** Andrea Alonso Gómez

**Authors:** Andrea Alonso Gómez[a], Ana Paula Flores Thomas[a], Carmen Soriano Herrador[a], José Luis Montesinos Vinader[a], Verónica Astillero López[a], Isabel Úbeda Bañón[a], Alicia Flores Cuadrado[a], Daniel Saiz Sánchez[a], Alino Martínez Marcos[a]

**Filiation:** [a]Neuroplasticity and Neurodegeneration Group, IB-UCLM, Ciudad Real Medical School, University of Castilla-La Mancha, IDISCAM

**Abstract:**

Alzheimer's disease (AD) is the most prevalent neurodegenerative disorder and the leading cause of dementia worldwide. Its incidence and prevalence are nearly twice as high in women as in men. However, biological sex has been systematically underrepresented in AD research. Neuropathologically, it´s characterized by the accumulation of aberrant proteins (amyloid-β and hyperphosphorylated tau), which promote neurodegeneration and reactive gliosis. Previous studies have reported the presence of these aggregates in the olfactory bulb (OB) during early stages of the disease. Interestingly, loss of smell (hyposmia) may appear before clinical diagnosis.

This study aims to stereologically and molecularly characterize alterations in volume, neurodegeneration, and glial reactivity in the human OB during AD, focusing on sex-based differences.

Fifty post-mortem OB samples from non-diseased individuals and patients with diagnosed AD were analyzed: 30 for stereological and 20 for molecular studies. All groups included a balanced representation of both sexes. Stereological analysis included OB volume estimation using the Cavalieri method, neuronal density via Optical Fractionator probe, and glial reactivity with the Area Fraction Fractionator probe. No significant differences in OB volume were observed between AD and control groups. Conversely, a significant reduction in neuronal density was found in AD cases, specifically in male individuals.

Future molecular analyses will evaluate disease-related proteins (p-Tau, amyloid-β) and markers of neurodegeneration (NeuN) and glial reactivity (Iba-1, GFAP) with western blotting.

We gratefully acknowledge the donors and the Spanish Biobank Network. Funding was provided by UCLM/ERDF (2022-GRIN-34200), JCCM/ERDF (SBPLY/21/180501) and MICINN (PID2019-108659RB). AAG was supported by a UCLM/FSE+ predoctoral contract.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 13

**Introduced by:** Victoria Pozzi-Ruiz

**Title:**

**PM20D1-DERIVED N-OLEOYL-LEUCINE INDUCES MICROGLIA ASSOCIATION WITH AMYLOID PLAQUES AND IMPROVES NEURONAL FITNESS IN ALZHEIMER'S DISEASE**

**First Author:** Victoria Pozzi-Ruiz

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**Abstract:**
Peptidase M20 Domain Containing 1 (PM20D1) has recently emerged as a novel neuroprotective factor for Alzheimer's disease (AD) and other neurodegenerative disorders. However, the mechanisms by which PM20D1 confers protection remain poorly understood. Here, we show that N-Oleoyl-Leucine (OLE), a bioactive metabolite of PM20D1, ameliorates AD-related pathologies across multiple experimental AD models. In the GMC101 strain of C. elegans, OLE alleviates motility deficits and amyloid aggregation. Similarly, in APP/PS1 transgenic mice, OLE reduces cognitive deficits and amyloid burden. Notably, in mice, OLE promotes the recruitment of microglia to amyloid (Aβ) plaques favoring Aβ compaction, particularly in large amyloid plaques, which is accompanied by a reduction in the peri-plaque neuronal damage. These effects are recapitulated in vitro, where OLE increases Aβ chemotaxis and clearance in microglia, and protects neurons from protein misfolding and oxidative stress. Finally, we also find evidence of a PM20D1- and OLE-mediated microglia association with amyloid plaques and enhanced neuroprotection in human AD brains. In sum, our results provide mechanistic insights on the protective role of PM20D1 in neurodegeneration and support the use of OLE as a microglia-modifying agent for the treatment of AD.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 14

**Introduced by:** Rocío Pérez-González

**Title:**

**PROTEOMIC PROFILING OF CIRCULATING EXTRACELLULAR VESICLES IN CARRIERS OF THE ALZHEIMER'S-LINKED PRESENILIN-1 E280A MUTATION**

**First Author:** Rocío Pérez-González

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**Abstract:**

Introduction: Circulating extracellular vesicles (EVs) are emerging as promising sources of biomarkers for neurodegenerative diseases. In this study, we characterized EVs derived from plasma of both non-symptomatic and symptomatic carriers of the familial Alzheimer's disease (AD)-associated "Paisa" E280A mutation in the presenilin-1 gene, recognized as the largest and most genetically homogeneous AD family cohort described to date.

Materials and Methods: EVs were isolated from EDTA-plasma using Size-Exclusion Chromatography (SEC) followed by ultrafiltration in three groups: non-symptomatic mutation carriers (N=20), symptomatic carriers (N=10), and healthy controls (N=10). For proteomic analysis, 200 ng of FASP-digested proteins were analyzed on a timsTOF Pro mass spectrometer with PASEF, coupled to an Evosep ONE liquid chromatography system. Data-independent acquisition (DIA) data were processed using DIA-NN software with default settings.

Results: SEC fractions 1–4, enriched in the EV marker CD9, were pooled for proteomic profiling. Mass-spectrometry analysis confirmed enrichment of canonical EV markers, blood microparticles, and lipoproteins, with 474 proteins consistently detected across all samples. Comparative analysis revealed 78 proteins differentially expressed between non-symptomatic and symptomatic carriers, including markers linked to EVs, immune and defense responses, and complement/coagulation pathways. In addition, 39 proteins, including proteins related to cholesterol metabolism, were differentially expressed between non-symptomatic carriers and controls.

Conclusions: Proteomic profiling of EVs from presenilin-1 E280A mutation carriers identified candidate protein biomarkers potentially indicative of disease onset and progression. Further research is necessary to test the utility of circulating EVs in the early detection and monitoring of familial AD that can be extrapolated to sporadic AD.

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### POSTER N.º 15

**Introduced by:** Carmen Marquez Marco

**First Author:** Inmaculada Cuchillo Ibañez

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**Abstract:**
Under reducing conditions, two apoE monomeric glycoforms at ~36 kDa and at ~ 34 kDa are found in all human samples, including the cerebrospinal fluid (CSF). ApoE is exclusively O-glycosylated and can be capped with one or two sialic acids. The 34- and 36-kDa species are likely different O-glycoforms, and the difference in their electrophoretic mobility could be a consequence of its sialylation. In CSF, the existence of two glycans per molecule of apoE has been demonstrated, and previous studies indicate that astrocytes secrete two differential glycoforms of apoE and that the sialo and asialo forms of apoE can both be secreted into the medium.
We previously found (Lennol MP et al., Apolipoprotein E imbalance in the cerebrospinal fluid of Alzheimer's disease patients. Alzheimers Res Ther. 2022) that the 36-kDa/34-kDa ratio in the CSF was lower in Alzheimer´s disease (AD) respect to that in controls for APOE ε3/ε3 and ε3/ε4. However, the 36-kDa/34-kDa ratio in APOE ε4/ε4 from AD CSF was closer to that in controls, rather than to the other AD genotypes.
We present here by glycoproteomic analysis that APOE3/3 glycosylation is diffent in C and AD CSF, and ApoE3/4 glycosylation seems to be different respect to other genotypes in both groups. Further research is needed to complete this study.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 16

**Introduced by:** Érika Sánchez-Aced

**Title:**

### OLIGOMERIC TAU, NOT TOTAL TAU, CORRELATES WITH SEEDING ACTIVITY IN ALZHEIMER'S DISEASE BRAIN EXTRACTS

**First Author:** Érika Sánchez-Aced

**Authors:** Érika Sánchez-Aced[cba], Aleyda Benítez-Amaro[c], Borja Moya-Llamas[cb], Martí Colom-Cadena[d], Tara Spires-Jones[d], Sònia Sirisi[ca], Alberto Lleó[ca]

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**Abstract:**

Background: Tau pathology spreads progressively through anatomically connected brain regions in Alzheimer's disease (AD), possibly via synaptic transmission of misfolded tau species. Oligomeric tau has been proposed as a key mediator of this process, yet its specific contribution to seeding activity remains unclear.

Methods: Tau seeds were isolated from temporal cortex homogenates and synaptoneurosomes of postmortem human brains of AD patients and neurologically healthy controls (n = 8) and controls (n = 8). CRL-3275™ tau RD P301S FRET biosensor cells, seeded on Matrigel-coated coverslips, were transfected with 16 ng of tau (quantified by total human tau ELISA) using Lipofectamine 2000 in Opti-MEM medium. After 72 h, cells were fixed, Hoechst-stained, and imaged. FRET-positive cells were quantified using 3DHISTECH scanning and ImageJ/MATLAB-based image analysis. Seeding activity was correlated with total and oligomeric tau levels, the latter derived from array tomography data in matched samples from a previous study.

Results: A higher percentage of FRET-positive cells was observed in cells transfected with AD-derived homogenates ($W = 6.5$, $p = 0.005$) and synaptoneurosomes ($W = 12.5$, $p = 0.5$) compared to controls. While total tau levels did not correlate with seeding activity from extracts derived from homogenates (Spearman's $\rho = -0.3$, $p = 0.252$), a strong positive correlation was found between tau seeding and oligomeric tau burden (Spearman's $\rho = 0.8169$, $p = 0.0002$).

Conclusions: These results suggest that oligomeric tau, rather than total tau, underlies the seeding capacity of pathological tau in AD brain extracts. Oligomeric tau may therefore play a central role in tau propagation and represent a key target for therapeutic intervention.

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## POSTER N.º 17

**Introduced by:** Astillero-Lopez V

**Title:**

**STEREOLOGICAL ANALYSIS AND SPATIAL PROTEOMIC MAPPING OF THE HUMAN SUBICULAR COMPLEX IN ALZHEIMER'S DISEASE**

**First Author:** Astillero-Lopez V

**Authors:** Astillero-Lopez V[a], Alonso-Gomez A[a], Flores-Thomas AP[a], Montesinos-Vinader JL[a], Soriano-Herrador C[a], Saiz-Sanchez D[a], Flores-Cuadrado A[a], Ubeda-Banon I[a], Martinez-Marcos A[a]

**Filiation:** [a]Neuroplasticity and Neurodegeneration Group, Ciudad Real Medical School, IB-UCLM, University of Castilla-La Mancha, IDISCAM, Spain

**Abstract:**
Alzheimer's disease (AD) is a progressive neurological condition clinically characterized by impaired cognitive function and behavioural alterations. Neuropathologically, deposits of amyloid-β and tau proteins accumulate in the brain in a six-stages predictable pattern. Neuronal loss and volume reduction have been largely reported in the entorhinal cortex (EC) and hippocampus (HP), which are key regions in the disease onset as well as in the observed cognitive deficits. In this sense, the subicular complex (SC, including subiculum, presubiculum and parasubiculum) represents the connecting bridge between the EC and the HP, but their role in AD remains poorly understood. Therefore, the aim of this work has been, first, to stereologically analyze the volume and neuronal changes within the human SC, and second, to assess the proteomic mapping profile.
Post-mortem human tissue was provided by the Spanish Biobank Network. Volume and neurons of the SC were quantified by Cavalieri and Optical Fractionator methods, respectively. A proteomic study was performed through matrix assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI).
Stereological results showed that SC volume decreases in all their regions, being more pronounced in the subiculum. However, no significant differences in SC neuron number were observed between AD and control groups. Future experiments will test the possible relationship between the volume loss and glial changes within the SC. Proteomic data revealed several peptides whose fingerprint could help to characterize proteomic changes in AD patients.
Funded by UCLM/ERDF (2022-GRIN-34200), the Autonomous Government of Castilla-La Mancha/ERDF (SBPLY/21/180501) and the Spanish Ministry of Science and Innovation (PID2019-108659RB).

# BOOK OF ABSTRACTS 2025

## POSTER N.º 18

**Introduced by:** Jose Luis Montesinos-Vinader

**Title:**

**DIFFERENTIAL INTERNEURON VULNERABILITY IN THE HUMAN AMYGDALA DURING ALZHEIMER'S DISEASE PROGRESSION**

**First Author:** Jose Luis Montesinos-Vinader

**Authors:** Jose Luis Montesinos-Vinader[a], Andrea Alonso-Gomez[a], Ana Paula Flores-Thomas[a], Carmen Soriano-Herrador[a], Veronica Astillero-Lopez[a], Alicia Flores-Cuadrado[a], Isabel Ubeda-Banon[a], Alino Martinez-Marcos[a], Daniel Saiz-Sanchez[a]

**Filiation:** [a]Neuroplasticity and Neurodegeneration Group, IB, IDISCAM, Ciudad Real Medical School, University of Castilla-La Mancha, Camino de Moledores S/N, 13071 Ciudad Real, Spain

**Abstract:**

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive cognitive decline, including memory loss and language impairment. Ageing is the main risk factor. AD pathology is marked by the accumulation of aberrant amyloid-β and tau isoforms, forming extracellular and intracellular aggregates, respectively. Tau accumulation begins decades before clinical diagnosis and progresses through six neuropathological stages, primarily affecting limbic regions such as the entorhinal cortex, hippocampus, and amygdala.

Recently, the amygdala has gained attention as a key region for early diagnosis and as a potential hub for tau propagation due to its connectivity with the locus coeruleus, anterior hippocampus, and entorhinal cortex. While limbic neurodegeneration is well-documented, the specific role of interneuron populations within the amygdala remains understudied.

In this work, interneurons expressing somatostatin and calcium-binding proteins calbindin, calretinin and parvalbumin were quantified in the human amygdala using unbiased stereological methods across three different groups of AD (stages 0-I, II-III and IV-V). We observed a significant reduction in the number of cells expressing somatostatin and calbindin in AD cases. Conversely, calretinin-expressing interneurons increased significantly, and there was no significant change in parvalbumin-expressing interneurons throughout disease progression.

These results evidence selective vulnerability linked with interneuron subtypes, indicating a particular weakness of those expressing somatostatin and calbindin whereas those expressing parvalbumin are resistant or even those expressing calretinin are increased.

We gratefully acknowledge the donors and the Spanish National Biobank Network. Funding was provided by UCLM/ERDF (2022-GRIN-34200), MICINN (PID2019-108659RB) and JCCM/ERDF (SBPLY/21/180501). JLMV was supported by a UCLM/JCCM/FSE+ INVESTIGO contract.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 19

**Introduced by:** Petra Riegerová

**Title:**

**SORLA DYSFUNCTION IMPAIRS THE ENDOLYSOSOMAL PATHWAY AND PROMOTES AMYLOID BETA ACCUMULATION IN NEURONS**

**First Author:** Petra Riegerová

**Authors:** Petra Riegerová[b], Petr Fojtík[a], Martin Hof[b]

**Filiation:** [a]J. Heyrovský Institute of Physical Chemistry, Prague, Czech Republic, [b]Faculty of Medicine, Masaryk University, Brno, Czech Republic

**Abstract:**
SORL1 (sortilin-related receptor 1) encodes SORLA, a type-I transmembrane sorting receptor recently implicated in the pathogenesis of Alzheimer's disease (AD). Under physiological conditions, SORLA dimerises at early endosomal membranes and facilitates the retromer-dependent trafficking of amyloid precursor protein (APP) back to the plasma membrane, thereby limiting its amyloidogenic processing.
To investigate how SORLA deficiency contributes to the development of the AD phenotype, we analysed human gene-edited iPSC-derived neurons lacking SORLA (SORLA KO). Consistent with previous studies, these cells exhibited elevated levels of amyloid beta (Aβ). Given the close relationship between Aβ processing and the membrane organelles, we examined the response of key components of the endolysosomal system using super-resolution fluorescence microscopy in both wild-type (SORLA WT) and SORLA KO neurons. Significant alterations were revealed in early endosomes. Focusing on the exosome secretory pathway, we further analysed the formation of multivesicular bodies (MVBs), whose biogenesis is closely linked to exosome production. Quantitative image analysis of CD63—a tetraspanin protein enriched in MVBs—revealed a marked increase in CD63 signal intensity in SORLA KO neurons.
In summary, our findings suggest that SORLA dysfunction perturbs early stages of the endolysosomal pathway, alters exosome biogenesis, and enhances amyloidogenic APP processing, ultimately contributing to Aβ accumulation and disrupted proteostasis in neurons.

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## POSTER N.º 20

**Introduced by:** Ana Garcia-Osta

**Title:**

**REPROGRAMMING LIPID METABOLISM FOR COGNITIVE RESTORATION IN ALZHEIMER'S VIA PLA2G4E**

**First Author:** Sara Badesso

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**Abstract:**
Alzheimer's disease (AD) is the leading cause of dementia worldwide, yet current treatments provide only modest benefits. Given the limited success of current therapies, novel strategies are urgently needed. Interestingly, some elderly individuals accumulate AD neuropathology without cognitive impairment, suggesting the presence of protective mechanisms. Inspired by this, we identified PLA2G4E, a neuron-specific phospholipase as a potential therapeutic target. We have demonstrated that its overexpression via AAV9 vectors in hippocampal neurons of AD mouse models fully restored memory and increased dendritic spine density. Furthermore, using a novel AAV capsid capable of crossing the blood-brain barrier (AAVP31), allowing systemic administration and widespread overexpression of PLA2G4E throughout the brain, not only rescued memory deficits in AD models, but also enhanced glucose brain metabolism and cognition in aged wild-type mice, confirming the therapeutic potential of PLA2G4E. Additionally, lipidomic profiling revealed that PLA2G4E expression corrected dysregulated lipid metabolism characteristic of AD. Importantly, lipidomic analyses of cerebrospinal fluid (CSF) from individuals with MCI and AD revealed that levels of specific N-acylethanolamines (NAEs)—such as PEA and OEA—correlate positively and significantly with patients' cognitive status, supporting the idea that PLA2G4E´s activity is functionally linked to synaptic maintenance and cognitive resilience in AD. These findings position this gene-based strategy as a promising therapeutic avenue to restore cognitive function and promote synaptic resilience in Alzheimer's disease. However, despite its strong potential, several translational challenges remain—particularly regarding AAV vector immunogenicity, biodistribution after systemic delivery, and scalable manufacturing—which must be carefully addressed to enable future clinical application.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 21

**Introduced by:** María de los Llanos Martínez-Poyato

**Title:**

**DISRUPTION OF CAV2.3 CHANNELS IN THE BRAIN OF THE 5XFAD MOUSE MODEL OF ALZHEIMER'S DISEASE**

**First Author:** María de los Llanos Martínez-Poyato

**Authors:** María de los Llanos Martínez-Poyato[b], Rocío Alfaro-Ruiz[ba], Ricardo Puertas-Avendaño[b], Alejandro Martín-Belmonte[ba], Miriam Fernández Fernández[ba], Ana Esther Moreno-Martínez[ba], Carolina Aguado Rubio[ba], Rafael Luján Miras[ba]

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**Abstract:**

Calcium plays fundamental roles in many facets of neuronal physiology such as gene expression, growth and differentiation, synaptogenesis, dendritogenesis, membrane excitability, neurotransmitter release, synaptic plasticity and learning and memory. Voltage-gated calcium (CaV) channels are required for many of those brain functions. Among the CaV channel family, R-type calcium (CaV2.3) channels play important roles in hippocampal functions including synaptic plasticity, a neuronal process known to be altered in neurodegenerative diseases. However, no information is available about the potential alteration of CaV2.3 in Alzheimer´s disease (AD). The goal of this work is to determine the possible alteration of CaV2.3 in Aβ pathology. Here, we provide a quantitative description on the expression and distribution patterns of CaV2.3 in the 5xFAD transgenic mouse model AD, combining histoblots and immunoelectron microscopic approaches. Using the histoblot technique, we observed that the protein content of CaV2.3 in female 5xFAD mice was downregulated in the hippocampus and caudate putamen at 5 months, with more pronounced downregulation at 10 months that also affected the septum. The hippocampus was the most affected region, where CaV2.3 immunodetection was significantly decreased in a few dendritic layers at 5 months, but this reduction extended to all layers and subregions by 10 months, demonstrating age- and laminar-dependent changes. The pattern in females differed from that seen in males. Immunoelectron microscopy of the hippocampus showed CaV2.3 in apical and oblique dendrites of CA1 pyramidal cells, with a significantly higher presence in dendritic spines. Quantification revealed a significant decrease in the density of CaV2.3 in secondary dendrites and dendritic spines of CA1 pyramidal cells, whereas apical dendrites and presynaptic compartments were unaffected in 5xFAD mice. Overall, this downregulation in postsynaptic CaV2.3 channels could impact neural circuit activity and contribute to the cognitive deficits observed in 5xFAD mice.

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## BOOK OF ABSTRACTS 2025

### POSTER N.º 22

**Introduced by:** Miren Ettcheto

**Title:**

**IRBESARTAN AS A MULTI-TARGET NEUROPROTECTIVE AGENT IN AN ALZHEIMER'S DISEASE MOUSE MODEL**

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**Abstract:**

Introduction:

Alzheimer's disease (AD) is a multifactorial neurodegenerative disorder involving amyloid β plaques, tau tangles, oxidative stress, neuroinflammation, and apoptosis. These mechanisms suggest that multi-target therapies may be more effective than single-target approaches. Although angiotensin receptor blockers (ARBs) and angiotensin-converting enzyme inhibitors (ACEIs) have been associated with a lower risk of AD in hypertensive patients, their poor brain penetration limits their effectiveness. This study aimed to assess the neuroprotective potential of three ARBs (losartan, valsartan, irbesartan) and one ACEI (enalapril) using in vitro and in vivo approaches.

Materials & Methods:

Three ARBs and three ACEIs were tested in N2a-wild-type and N2a-APPswe cells to assess neuronal survival and oxidative stress. Irbesartan was selected for intranasal administration (40 mg/kg, 10 days) in 4-month-old male APP/PS1 mice. Behavioral performance, synaptic integrity, mitochondrial function, oxidative stress, neuroinflammation, and blood-brain barrier (BBB) integrity were evaluated.

Results:

Irbesartan significantly increased p-AKT and HMOX1 levels in N2a-APPswe cells ($p<0.01$), indicating enhanced survival and reduced oxidative stress. In vivo, irbesartan improved memory (novel object recognition and Morris water maze; $p<0.05$ and $p<0.001$, respectively), increased synaptic spine density ($p<0.05$), restored mitochondrial function ($p<0.05$), and reduced oxidative damage (lower MDA and 4-HNE, $p<0.05$ and $p<0.01$). Antioxidant enzyme Gpx1 was upregulated ($p<0.05$), BBB integrity improved, and neuroinflammatory markers decreased ($p<0.05$).

Conclusion:

Intranasal irbesartan showed robust neuroprotective effects in the APP/PS1 model, suggesting its promise as a multi-target strategy to delay AD progression.

Acknowledgements:

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# BOOK OF ABSTRACTS 2025

## POSTER N.º 23

**Introduced by:** Mª Ascensión Zea Sevilla

**Title:**

**MADRID-FRONTOTEMPORAL DEMENTIA (FTD). CREATION OF FTD STUDY COHORT FOR THE VALIDATION OF CUTTING-EDGE BIOMARKERS**

**First Author:** Mª Ascensión Zea Sevilla

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**Filiation:** [a]CIEN Foundation, Reina Sofia Foundation Alzheimer Centre, Madrid, Spain. [b]Memory units in the Autonomous Community of Madrid

**Abstract:**

Introduction

FTD is the third leading cause of neurodegenerative dementia in our setting. Diagnosis is complex and uncertain without neuropathological study. The development of any diagnostic technique or biomarker would be of utmost importance for clinical practice. The most common misfolded proteins are Tau and TDP-43. Identifying specific pathogenic species of tau and TDP-43 correlated with the disease would represent an advance in the diagnostic approach.

Material and methods

The Madrid-FTD Consortium is a multicenter project (memory units in the Autonomous Community of Madrid) for patients with behavioral variant (BV) or primary progressive aphasia (PPA). Clinical data, blood samples, cerebrospinal fluid samples (CFS), and MRI (3 Tesla) scans will be collected. RT-QuIC will be performed to detect pathogenic tau 3R and 4R isoforms, and TDP-43 will be quantified in extracellular vesicles using SIMOA technology. In addition, the diagnostic utility of plasma/CSF biomarkers using SIMOA (TDP43, p-Tau 181, t-Tau, ABeta 40, ABeta42, NfL, and GFAP) and their combination with RT-QuIC will be evaluated. In a neuropathological cohort of the BT-CIEN, we will study the same biomarkers for validation purposes. This project has been funded by the Carlos III Health Institute (PI23/01314.AES-ISCIII).

Results

In a year recruitment period, 136 patients and 43 samples (blood and CSF) from patients with a clinical diagnosis of FTD were recruited. To date, 97 patients have been evaluated at CIEN. The mean age at dementia onset was 65.02±9.16 years. Of the participants, 64.9% were male and 35.1% female, with a current mean age of 71.49±8.67 years. The cohort included 60.2% BV cases and 39.8% PPA. Most cases (96.6%) were sporadic while 3.4% had a familial forms. Currently, CSF samples are available for 59 patients, with AD biomarkers analyzed in 30 of them. Aditionally, 76 patients have undergone MRI scans.

Conclusions

We are committed to creating a deeply phenotyped cohort of FTD patients, with the goal of validating novel biomarkers, improving FTD diagnosis by integrating precision medicine tools, and creating a patient identification platform for future clinical trials.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 24

**Introduced by:** Iván Burgueño García

**Title:**

**HIPPOCAMPAL SCLEROSIS: WITH OR WITHOUT LATE**

**First Author:** Iván Burgueño García

**Authors:** Iván Burgueño García[a], Alicia Uceda Heras[a], Paloma Ruiz Valderrey[a], Sandra Lázaro Gonzalez[a], Laura Saiz Aúz[a], María José López Martínez [a], Alberto Rábano[a]

**Filiation:** [a]Reina Sofia Alzheimer Center, CIEN Foundation, ISCIII, Madrid, Spain

**Abstract:**

Introduction

In advanced age and neurodegenerative dementia, hippocampal sclerosis (HS) and limbic associated TDP-43 encephalopathy (LATE) are closely associated entities. However, their possible pathogenic relationship is under discussion.

Objectives

Our objetive is compare HS cases with or without associated LATE in a series of postmortem brains from advanced age patients with dementia.

Material and Methods

We analyzed 210 dementia cases from the BT-CIEN brain bank cohorts (mean age at death= 82.8+/-10.7; females = 69.5%; 83.2% with Alzheimer's disease [AD] as main neuropathological diagnosis, including 29.1% of early-onset AD (EOAD)). All cases underwent full neuropathological work-up limited to the left hemibrain, including a HS staging scheme developed by our group. Brains with HS-like hippocampal microinfarcts were identified and excluded as HS.

Results

HS was more prevalent among EOAD brains than in late onset AD (LOAD) cases (Chi-square, $p<0.01$). From the 141 EH+ cases identified (including early stages), 23 brains were LATE(-) (16,3%). This group displayed a significantly lower age at death and survival time, and a higher brain weight than the LATE(+) group (Mann-Whitney, $p<0.05$). LATE(-) HS(+) brains showed also lower vascular scores, presented predominantly early HS stages (Mann-Whitney, $p<0.01$), and a lower prevalence of ARTAG (Mantel-Haenzel, $p<0.001$). No significant differences were observed between LOAD and EOAD cases, and no association with APOE e4 haplotype was observed.

Conclusions

TDP-43(-) HS is more prevalent in early HS. LATE could be a driver for advanced (full) HS in cases with early stages of sclerosis, together with microvascular and ARTAG combined pathologies.

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## POSTER N.º 25

**Introduced by:** Anabela Câmara

**Title:**

**FRONTOTEMPORAL DEMENTIA WITH PROGRANULIN MUTATION: A CASE REPORT**

**First Author:** Anabela Câmara

**Authors:** Anabela Câmara 1,2, Joana Milhazes Pinto 2, Eduardo Freitas 2, Sofia Rocha 2

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**Abstract:**
Frontotemporal dementia (FTD) comprises a heterogeneous group of neurodegenerative syndromes characterized by progressive behavioral, executive, language, and motor dysfunction.
We report the case of a 65-year-old woman, previously autonomous, referred to neurology due to behavioral changes. Her medical history included hypertension, dyslipidemia, and depression, with no family history of neurological disorders. Initial symptoms included social withdrawal, apathy, and loss of empathy, initially attributed to bereavement. She experienced multiple car accidents due to visuospatial disorientation and occasional nonsensical speech, although she remained independent in daily activities. Neurological examination revealed subcortical signs and symmetric parkinsonism. Laboratory workup was unremarkable. Brain MRI showed global cortical and subcortical atrophy, with predominance in frontal, superior parietal, and anterior temporal lobes, sparing the hippocampi (MTA grade II). Marked brainstem and cerebellar atrophy were also noted. 123I-Ioflupane (DaTSCAN) demonstrated bilateral nigrostriatal dopaminergic degeneration. At follow-up, she exhibited clinical deterioration with levodopa-unresponsive parkinsonism, naming deficits, verbal perseveration, REM sleep behavior disorder, postural instability, and frequent falls. Alzheimer's biomarkers were negative. Neuropsychological assessment confirmed severe multidomain dementia. Genetic testing identified a progranulin (GRN) mutation. Multidisciplinary management was initiated, including family support, genetic counseling, rehabilitation, and palliative care. The patient was also referred for brain donation. This case highlights that genetic forms of FTD, though rare, may present with late-onset symptoms. Genetic testing should be considered even in older patients. Emerging disease-modifying therapies—such as gene therapy, monoclonal antibodies, and epigenetic agents—offer promising future perspectives.

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## POSTER N.º 26

**Introduced by:** Sonia Wagner-Reguero

**Title:**

**RT-QUIC AS A POST-MORTEM DIAGNOSTIC TOOL FOR SYNUCLEINOPATHIES**

**First Author:** Sonia Wagner-Reguero

**Authors:** Sonia Wagner-Reguero[a], Sezgi Canaslan[b], Minerva Martínez-Castillo[a], Inga Zerr[b], Maria José López-Martínez[a], Laura Saiz-Aúz[a], Alberto Rábano[a], Aitana Sogorb-Esteve[a], Pascual Sánchez-Juan[c]

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**Abstract:**
Recent advances in seed amplification assays (SAAs) have enabled the detection of misfolded alpha-synuclein (α-syn) pathogenic seeds in body fluids and tissues, which appear to correlate with the presence of clinical symptoms in living individuals. Among these, the real-time quaking-induced conversion assay (RT-QuIC) has emerged as a transformative technique, offering unprecedented sensitivity and specificity in identifying pathological forms of α-syn, which are hallmark features of synucleinopathies such as Parkinson's disease (PD) and dementia with Lewy bodies (DLB). We evaluated the utility of RT-QuIC for detecting misfolded α-syn in post-mortem cerebrospinal fluid (CSF) samples from individuals with neuropathologically confirmed diagnoses, aiming to assess the robustness of the assay under post-mortem conditions and to determine its sensitivity and specificity in distinguishing synucleinopathy cases. A total of 250 post-mortem CSF samples were obtained from the CIEN Tissue Bank. RT-QuIC assays were conducted under optimized conditions to amplify misfolded α-syn seeds, with fluorescence kinetics analyzed to determine positivity thresholds. This study highlights the value of RT-QuIC technique in detecting pathological alpha-synuclein aggregates, even in CSF samples affected by post-mortem degradation. We assessed the capacity to accurately discriminate between synucleinopathy-related and non-synucleinopathy cases. RT-QuIC could be a promising tool for the post-mortem biochemical confirmation of synucleinopathies. These findings support its potential role in refining clinicopathological correlations and validating biomarker-driven diagnostic frameworks. Beyond post-mortem applications, RT-QuIC paves the way for antemortem molecular diagnosis, contributing to a paradigm shift in which synucleinopathies may be defined by pathogenic protein signatures rather than solely by clinical criteria.

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## POSTER N.º 27

**Introduced by:** Ana Luísa Pires

**Title:**

**WELDING THE CLUES TOGETHER: A CASE OF UNUSUAL PARKINSONISM**

**First Author:** Ana Luísa Pires

**Authors:** Ana Luísa Pires[a], Cátia Oliveira[a], Pedro Monteiro Moreira[a], Rita Rodrigues[a]

**Filiation:** [a]Unidade Local de Saúde Entre Douro e Vouga

**Abstract:**

Background: Early-onset Parkinson's disease (PD) is rare and often linked to genetic mutations, typically inherited in an autosomal recessive (AR) fashion. However, de novo mutations and environmental triggers may play a role.

Clinical Case: A 50-year-old healthy male welder presented with a 3-year history of rightpredominant tremor and bradykinesia. He had no family history of neurological disorders.

Examination revealed asymmetrical parkinsonism, hypomimia, and diminished right arm swing.

He scored 15 points on the MDS-UPDRS Part III. Workup included an unremarkable brain MRI; a DaTSCAN showing reduced dopamine transporter uptake in the left striatum; and normal iron and copper studies. Genetic testing revealed a heterozygous DNAJC6 mutation of uncertain significance. The patient responded well to Levodopa/Carbidopa and Ropinirole, with an MDSUPDRS score reduction to 6. Over time, motor fluctuations developed and were refractory to medication adjustments. Sublingual apomorphine was initiated with good effect.

Discussion: DNAJC6-related PD is typically a juvenile-onset, AR disorder with rapid progression and prominent cognitive and psychiatric features. In this case, the later onset, milder course, and heterozygous mutation raise questions about causality. Environmental exposure—particularly to heavy metals—may have contributed, as literature suggests potential gene–environment interactions involving heat shock proteins like DnaJ/Hsp40.

Conclusion: This case illustrates an atypical form of early-onset PD, possibly shaped by environmental and genetic interplay. Further research is needed to clarify the role of DNAJC6 and occupational exposure in modifying disease expression.

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## POSTER N.º 28

**Introduced by:** Mar Cuadrado-Tejedor

**Title:**

**ADVANCING NEUROPROTECTIVE THERAPIES FOR PARKINSON'S DISEASE**

**First Author:** Marta García-Gómara

**Authors:** Marta García-Gómara[a], Sara Badesso[b], María Espelosín[b], Ana García-Osta[b], Mar Cuadrado-Tejedor[a]

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**Abstract:**
PLA2G4E, which encodes cytosolic phospholipase A2 epsilon (cPLA2ε), is a neuronal enzyme involved in membrane lipid remodeling and intracellular trafficking. Although less studied than other phospholipase isoforms, emerging evidence suggests cPLA2ε plays a role in synaptic maintenance and neuroprotection. In this study, we investigated the therapeutic potential of PLA2G4E in a neuromelanin (NM)-based mouse model of Parkinson's disease (PD). Using an AAV2/9 vector carrying human PLA2G4E under the neuron-specific synapsin promoter (AAV2/9-hSynapsin-HA-PLA2G4E), we achieved efficient expression of PLA2G4E following intraparenchymal administration into the substantia nigra pars compacta (SNpc), which significantly alleviated the PD-like phenotype. In this NM-based model, generated by expressing human tyrosinase to induce NM accumulation and mimic Parkinsonian pathology, mice co-expressing PLA2G4E exhibited improved motor performance, preservation of tyrosine hydroxylase positive neurons in the SNpc, and maintenance of dopaminergic terminals in the striatum. Notably, PLA2G4E expression reduced NM accumulation and attenuated neuroinflammatory responses, as evidenced by decreased expression of GFAP, Iba1, CD68. These findings indicate that PLA2G4E exerts both neuroprotective and anti-inflammatory effects, establishing it as a promising disease-modifying candidate for PD. While non-invasive gene delivery strategies are promising for diffuse neurodegenerative conditions, intraparenchymal delivery remains the gold standard for focal disorders like PD, where localized and precise transduction is essential. This supports the clinical relevance of our approach and its feasibility for future translation. These data have been included in a recent patent application (PCT/IB2025/000271), supporting the clinical development and intellectual property framework for PLA2G4E-based gene therapy in neurodegeneration associated with PD.

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## POSTER N.º 29

**Introduced by:** Jesús Silva-Rodríguez

**Title:**

**LONG-TERM TRAJECTORIES OF COGNITION, NEURODEGENERATION, AND CLINICAL PROGRESSION IN COGNITIVELY UNIMPAIRED INDIVIDUALS WITH ELEVATED LEVELS OF PLASMA %P-TAU217: A LONGITUDINAL COHORT STUDY**

**First Author:** Jesús Silva-Rodríguez

**Authors:** Jesús Silva-Rodríguez[a], Linda Zhang[a], Luca Kleineidam[b], Sonia Wagner-Reguero[a], Francisco J. López-González[a], Cristina Sánchez-Martín[a], Elizabeth L. Valeriano-Lorenzo[a], Teodoro del Ser[a], Michel J. Grothe[a], Pascual Sánchez-Juan[a]

**Filiation:** [a]Reina Sofía Alzheimer Centre, CIEN Foundation, ISCIII, Madrid, Spain, [b]Department of Department of Old Age Psychiatry and Cognitive Disorders, University Hospital Bonn, Bonn, Germany

**Abstract:**

Background: The ratio of phosphorylated to non-phosphorylated tau at threonine 217 (%p-tau217) has emerged as a promising plasma biomarker for Alzheimer's disease (AD) pathology, reaching performance levels comparable to CSF-based measures. However, its predictive value for long-term neurodegeneration and cognitive decline in cognitively unimpaired (CU) individuals remains to be further explored.

Methods: We studied 982 CU older adults (mean age: 75 ± 4 years; 64% female) from the Vallecas Project (CIEN, Madrid, Spain), with annual follow-ups over up to 12 years (mean: 7.9 ± 3.3 years). Baseline plasma %p-tau217 was quantified using mass spectrometry and used to stratify subjects in four risk categories at baseline using a predefined three-cut-off model. Longitudinal changes in a) cognition, via an in-house modified version of the PACC (mPACC) and MMSE; b) hippocampal volume; c) plasma biomarkers of astrocytic activation (GFAP) and neurodegeneration (NfL); and d) clinical/functional measures (CDR-SoB, FAQ) were assessed. Risk of progression to MCI or dementia was evaluated using survival analysis. All models were adjusted for age, sex, and APOE4 status. Positive and Negative predictive value (PPV, NPV) were estimated through time-dependent ROC analysis.

Results: Participants were classified as having "Low" (n=674, 68.6%), "Intermediate" (n=145, 14.8%), "Elevated" (n=103, 10.5%), or "High" (n=60, 6.1%) %p-tau217 levels. Cognitive decline (mPACC, MMSE) accelerated with increasing %p-tau217, most notable in mPACC at early stages ($p<0.001$, Fig1). GFAP showed baseline group differences, but steeper longitudinal increases were restricted to the "High" group (Fig2A, $p<0.001$). NfL changes followed similar, though less significant patterns (Fig2B). Hippocampal atrophy was significantly faster in both "Elevated" and "High" groups compared to "Low"/"Intermediate" (Fig2C, $p<0.001$), so was clinical (CDR-SoB) and functional (FAQ) decline (Fig3, A-B; $p<0.001$;). Survival analysis (Fig3, C-F) showed significantly increased risk of progressing to MCI ($\chi^2=179$, $p<0.001$) and dementia ($\chi^2=137$, $p<0.001$) in higher %p-tau217 groups, with HR>6 for the "Elevated" and "High" groups. The "Low" group showed strong NPV for MCI conversion even at 10 years (92.1%), while "High" showed moderate PPVs for MCI (55% at 5 years, 71% at 10 years) and dementia (34% and 41%).

Discussion: Plasma %p-tau217 represents a robust and non-invasive biomarker for early identification of CU individuals at increased risk of AD-related cognitive and neurodegenerative decline, reinforcing its potential role for risk stratification in both clinical practice and research trials. Notably, individuals in the lower %p-tau217 categories demonstrated minimal risk of clinical progression over time.

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## POSTER N.º 30

**Introduced by:** Rubèn López-Vales

**Title:**

**ALS-LINKED SOD1G93A MUTATION DISRUPTS MICROGLIAL FUNCTIONS IN A CELL-AUTONOMOUS MANNER IN HUMAN ESC-DERIVED MICROGLIA IN VITRO**

**First Author:** Joana Garcia Garcia

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**Abstract:**

Microglia are well-stablished to contribute to ALS pathogenesis. Mutations in the SOD1 gene are among the genetic factors that cause ALS, which have facilitated the generation of ALS mouse models. However, the most widely used ALS mouse model overexpresses human mutant SOD1G93A, hindering the possibility to fully elucidate the physiopathological contribution of mutant SOD1 to ALS-relevant cell types. Besides, species differences have been shown to be relevant in microglia, especially regarding the altered expression of neurodegenerative disease-associated risk genes in the mouse microglial transcriptome and the incomplete representation of the heterogeneity and complexity of human microglial states in the mouse microglia. Moving to more human-based biomedical research, the ability to differentiate human stem cells to microglia in vitro, combined with the advances in gene editing approaches, allows a more accurate assessment of the causative relationship between a genetic background and the associated phenotype.

In this context, we aimed at assessing the effects of mutant SOD1 to microglial function in vitro. By generating an isogenic human embryonic stem cell (ESC) line carrier for the SOD1G93A point mutation by CRISPR/Cas9 technology, we characterized SOD1G93A ESC-derived microglia phenotypically and functionally in vitro compared to the control. In this sense, we evaluated how mutant SOD1G93A affects the microglial cytokine profile, phagocytic function and cell metabolism at baseline conditions and in response to a pro-inflammatory stimulus. SOD1G93A microglia showed a disrupted cytokine expression profile in basal conditions and an exacerbated reactivity to LPS stimulation. Additionally, mutant SOD1G93A altered microglial phagocytosis, measured by the digestion of pHrodo-conjugated myelin debris, and cell metabolism, evaluated by Seahorse technology. Finally, we assessed the neurotoxic potential of SOD1G93A microglial conditioned media (CM) in control iPSC-derived motor neurons. In both basal and LPS conditions, SOD1G93A microglial CM led to greater toxicity to control iPSC-derived motor neurons in comparison with control microglial CM. Overall, our results suggest a cell-autonomous microglial dysfunction driven by mutant SOD1 in human ESC-derived microglia.

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## POSTER N.º 31

**Introduced by:** Ines Moreno-Gonzalez

**Title:**

**INOCULATION OF BLOOD FROM TAU TRANSGENIC ANIMALS EXACERBATES BRAIN TAU-ASSOCIATED PATHOLOGY**

**First Author:** Ines Moreno-Gonzalez

**Authors:** Laura Vegas-Gomez[a], Jesus Garcia-Martin[a], Maria Angeles Arredondo-Alcala[a], Antonia Gutierrez[c], Claudia Duran-Aniotz[d], Ines Moreno-Gonzalez[b]

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**Abstract:**
Alzheimer's disease (AD) is marked by the accumulation of extracellular amyloid-β plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau, with growing evidence suggesting that tau can propagate in a prion-like manner. Although tau aggregates have been detected in peripheral tissues and biological fluids, such as blood, their role in central tau pathology remains insufficiently understood. The objective of this study is to elucidate whether peripheral administration of blood from aged PS19 tau transgenic mice (P301S tau), a well-established model of tauopathy, can exacerbate tau-associated neurodegeneration in young P301S recipients. Blood was delivered via intraperitoneal and intravenous injections, and recipient mice were evaluated through behavioral tests, biochemical analyses, and histological examination. Our results show that blood from aged tauopathy mice promotes enhanced tau deposition in the hippocampus, increases glial inflammatory response, and worsens motor deficits in young recipients. These findings support the hypothesis that blood-borne tau aggregates act as pathological seeds capable of influencing tau dynamics within the central nervous system, together with other factors in the bloodstream. The observed peripheral-to-central propagation of tau pathology underscores a potential systemic component in AD progression, opening new avenues for research into the mechanisms by which peripheral tau contributes to neurodegeneration. Ultimately, understanding the routes and consequences of peripheral tau dissemination could lead to novel diagnostic biomarkers and therapeutic strategies aimed at halting or slowing tau-driven pathology in AD and related tauopathies.

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### POSTER N.º 32

**Introduced by:** Ana Paula Flores Thomas

**Title:**

**HUMAN OLFACTORY BULB INVOLVEMENT IN HUNTINGTON'S DISEASE: AN ANALYSIS FROM A SEX PERSPECTIVE**

**First Author:** Ana Paula Flores Thomas

**Authors:** Ana Paula Flores Thomas[a], Elena Retamosa Sanchez, Andrea Alonso Gomez[a], Carmen Soriano Herrador[a], Jose Luis Montesinos Vinader[a], Alicia Flores Cuadrado[a], Daniel Saiz Sanchez[a], Veronica Astillero Lopez[a], Alino Martinez Marcos[a], Isabel Ubeda Banon[a]

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**Abstract:**

Huntington's disease (HD) is a rare genetic neurodegenerative disorder characterized by motor impairments such as choreiform movements provoked by striatal pathological involvement. The associated proteinopathy, mutated huntingtin, has been reported in many brain regions beyond striatum. Interestingly, one of such regions is the olfactory bulb (OB) provoking olfactory deficits. Prodromal hyposmia is a common feature in other neurodegenerative diseases such as Alzheimer's and Parkinson's, associated with proteinopathy accumulation in the OB, which also exhibits neurodegeneration, astrogliosis, and microgliosis with clear sexual dimorphism. However, HD has not been studied from this perspective. The hypothesis is that the OB could suffer sexually dimorphic alterations by associated pathology. Therefore, this study aims to analyze volume and gliosis in the human OB of patients suffering the disease from a sex perspective.

Fixed samples from Huntington's patients and controls were sectioned using a freezing sliding microtome. Histological (Nissl staining), immunohistochemical (glial markers) and stereological methods (Cavalieri estimator and area fraction fractionator probe) were applied to evaluate volume and gliosis in distinct OB layers and the anterior olfactory nucleus. Results showed no significant differences in OB volume between sexes or between patients and controls. However, a negative correlation between OB volume and disease progression was observed exclusively in females. Findings support sex-specific involvement and highlights the relevance of considering sex as a research variable.

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## POSTER N.º 33

**Introduced by:** Luis M. Valor

**Title:**

**OCULOMOTOR CHARACTERISTICS IN HUNTINGTON'S DISEASE PATIENTS**

**First Author:** Ainhoa Molina-Martín

**Authors:** Ainhoa Molina-Martín[d], David P. Piñero[db], Dolores de Fez[d], Alexandra Muñoz-Ambit[e], Pau Mahiques[e], Manuel Dieter-Warnken[e], Silvia Martí-Martinez[e], Luis M. Valor[ca]

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**Abstract:**

Huntington's disease (HD) is a fatal neurodegenerative disorder caused by an aberrant expansion of CAG triplets in the HTT gene that primarily affects basal ganglia and corticostriatal circuitry in the forebrain. For a fast, affordable and non-invasive monitoring of mutation carriers during clinical management, increasing attention is being paid to the eye dysfunction as they can be correlated with deep brain pathological processes. The aim of this work is the analysis of the oculomotor characteristics of HD patients compared to normal subjects.We have screened volunteers using a battery of tests including retina imaging, optical and oculomotor measurements and motor scales, to establish potential correlations between eye abnormalities and disease stage. At the moment, the most relevant result for our ongoing analysis has been obtained in the performance of pursuit and saccadic eye movements measured using the subjective NSUCO oculomotor test and the objective and quantifiable Eye-Tracking technology which retrieved significant differences despite examining a small cohort: the NSUCO test showed higher scores in the control group compared to the study group, and Eye-Tracking parameters showed a lower number of fixations in the study group, indicating missed stimuli compared to the control group. We also investigated potential correlations of these parameters with Total Functional Capacity and Unified HD Rating Scale and molecular traits, such as the number of CAG repeats and peripheral DNA methylation patterns. We conclude that oculomotor analysis in HD mutation carriers (which does not require sophisticated equipment) should be considered in clinical evaluations of HD.

This work is supported by CNS2022-136169 (MICIU-NextGenerationEU) and PI23/01858 (ISCIII-ERDF)

# BOOK OF ABSTRACTS 2025

## POSTER N.º 34

**Introduced by:** Juan F. Gallego-Serna

**Title:**

**SINGLE-CELL TRANSCRIPTOMICS AND MOUSE MODEL PHENOTYPING FOR BIOMARKER SCREEN OF PERIPHERAL BLOOD BIOMARKERS IN HUNTINGTON'S DISEASE**

**First Author:** Paula Martín-Climent

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**Abstract:**

Transcriptional dysregulation is among the most prominent molecular alterations in Huntington's disease (HD). It is not confined to brain but is also extended to peripheral tissues and cells, enabling minimally invasive screens aimed at identifying transcriptional surrogates of the health status in HD mutation carriers. Nonetheless, transcriptomics approaches have failed to identify consistent candidates from peripheral blood, probably due to the low impact of the HD mutation in the transcriptional profiles of circulating cells that can be masked by the high cellular complexity of this biofluid. In this study, we applied for the first time single-cell RNA-seq in peripheral blood mononuclear cells (PBMCs) to determine those cellular compartments that accumulate the most prominent gene expression changes as potential sources of reliable biomarkers. However, we observed that specificity of the transcriptional changes were concentrated on the largest cell subpopulations while some alterations were shared among different cell subtypes, justifying that they were also observable across bulk transcriptomics datasets from previous studies. To relate these gene expression patterns with disease progression in the absence of a large cohort of patients, we examined selected candidates in a phenotypically characterized cohort of transgenic R6/1 mice. Of the tested genes, only the changes in the interferon related gene Irf7 in blood were correlated with motor coordination performance in mutant mice. Notably, this gene was significantly upregulated in the striatum of these animals. Overall, transcriptional-based changes in peripheral blood can be linked to HD but dissection of individual blood cells in combination with subsequent validation in mouse models emphasizes the challenges in obtaining clinically relevant biomarkers in HD

# BOOK OF ABSTRACTS 2025

## POSTER N.º 35

**Introduced by:** Laura Saiz-Aúz

**Title:**

**THE GADIR PROJECT: A CONSENSUS PROTOCOL FOR UPDATING AND CODING NEUROPATHOLOGICAL DIAGNOSIS AND CLASSIFICATION**

**First Author:** Laura Saiz-Aúz

**Authors:** Laura Saiz-Aúz[a], María José López[a], Iván Burgueño-García[a], Alicia Uceda[a], Paloma Ruiz[a], Sandra Lázaro[a], Alberto Rábano[a], GADIR Consortium

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**Abstract:**
The GADIR (Genomics And Digital neuropathological phenotyping of Iberian bRains) project is an ambitious genetic and neuropathological study aimed at obtaining GWAS data from all brains donated to brain banks in Spain and Portugal. Initially the study will be limited to brains with available frozen tissue (n = 3500-4000). A total of 16 brain banks are currently participating in the project. Genetic data from included brains will be correlated to neuropathological diagnoses (main diagnoses and co-pathologies), to classification data (stages, scores, frequency of lesions) and to quantitative and qualitative data obtained through AI-guided analysis of histological sections (in Alzheimer's pathology).
Recently (March 2025) all collaborating brain banks took part in the First GADIR Workshop, where consensus criteria were adopted for updating previous cases. Pathologies included in these criteria were: Alzheimer's, Lewy body, cerebral amyloid angiopathy, cerebrovascular pathology (non-amyloid), Limbic-predominant age-related TDP-43 encephalopathy (LATE), hippocampal sclerosis, argyrophilic grain disease, Aging-related tau astrogliopathy (ARTAG), Primary age-related tauopathy (PART), and amyotrophic lateral sclerosis.
Here we present the GADIR consensus criteria together with an algorithm for updating individual brains, in terms of a minimal set of tissue blocks, immunohistochemical studies and the need of new histological assessments. Three levels of final classification are envisaged, based on the availability of brain tissue, and a further consensus will be established within the Consortium for the generic and specific denomination of all final neuropathological diagnoses. These diagnoses will be coded according to the SNOMED-CT, CIE-11 and ORPHANET systems. Some examples will be here presented.

## BOOK OF ABSTRACTS 2025

### POSTER N.º 36

**Introduced by:** Minerva Martinez-Castillo

**Title:**

**TOWARD PLASMA BIOMARKERS FOR LEWY PATHOLOGY: ASSOCIATION WITH NEURONAL LOSS AND NEUROPATHOLOGICAL ASSESSMENTS**

**First Author:** Minerva Martinez-Castillo

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**Abstract:**
Lewy body (LB) pathology is a common contributor to cognitive decline, yet it remains difficult to detect clinically. CSF DOPA decarboxylase (DDC) has been proposed as a novel biomarker with increased concentrations in LB disorders. However, findings on plasma DDC are inconsistent. Plasma integrin alpha-M (ITGAM) and integrin alpha-V (ITGAV) have recently gained attention as promising candidates for LB pathology. Patients from Vallecas Alzheimer Reina Sofía (VARS) cohort were demented, and diagnoses were confirmed by autopsy (Alzheimer's disease [AD], N=79; AD with LB pathology [AD-DLB], N=28; vascular dementia [VD], N=14; dementia with Lewy bodies [DLB], N=7). Additionally, patients were grouped considering LB burden into low (α-syn Braak staging<=3; N=93) and high (α-syn Braak staging>3; N=35). Substantia nigra (SN) neurons were quantified in three predefined regions, being the mean value a proxy for depigmentation resulting from neuronal loss. Plasma ante-mortem levels of DDC, ITGAM, and ITGAV were quantified as part of the Olink Explore 3072. Group comparisons were performed using generalized linear models, adjusted for age and sex. Parametric correlations were assessed using Pearson's coefficient, and non-parametric correlations using Spearman's rank correlation. Patients with higher LB pathology exhibited a lower number of SN neurons and reduced levels of ITGAM and ITGAV. Additionally, neuron counts were positively associated with both integrin levels. Finally, negative associations were observed between these integrins and key LB assessments. No significant results were found for DDC. In brief, ITGAM and ITGAV are promising candidates for Lewy-related neurodegeneration, offering valuable insights into underlying neuropathology.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 37

**Introduced by:** M. Belén Frades-Payo

**Title:**

### HEALTH STATUS IS A RISK FACTOR FOR COGNITIVE DECLINE AND DEMENTIA

**First Author:** M. Belén Frades-Payo

**Authors:** M. Belén Frades-Payo[a], Lucía Valeriano Lorenzo[a], Francisco J López[a], Mario Ricciardi[a], María Ascensión Zea[a], Merixell Valentí[a], Minerva Martínez[a], Sonia Wagner[a], Pascual Sánchez Juan[a], Félix Bermejo[b], Teodoro del Ser[a]

**Filiation:** [a]Fundación CIEN, [b]Instituto de investigación I+12

**Abstract:**

Objectives.

The incidence of dementia is decreasing in developed countries, although the causes of this trend are not well understood. Improvements in population health status could be one contributing factor.

This study examines whether health status—assessed through both objective and subjective parameters—is a risk factor for the development of mild cognitive impairment (MCI) and dementia in a cohort of volunteers over the age of 65.

Methods.

A total of 1,052 cognitively normal individuals (aged 69 to 85 years; 64% women) were followed for more than 10 years. During follow-up, 147 developed MCI and 73 developed dementia. Baseline variables included demographic data, lifestyle habits, functional status (Functional Activities Questionnaire), vascular risk factors, comorbidities across 11 systemic domains, number of medications, Charlson-Romano Comorbidity Index, self-perceived health (0–100 nomogram and comparison with health status one year prior), brain volumes on MRI, ApoE genotype, and plasma biomarkers of neurodegeneration. These were analyzed as potential risk factors for the incidence of MCI or dementia. Risk was assessed using univariate and multivariate Cox proportional hazards models.

Results.

In this cohort, age, self-perceived health status, functional status, ApoE ε4 genotype, and plasma p-tau217 levels were significantly associated with MCI incidence (HR 1.1 [95% CI 1.02–1.15], 0.98 [95% CI 0.97–0.993], 1.5 [95% CI 1.22–1.78], 1.6 [95% CI 1.03–2.47], and 1.4 [95% CI 1.35–1.53], respectively). Worsening self-perceived health over the previous year and elevated plasma p-tau217 levels were associated with dementia incidence (HR 3.2 [95% CI 1.56–6.44] and 1.4 [95% CI 1.27–1.48], respectively).

Conclusions.

Self-perceived health status is a stronger predictor of cognitive decline and dementia than objective health status.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 38

**Introduced by:** Arnaldo Parra-Damas

**Title:**

**CELL TYPE-SPECIFIC HIPPOCAMPAL ALTERATIONS ASSOCIATED WITH EARLY MEMORY DEFICITS IN APP/TAU MICE**

**First Author:** Arnaldo Parra-Damas

**Authors:** Ángel Deprada[ac], María Dolores Capilla-López[ac], José Rodríguez Álvarez[ac], Carlos A. Saura[ac], Arnaldo Parra-Damas[ac]

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**Abstract:**
Excitatory/inhibitory neurotransmission imbalance in memory neural circuits affected by amyloid-β and tau pathologies are thought to underlie memory deficits in Alzheimer's disease (AD). However, the sex-specific cellular mechanisms by which these neuropathological hallmarks induce dysfunction of excitatory and inhibitory hippocampal neurons remain poorly understood. Here, we combined behavioral, molecular, biochemical, cell type-specific RNA-seq, as well as conventional and advanced histological and microscopy analyses, including tissue clearing and expansion microscopy, to assess the effect of Aβ and Tau accumulation in the hippocampus of male and female APP/Tau mice, focusing on Pvalb-expressing interneurons. Our results show early Aβ and tau pathology in hippocampal excitatory neurons of 6 month-old APP/Tau mice, as well as tau accumulation at hippocampal synapses and reduction of synaptic proteins, coinciding with early sex-dependent spatial learning deficits. Interestingly, we observed selective reduction, disrupted morphology, and altered expression of synaptic genes in hippocampal Pvalb+ interneurons from 6 month-old APP/Tau female mice, despite absence of Aβ and tau accumulation in these cells, suggesting that excitatory-expressed Aβ and tau exert cell non-autonomous effects causing structural and transcriptional alterations in Pvalb+ neurons from APP/Tau female mice. Taken together, our results suggest that early transcriptional and structural changes in Pvalb+ interneurons may contribute to sex-specific vulnerability to AD pathology and memory dysfunction in APP/Tau mice.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 39

**Introduced by:** Sarka Pokorna

**Title:**

**LIPID ACCUMULATION LEADS TO BIOPHYSICAL CHANGES IN LIPID DROPLETS AND CELLULAR MEMBRANES OF GAUCHER DISEASE NEURONAL CELL MODELS**

**First Author:** Sarka Pokorna

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**Abstract:**

Gaucher disease (GD), caused by mutations in the GBA1 gene, is one of the most common lysosomal storage disorders.1 Although GD presents with heterogeneous symptoms, it is classified into three types, with the severe forms, types 2 and 3, involving neuropathology. In addition to GD, GBA1 mutations are recognized as the highest genetic risk factor for Parkinson's disease (PD). The GBA1 gene encodes the lysosomal enzyme acid β-glucosidase (GCase), which is responsible for degrading the sphingolipid glucosylceramide (GlcCer). When GCase is deficient, GlcCer accumulates, primarily within lysosomes.

Using neuronal cell models of GD we identified what are the changes in biophysics of several lipid-based organelles: plasma membrane - a key player in neuronal function, lysosomal membrane - an initial place of GlcCer accumulation and lipid droplets – organelles central to cellular lipid metabolism. Our data show complex changes in the plasma membrane organization and decreased lysosomal membrane fluidity upon GlcCer accumulation. Moreover, in GD cells we observed huge accumulation of lipid droplets, along with changes in their biophysical properties. Consistent with this, studies have shown upregulation of lipid droplet-related genes in GD mouse models.2 Additionally, altered levels of various sphingolipids—not just GlcCer—have been observed in GD cells. Given that crucial neuronal functions are facilitated by plasma membrane ion channels, whose activity is regulated by their lipid environment, alterations in plasma membrane fluidity may play a significant role in neuropathology. Moreover, disbalanced lipid droplet homeostasis has been described in various neurodegenerative diseases3, including PD, highlighting their potential relevance in understanding the connection between GD and neurodegeneration.

1 Grabowski, G. A. et al, Crit Rev Biochem Mol Biol 25 (1990).
2 Blumenreich, S. et al, J Neurochem 156 (2021).
3 Farmer, B. C. et al, Front Neurosci 14, (2020).

# BOOK OF ABSTRACTS 2025

## POSTER N.º 40

**Introduced by:** Alba M. Lucart Sanchez

**Title:**

**CELL-TYPE-SPECIFIC EV PROTEOMES IN THE BRAIN UNCOVER FUNCTIONAL SPECIALIZATION AND NOVEL TARGETS FOR EV-SUBTYPE SELECTION**

**First Author:** Alba M. Lucart Sanchez

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**Abstract:**

Introduction: Extracellular Vesicles (EVs) are nanoparticles secreted by cells into extracellular spaces and biological fluids, playing critical roles in intercellular communication. Their study offers insights into the physiopathological mechanisms of diseases, including neurodegenerative disorders. Several markers have been proposed for isolating brain-derived EVs by cellular origin, however, there is still a lack of consensus. This study provides a comprehensive proteomic characterization of neuronal, microglial, and astroglial EVs from brain tissue, improving our understanding of cell-type-specific roles in brain homeostasis and highlighting potential key proteins for EV subtype selection.

Methods: Cell-type-specific EVs were isolated from mouse brain tissue by differential ultracentrifugation followed by immunocapture with microbeads conjugated to antibodies targeting Neuronal- (NDEV), Microglial- (MDEV), and Astroglial-Derived EVs (ADEV). EV subtypes were validated using Western blotting (WB), nanoparticle tracking analysis (NTA), and electron microscopy (EM). For proteomic analysis, digested proteins were analyzed using data-dependent acquisition. Protein identification and quantification were performed using FragPipe with standard parameters. MaxLFQ intensity values were log□-transformed and grouped by condition. The main findings were validated in human post-mortem brains.

Results: Characterization by WB showed enrichment of EV and cell-type-specific markers. NTA and EM confirmed the presence of nanoparticles with the size and morphology corresponding to EVs. Proteomic analysis revealed 962 proteins shared across all samples, while 199, 56, and 64 proteins were uniquely upregulated in NDEV, MDEV, and ADEV, respectively. Gene Ontology analysis showed enrichment in vesicle-related proteins and distinct functional pathways: NDEV was associated with synaptic and ion transport functions, MDEV with immune defense, and ADEV with metabolic activity. Comparative profiling identified differentially expressed proteins across cell-type-specific EVs, including cell-type and EV-specific markers.

Conclusion: This study provides a comprehensive proteomic characterization of brain cell-type specific EVs, highlighting their functional specialization and identifying novel markers for EV subtype selection with potential implications for circulating EV-based diagnostics.

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### POSTER N.º 41

**Introduced by:** Carlos Avilés Granados

**Title:**

**GLUN2A-DEPENDENT IONIC CURRENTS AND CALCIUM SIGNALING IN HUMAN IPSC-DERIVED NEURONS**

**First Author:** Carlos Avilés Granados

**Authors:** Carlos Avilés Granados[iae], Sergio Escamilla[iae], Francisco Andrés Peralta[i], Ana V Paternain[i], Maria-Ángeles Cortés-Gómez[i], Henrik Zetterberg[hbcfdg], Elvira de la Peña[i], Juan Lerma[i], Federico Salas-Lucia[j], Javier Sáez-Valero[iae], Inmaculada Cuchillo-Ibáñez[iae]

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**Abstract:**
Gene expression data indicate that during human brain development, glutamatergic neurons change the main subunits of their glutamate receptors to modulate their function. This change favors the subunit GluN2A over GluN2B. That the function of these neurons depends on GluN2A is a well-established concept and stands as a hallmark of neuronal maturation. However, functional evidence supporting this concept in human neurons was missing. Here, we complete the picture and provide evidence that GluN2A drives ionic currents and calcium signaling in mature human glutamatergic neurons derived from induced Pluripotent Stem Cells (iPSCs). Confocal imaging shows a significant increase during neuronal maturation in the number of synaptic NMDARs. Integrated whole-cell current clamp, calcium imaging, and pharmacological modulation show that at least half of the variations in ion currents and calcium signaling in mature glutamatergic neurons depend on GluN2A. Our results provide insight into how glutamate receptor subunits act during brain development and function, laying the groundwork for delineating the mechanisms of action of these components in health and disease.

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### POSTER N.º 42

**Introduced by:** Rachele Marino

**Title:**

**DISRUPTED TDP-43 SUMOYLATION AND SUMO-1 INTERACTION DRIVES MIS-LOCALIZATION AND AGGREGATION IN OXIDATIVE STRESS INDUCED CELLULAR MODEL**

**First Author:** Rachele Marino

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**Abstract:**

Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disease characterized by progressive motor neuron loss. A pathological hallmark of ALS is the mislocalization of the nuclear RNA/DNA-binding protein TDP-43 to the cytoplasm, where it forms toxic aggregates. This mislocalization is associated with stress granule (SG) formation and is influenced by post-translational modifications (PTMs), including SUMOylation. Recent studies have identified lysine 136 on TDP-43 as a site of SUMOylation, a modification known to regulate protein localization, interactions and functions. Impairment of this process has been linked to increased TDP-43 cytoplasmic accumulation and dysfunction.

To investigate this, we modeled stress-induced aggregation in SH-SY5Y neuroblastoma cells using sodium arsenite (SA) treatment, followed by immunofluorescence (IF), western blotting (WB), and co-immunoprecipitation (co-IP) analysis.

Our data show cytoplasmic co-localization of TDP-43 with SUMO-1 and the SG marker G3BP1 in stress-induced aggregates. Upon SA treatment, we observed a significant increase in the number of TDP-43 and SUMO-1 aggregates.

Co-IP analysis revealed a non-covalent interaction between SUMO-1 and TDP-43 under basal conditions, which was disrupted after SA exposure, coinciding with decreased SUMOylation. A similar interaction was detected in the nuclear fraction, supporting the idea that SUMO-1 contributes to TDP-43 nuclear retention and stability.

Importantly, modulation of TDP-43 SUMOylation altered its behavior: in a model expressing a SUMOylation-deficient TDP-43 mutant, the protein still aggregated after stress but remained confined to the nucleus. This suggests that SUMOylation is essential for TDP-43 nucleocytoplasmic shuttling and proper stress response.

These findings suggest that SUMO-1 is critical for the proper localization and function of TDP-43. Disruption of the SUMO-1/TDP-43 interaction appears to promote pathological cytoplasmic aggregation, highlighting a mechanistic role for SUMOylation in ALS pathogenesis.

Based on our preliminary data, the SUMO-1/TDP-43 interaction represents a potential checkpoint in preventing TDP-43-mediated neurodegeneration. Moreover, our results indicate that SUMOylation is essential for the nucleocytoplasmic shuttling of TDP-43, further underscoring its importance in maintaining TDP-43 homeostasis under stress conditions.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 43

**Introduced by:** Patricia Regina Manzine

**Title:**

**BLOOD ISOFORMS' LEVELS OF ADAM10 IN DIFFERENT TYPES OF DEMENTIA**

**First Author:** Patricia Regina Manzine

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**Abstract:**
A disintegrin and metalloproteinase protein 10 (ADAM10) is the main alpha-secretase involved in the non-amyloidogenic cleavage of amyloid precursor protein (APP). ADAM10 exists in multiple isoforms, including the membrane-bound form (mADAM10), mainly expressed in platelets and neuronal cells, and the soluble form (sADAM10), detectable in plasma, serum, and CSF. Previous studies have shown alterations in platelet and plasma ADAM10 levels in Alzheimer's disease (AD) compared to cognitively healthy controls. However, few investigations have explored whether these alterations also occur in non-AD dementias. This study aimed to investigate the blood forms of ADAM10 in AD, frontotemporal dementia (FTD), Parkinson's disease dementia (PD), and Lewy body dementia (LBD). It was a multicenter, cross-sectional, and analytical study carried out among community-dwelling older adults aged ≥ 60 in the interior of the State of São Paulo, Brazil. Analyses were performed using one-way ANOVA with Kruskal-Wallis, two-tailed Mann-Whitney tests, Receiver Operating Curves, GraphPad Prism, and MedCalc. It included 38 participants, 10 AD, 13 FTD, 8 PD, and 7 LBD. The highest mADAM10 levels were observed in the PD group, with significantly elevated values compared to all other dementia types. The AD group exhibited the lowest sADAM10, with statistically significant differences observed between this group and all other dementia types. Additionally, the FTD group showed a significant difference compared to the PD group. The association of isoforms did not demonstrate improvements in differentiating between dementias. Only the AD group showed a marked distinction between the isoforms, underscoring the greater diagnostic relevance of sADAM10 particularly for AD.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 44

**Introduced by:** Rafael Fernández-Chacón

**Title:**

**CSPα/DNAJC5 IS ESSENTIAL FOR THE MAINTENANCE OF ADULT NERVOUS SYSTEM HOMEOSTASIS**

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**Abstract:**
The continuous maintenance of synaptic proteins is fundamental for neuronal viability and function throughout life, yet the underlying molecular mechanisms remain incompletely understood. The co-chaperone Cysteine String Protein alpha (CSPα/DNAJC5) has been implicated in protecting synapses from degeneration, but its precise cellular and molecular roles are still being elucidated. Mutations in DNAJC5 cause adult-onset autosomal dominant neuronal ceroid lipofuscinosis (CLN4/Kufs disease), a devastating neurodegenerative disorder affecting young adults. Conventional CSPα/DNAJC5 knockout (KO) mice exhibit early lethality, limiting the study of its function in the adult or aging brain in vivo. To overcome this limitation, we developed a tamoxifen-inducible conditional knockout mouse model (UBCCreERT2:Dnajc5flox/flox) that allows temporal deletion of CSPα/DNAJC5 in adulthood. Acute loss of CSPα/DNAJC5 in these mice resulted in severe neurological decline and premature death, revealing its critical function in the mature nervous system. Importantly, this phenotype occurred without evidence of lipofuscin accumulation, confirming that CSPα/DNAJC5 deficiency does not mimic CLN4 pathology, as recently described (Lopez-Begines, Borjini et al., Science Advances, 2025). Unexpectedly, CSPα/DNAJC5 deletion also led to skin hyperpigmentation and keratinocyte abnormalities, suggesting a novel role in skin homeostasis. Transcriptomic profiling of cortical tissue revealed dysregulation in genes associated with lipid metabolism, synaptic integrity, glial-neuronal signalling, and myelination. Although systemic adeno-associated virus (AAV) delivery of CSPα/DNAJC5 using the PHP.eB capsid achieved widespread neuronal transduction, it failed to rescue the severe neurological phenotype. This suggests that once neuronal dysfunction is initiated, virally delivered CSPα/DNAJC5 may be insufficient to reverse the damage, possibly due to inadequate viral load. Our results demonstrate that CSPα/DNAJC5 is indispensable not only during postnatal development but also for sustaining neuronal function in the mature and aging adult brain. Furthermore, this study highlights novel molecular pathways potentially involved in CSPα/DNAJC5-related neurodegeneration. Supported by: Projects PID2019-105530GB-I00, PID2022-138957NBI00, FPU18/01700 funded by MICIU/AEI/10.13039/501100011033) and ERDF. Projects PY20-RE-053-USE, P18-FR-2144 funded by Junta de Andalucía-Consejería de Universidad, Investigación e Innovación and ERDF. CIBERNED, ISCIII and Fundación Tatiana Pérez de Guzmán El Bueno.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 45

**Introduced by:** Mario Lopez-Manzaneda

**Title:**

**IMAGING MITOCHONDRIAL PROTEIN IMPORT IN REAL TIME USING A GREEN FLUORESCENCE PROTEIN SPLIT SYSTEM**

**First Author:** Mario Lopez-Manzaneda

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**Abstract:**
Mitochondrial biogenesis is heavily dependent on the nuclear genome. From its almost 2000 proteins, 99% of its are nuclear encoded. These proteins are synthesized on cytosolic ribosomes and transferred into the organelle in a process termed as mitochondrial protein import. Several neurological and neurodegenerative diseases (like spinocerebellar ataxia, autosomal recessive (SCAR2), multiple mitochondrial dysfunctions syndrome 6 (MMD6) or Mohr-Tranebjaerg syndrome (MTS)) are directly linked to alterations or mutations in different proteins that conform the machinery in charge of this process. Additionally, there is evidence of alterations in this process in other neurodegenerative diseases such as Parkinson's or Alzheimer's diseases. Nevertheless, little is known about the mechanisms that regulate mitochondrial protein import and virtually nothing about how this process adapts to metabolic demands or external challenges in mammalian cells. We have engineered a Green Fluorescence Protein (GFP) Split System that allows for the first time the dynamic study of mitochondrial protein import. This biosensor explores the major import route in charge of transferring two-thirds of all mitochondrial proteins (mitochondrial pre-sequence pathway). Using this tool, we can start to gain unprecedented information about mitochondrial protein import and its regulation with single-cell resolution in health and disease.
Supported by: (1) "Ayuda para la recualificación del sistema universitario español Modalidad Margarita Salas Project" to MLM; ERC Starting Grant (SynaptoEnergy, European Research Council; ERC-StG-852873), 2019 ATIP-Avenir Grant (CNRS, Inserm) and a Big Brain Theory Grant (ICM) to JdJS (2) Project PID2022-138957NBI00, funded by MICIU/AEI/10.13039/501100011033) to RFC.

## BOOK OF ABSTRACTS 2025

### POSTER N.º 46

**Introduced by:** Elizabeth Valeriano-Lorenzo

**Title:**

**MODULATORY EFFECT OF GLIAL FIBRILLARY ACIDIC PROTEIN (GFAP) LEVELS ON THE ASSOCIATION BETWEEN PLASMA P-TAU217 LEVELS AND COGNITIVE DECLINE IN OLDER DULTS**

**First Author:** Elizabeth Valeriano-Lorenzo

**Authors:** Elizabeth Valeriano-Lorenzo[a], Mario Ricciardi[a], Sonia Wagner-Reguero[a], Minerva Martinez[a], Belén Frades[a], Mª Ascensión Zea-Sevilla[a], Meritxell Valentí[a], Teodoro del Ser[a], Pascual Sánchez-Juan[a]

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**Abstract:**

Background: Recent studies demonstrate an association between glial fibrillary acidic protein (GFAP) levels and post-mortem tau pathology and highlight its role as a link between amyloid and tau pathology in Alzheimer's disease (AD) [Sánchez-Juan, Pascual, et al., Brain 147.5 (2024): 1667-1679.]. Additionally, growing evidence suggests that neuroinflammation may modulate the effects of tau spread on cognitive impairment in AD [Peretti, Débora E., et al., Brain 147.12 (2024): 4094-4104]. In this context, this study aims to assess the synergistic effect on cognitive decline of plasma levels of GFAP and p-tau217, as surrogate biomarkers of reactive astrogliosis and AD pathophysiology, respectively.

Method: We included 354 cognitively unimpaired individuals (mean age = 74.1±3.6 years; 61.9% women) from the Spanish Vallecas Project, a longitudinal study of elderly volunteers. Plasma GFAP concentrations were measured at three time points of the follow-up (baseline, intermediate, and final visits) using the highly sensitive single molecular array (SIMOA), and those >141.87pg/mL were considered high (GFAP+), additionally, an annual rate of change >10.26pg/mL was considered fast (GFAPfast.rate). Plasma p-tau217 levels at baseline were measured using the Lumipulse platform, and those >0.247pg/mL were considered high (p-tau217+). Cognition was assessed annually over a 10-year period using a modified Preclinical Alzheimer Cognitive Composite (PACCm). Linear mixed-effect models were used to analyse the longitudinal trajectories of cognition and GFAP and to examine the moderation effect of GFAP, controlling for education, sex, age and ApoE4.

Result: 58(16,4%) participants were classified as p-tau217+, 176 (49,7%) as GFAP+, and 173(48,9%) showed GFAPfast.rate. Participants with p-tau217+ and higher annual GFAPfast.rate showed a significantly faster cognitive decline (βTime*pTau217*GFAPfast.rate = -0.158; P<0.001) than those with non-GFAPfast.rate. However, baseline levels of GFAP and p-tau217 did not show a significant interaction (βTime*pTau217*GFAPbaseline = -0.076; P=0.094).

Conclusion: Our results indicate that GFAPfast.rate modulates the relationship between p-tau217 and cognitive decline independently of age, sex and ApoE4, with a stronger decline observed in individuals with p-tau217+ who likely present a reactive astrogliosis. Further studies are needed to examine the mechanisms underlying the interaction between reactive astrogliosis and tau spread in the AD continuum. This could help us better understand neuroinflammation as a potential target for therapeutic strategies.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 47

**Introduced by:** Jaime Pignatelli Garrigós

**Title:**

**INSULIN MEDIATES THE CROSSTALK BETWEEN THE BRAIN FUNCTION AND METABOLISM BY MODULATING FOOD VALENCE THROUGH ASTROCYTES**

**First Author:** Jaime Pignatelli Garrigós

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**Abstract:**
Increasing evidence supports the notion that Alzheimer's disease (AD), a condition that presents heterogeneous pathological disturbances, is also associated with perturbed metabolic function affecting insulin. Impaired insulin activity leading to insulin resistance has been associated with cognitive decline and AD, and with non-cognitive alterations as anxiety, depression, apathy, etc. Eating poses an affective value (i.e.: valence), recruiting sensory, memory, and mood brain functions; however, brain cells involved in assigning valence to brain states are not well described yet. Since astrocytes modulate brain states, and insulin regulates feeding behavior and exerts its central actions in part through astrocytes, we analyzed the role of the insulin receptor in astrocytes in assigning valence to food. We examined the modulatory actions of food on anxiety and fear, as proxies of the affective influence of food on mood. Mice lacking insulin receptors (IR) in GFAP astrocytes (GFAP-IR KO mice) showed increased anxiety and fear in response to food, as compared to control littermates. Further, we observed that orexin neurons in the lateral hypothalamus (LH) were deregulated in GFAP-IR KO mice. Transcriptomic analysis revealed alterations in FKBP5 gene expression in the hippocampus and the hypothalamus from GFAP-IR KO mice. Those data suggest that astrocytic insulin acts on at least two sites: regulating FKBP5, hypothalamic Orexin neurons, and modulating behavioral responses to food by affecting oxidative stress levels in response to food. We speculate that cellular mechanisms underlying eating disorders may involve insulin modulation of food valence through astrocytes, such as those found in AD patients.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 48

**Introduced by:** Orfeas Vourkas

**Title:**

**FDG-PET OUTPERFORMS MRI IN DETECTING EARLY NEURODEGENERATIVE CHANGES LINKED TO NEUROFIBRILLARY TANGLE PATHOLOGY: AN IMAGING-PATHOLOGY CORRELATION STUDY**

**First Author:** Orfeas Vourkas

**Authors:** Orfeas Vourkas[a], Linda Zhang[a], Alberto Rabano[a], Pascual-Sanchez Juan[a], Jesús Silva Rodriguez[a], Michel J. Grothe[a]

**Filiation:** [a]Reina Sofia Foundation Alzheimer Center, CIEN Foundation, ISCIII

**Abstract:**

Background

Neurofibrillary tangle pathology (NFTp) in Alzheimer's disease (AD) is closely related to neurodegeneration, which can be measured in vivo using structural MRI or FDG-PET. We aimed to assess the relative sensitivities of FDG-PET-measured hypometabolism, and MRI measured gray matter (GM) atrophy to early stages of NFTp as assessed by post-mortem neuropathological examination.

Methods

We studied 88 individuals from the Alzheimer's Disease Neuroimaging Initiative (ADNI) autopsy cohort who had Braak NFTp staging performed at autopsy and had FDG-PET and structural T1-MRI scans acquired before death (imaging-to-death interval: 3.4±2.3 years). Associations of Braak stages with regional FDG-PET SUVRs and GM volumes on MRI were assessed in exploratory brain-wide Spearman correlation analyses across 52 cortical and subcortical brain regions. For regions showing a significant association ($p<0.05$, FDR-corrected), we then performed pair-wise comparisons between grouped Braak stages 0/I/II (N=19), III-IV (N=13), and V/VI (N=56).

Results

Higher Braak stages were significantly associated with lower FDG-PET SUVR in several temporo-parietal cortical regions typically affected by AD. Compared to the Braak 0/I/II reference group, most of these regions showed significant and pronounced (Cohen's $d>0.9$) hypometabolism in early Braak stages III-IV, and severity of hypometabolism further increased in Braak stages V/VI. Although GM volume on MRI showed a similar regional association with Braak stages, effect sizes were considerably lower and differences to the Braak 0/I/II reference group were only significant for advanced Braak stages V/VI.

Conclusions

Glucose hypometabolism as measured by FDG-PET is a sensitive neuroimaging marker of the neurodegenerative changes that accompany progressive stages of neurofibrillary tangle pathology. Earliest NFTp-related neurodegenerative changes captured by FDGPET hypometabolism appear to precede macrostructural gray matter atrophy as measured by MRI.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 49

**Introduced by:** Jorge Sáez Leyva

**Title:**

**APOLIPOPROTEIN E DECREASES IN COVID-19 PATIENTS**

**First Author:** Jorge Sáez Leyva

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**Abstract:**

Apolipoprotein E (apoE) is a secreted glycoprotein that is present in plasma, cerebrospinal fluid and other biological fluids. ApoE is a multifunctional protein involved in lipid metabolism and cholesterol homeostasis, but also unlipidated apoE can modulate key cellular signaling pathways through receptor interactions. In humans, three major allelic variants of the APOE gene exist: ε2, ε3, and ε4. The ε4 allele (APOE4) is a well-established genetic risk factor for Alzheimer's disease, and emerging evidence suggests a possible association between APOE4 and both susceptibility to and severity of COVID-19. Although, little is known about how apoE protein levels are altered in the context of COVID-19. In this study, we assessed plasma apoE levels in patients during the acute phase of COVID-19 infection and following recovery. Given the coexistence of immature and mature glycoforms, we employed electrophoresis and western blotting techniques to separate and quantify these distinct apoE species. Our findings reveal that patients in the acute phase of COVID-19 exhibit significantly decreased levels of mature apoE species in comparison with levels assessed two months post-recovery. In addition, apoE was examined in cerebrospinal fluid of individuals experiencing long COVID. We further examined their levels in the serum of a transgenic K18-hACE2 mice challenged with a lethal dose of SARS-CoV-2. In K18-hACE2 infected mice, we also observed a decrease in the levels of serum apoE. In summary, we report a marked decrease in circulating apoE during active COVID-19 infection, which may reflect compromise in its diverse biological functions and potentially contribute to disease pathophysiology.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 50

**Introduced by:** Ana Quelle Regaldie

**Title:**

**MODELING SPINOCEREBELLAR ATAXIA TYPE 36 IN ZEBRAFISH: INSIGHTS INTO POLY-GP TOXICITY AND MOLECULAR PATHWAYS**

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**Abstract:**

Spinocerebellar ataxia type 36 (SCA36) is a rare late-onset neurodegenerative disorder caused by a GGCCTG hexanucleotide repeat expansion in the first intron of the NOP56 gene. Clinically, it presents with cerebellar ataxia, sensorineural hearing loss, and lower motor neuron involvement. Notably, the pathogenic expansion is structurally and mechanistically similar to the GGGGCC repeat expansion in C9ORF72, the most common genetic cause of ALS and FTD. Both expansions undergo repeat-associated non-ATG (RAN) translation, generating toxic dipeptide repeat proteins (DPRs). Among the DPRs produced, poly-GP and poly-PR are common in both diseases, suggesting common pathogenic mechanisms. Although poly-GP has long been considered non-toxic, recent studies suggest it can trigger neurotoxicity in the context of partial gene haploinsufficiency.

In order to elucidate the molecular mecanisms of SCA36, we developed the first zebrafish models for SCA36, expressing the NOP56 intronic expansion producing poly-GP with and without nop56 haploinsufficiency. Phenotypic characterization included analysis of cerebellum, motor neurons, motor behaviour, muscle structure and poly-GP aggregation. Transcriptomic, proteomic and metabolomic profiling were performed to uncover shared pathways.

SCA36 zebrafish exhibited neurodegenerative phenotypes and differential DPR aggregation depending on nop56 dosage. Poly-GP aggregates were more prominent and insoluble under haploinsufficiency, correlating with greater neurotoxicity. Omics analyses revealed overlapped dysregulated pathways in SCA36 zebrafish models including alterations in RNA metabolism, proteolysis, and mitochondrial function.

Studying the mechanisms underlying SCA36 is essential to identify biomarkers and shared therapeutic targets across repeat expansion neurodegenerative diseases.

# BOOK OF ABSTRACTS 2025

## POSTER N.º 51

**Introduced by:** Viñas Andrés-Simón

**Title:**

**BRAIN STS INHIBITION AND NEUROSTEROID MODULATION BY STX64 IN A RAT MODEL OF MEMORY IMPAIRMENT**

**First Author:** Marta Alaiz-Noya

**Authors:** Marta Alaiz-Noya[c], Juan Antonio Fernández Cabrera[b], Elena Rodríguez Sandoval[b], Cristina García Gutiérrez [a]Javier Valle Galisteo [c], Mercedes María Pérez Jiménez[a], Antonio Aires[c], Daniel Zamanillo[c], Sandra Gavaldá[c], Viñas Andrés-Simón[c], Ángel Cebolla[c], Manuel Jesús Muñoz[a], Ángel Manuel Carrión[b]

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**Abstract:**

STX64 (formerly Irosustat) is a steroid sulfatase (STS) inhibitor being developed as a novel therapy for neurodegenerative disorders. By inhibiting STS, STX64 increases levels of sulfated neurosteroids that may support cognitive function. Here we evaluated the pharmacodynamic properties of STX64 in a scopolamine-induced amnesia rat model. Rats were treated with STX64 (1 or 4 mg/kg) or donepezil in a standard memory task paradigm. STX64 significantly improved memory performance compared to vehicle controls, similar to the cognitive benefit seen with donepezil.

To confirm target engagement, plasma and brain samples were collected 24 hours after the last dose. In STX64-treated rats, brain STS activity was inhibited by more than 85% at both dose levels, with no inhibition observed in the other groups. Several sulfated neurosteroids were analyzed in plasma, with pregnenolone sulfate showing the most prominent increase: levels were more than three times higher in STX64-treated animals compared to non-treated groups.

Notably, no clear dose–response relationship was observed in cognitive performance, STS inhibition, or neurosteroid levels, suggesting that lower doses may still achieve biological efficacy. The persistence of STS inhibition 24 hours post-administration supports this hypothesis.

These findings provide the first evidence of brain pharmacodynamic action of STX64, indicating that this compound crosses the blood–brain barrier and engages its enzymatic target in the central nervous system. The data suggest that effective modulation of STS activity may be achieved with doses lower than those previously tested, potentially expanding the therapeutic window and safety margin. This favorable profile may be explained by the irreversible inhibition of STS and the reversible binding of STX64 to erythrocytes, creating a systemic reservoir that enables gradual tissue delivery without the need for sustained-release formulations.

In conclusion, STX64 demonstrated both cognitive efficacy and central target engagement in a rat model of memory impairment, supporting its further development for neurodegenerative diseases.

## BOOK OF ABSTRACTS 2025

### POSTER N.º 52

**Introduced by:** Jose Felix Moruno Manchon

**Title:**

**SEX DIFFERENCES IN IRON METABOLISM IN AN AGED MOUSE MODEL OF VASCULAR DEMENTIA**

**First Author:** Jose Felix Moruno Manchon

**Authors:** Jose Felix Moruno Manchon[a], Areej Ashraf[a], Sheelu Monga[a]

**Filiation:** [a]McGovern Medical School at UTHealth Houston

**Abstract:**
Impairment of the iron metabolism in the brain is associated with multiple brain pathologies, including vascular contributions to cognitive impairment and dementias (VCID). However, the underlying mechanisms are not well understood yet.
We utilize an aged mouse model of VCID, where micro-coils (0.18 mm diameter) are surgically implanted around the two bilateral carotid arteries (BCAS, bilateral carotid artery stenosis). Mice were maintained for two months. Mice were tested for behavior (open field, elevated plus maze, novel object recognition, and fear conditioning), and their brains were analyzed by IHC, Western blotting, and qPCR. We found that female BCAS mice exhibited cognitive deficits, neuroinflammation, and demyelination, compared with female sham mice. We also found that the brains of aged female BCAS mice had enhanced levels of ferrous iron and increased iron deposition, compared with female sham mice. Interestingly, these differences were not observed between male sham and male BCAS mice. We found that the expression of genes involved in iron transport and iron storage was significantly increased in the brains of male BCAS mice, but not in female BCAS, compared with sham mice. Western blot data revealed that ferritinophagy was more efficiently inhibited in the brains of male BCAS mice, compared with male shams, but not in female BCAS mice.
Our study establishes a foundation for sex differences in brain iron metabolism in a mouse model of VCID in aged mice, which may help to identify different approaches to treat patients of both sexes with vascular dementia.

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