NEAPOLITAN
BRAIN GROUP

20 Novembre 2026

BIOMARKERS IN NEUROSCIENCE:

PROGRESS, CHALLENGES, AND PERSPECTIVES

XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Università degli Studi di Napoli Federico II

Aula Magna (CESTEV)
via Tommaso De Amicis 95, Napoli

BOOK OF ABSTRACTS



SCIENTIFIC RATIONALE

Il progresso delle neuroscienze dipende sempre più dalla capacità di integrare informazioni provenienti da differenti livelli di indagine, dalla biologia molecolare e cellulare alla fisiopatologia, fino alla caratterizzazione clinica delle malattie neurologiche e neuropsichiatriche. In questo scenario, i biomarcatori rappresentano strumenti fondamentali per comprendere i meccanismi alla base delle patologie del sistema nervoso, identificare precocemente le alterazioni biologiche, monitorare la progressione della malattia e individuare nuove opportunità terapeutiche.

Il XIV Neapolitan Brain Group Meeting 2026, dedicato al tema *"Biomarkers in Neuroscience: Progress, Challenges, and Perspectives"*, si propone come un'importante occasione di confronto e di condivisione delle più recenti acquisizioni scientifiche nel campo delle neuroscienze. Il congresso affronterà il ruolo dei biomarcatori attraverso un approccio multidisciplinare, che comprende analisi molecolari e omiche, proteomica, metabolomica, neuroimaging, tecniche elettrofisiologiche, neurofisiologia clinica e modelli sperimentali avanzati. Particolare attenzione sarà dedicata all'identificazione di nuovi marcatori diagnostici, prognostici e predittivi nelle malattie neurodegenerative, neuroinfiammatorie, del neurosviluppo e psichiatriche, esplorando al contempo i meccanismi molecolari e cellulari che contribuiscono alla disfunzione del sistema nervoso. Dalle alterazioni sinaptiche e metaboliche alla neuroinfiammazione, dalla comunicazione intestino-cervello alla disfunzione neurovascolare, fino alla ricerca di nuovi bersagli farmacologici, i contributi scientifici offriranno una panoramica delle molteplici direzioni in cui si sta evolvendo la ricerca neuroscientifica.

Un obiettivo centrale dell'incontro sarà promuovere il dialogo tra ricerca di base e ricerca clinica, favorendo l'integrazione di approcci sperimentali e diagnostici e la traduzione delle conoscenze biologiche in strumenti concretamente applicabili alla pratica clinica. La crescente disponibilità di tecnologie ad alta sensibilità e di strategie di analisi integrata apre infatti nuove prospettive per una caratterizzazione più accurata delle patologie neurologiche e per lo sviluppo di approcci sempre più personalizzati.

Il **Neapolitan Brain Group Meeting** intende quindi consolidare il proprio ruolo di piattaforma di incontro per ricercatori, neuroscienziati, clinici e giovani studiosi, stimolando collaborazioni interdisciplinari e nuove prospettive di ricerca. Attraverso la condivisione di risultati originali, esperienze e idee, il congresso vuole contribuire ad affrontare le sfide ancora aperte nelle neuroscienze e a delineare nuove opportunità per la diagnosi, il monitoraggio e il trattamento delle malattie del sistema nervoso.

SCIENTIFIC RATIONALE

Progress in neuroscience increasingly relies on the integration of information across multiple levels of investigation, from molecular and cellular biology to pathophysiology and the clinical characterization of neurological and neuropsychiatric disorders. Within this evolving landscape, biomarkers represent essential tools for understanding disease mechanisms, detecting early biological alterations, monitoring disease progression, and identifying novel therapeutic opportunities.

The XIV Neapolitan Brain Group Meeting 2026, entitled *"Biomarkers in Neuroscience: Progress, Challenges, and Perspectives"*, aims to provide an important forum for discussing and sharing the latest scientific advances in neuroscience. The meeting will explore the role of biomarkers through a multidisciplinary perspective, encompassing molecular and omics approaches, proteomics, metabolomics, neuroimaging, electrophysiological techniques, clinical neurophysiology, and advanced experimental models.

Particular emphasis will be placed on the identification of novel diagnostic, prognostic, and predictive biomarkers across neurodegenerative, neuroinflammatory, neurodevelopmental, and psychiatric disorders. At the same time, the meeting will address the molecular and cellular mechanisms underlying nervous system dysfunction. From synaptic and metabolic alterations to neuroinflammation, from gut–brain communication to neurovascular dysfunction, and from disease-associated molecular signatures to the identification of novel pharmacological targets, the scientific contributions will highlight the expanding scope and complexity of contemporary neuroscience research.

A central objective of the meeting is to strengthen the dialogue between basic and clinical research, fostering the integration of experimental and diagnostic approaches and facilitating the translation of biological discoveries into clinically relevant applications. The increasing availability of high-sensitivity technologies and integrated analytical strategies is opening new opportunities for more accurate disease characterization and the development of increasingly personalized approaches to diagnosis and treatment.

The **Neapolitan Brain Group Meeting** therefore seeks to consolidate its role as a platform for interaction among researchers, neuroscientists, clinicians, and early-career investigators, encouraging interdisciplinary collaborations and new research perspectives. By bringing together original findings, scientific expertise, and innovative ideas, the meeting aims to contribute to addressing current challenges in neuroscience and to identifying new opportunities for the diagnosis, monitoring, and treatment of disorders affecting the nervous system.

SCIENTIFIC CHAIR:

Ennio Del Giudice, Presidente Neapolitan Brain Group (NBG) – UNINA

SCIENTIFIC PROGRAMME COMMITTEE

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GENERAL INFORMATION

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For registration: Please visit
https://www.mgmcongress.org/index.php?route=product/product&product_id=1763

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During the Congress, participants may contact the MGM Secretariat at the dedicated desk.

Congress Venue

AULA MAGNA
CESTEV – Università degli Studi di Napoli Federico II
Via Tommaso De Amicis, 95
80131 Napoli (NA), Italia

AULA MAGNA
CESTEV – University of Naples Federico II
95, Via Tommaso De Amicis
80131 Naples, Italy

How to reach the Venue

- In metropolitana: prendere la Linea 1 (direzione Piscinola) e scendere alla fermata Policlinico. Da qui, proseguire a piedi per circa 5 minuti fino alla sede del CESTEV in Via Tommaso De Amicis, 95.
- In taxi: chiedere al conducente di raggiungere il CESTEV – Dipartimento di Scienze Biotecnologiche, Università Federico II, Via Tommaso De Amicis, 95 (zona Policlinico).
- Dalla Stazione Centrale (Piazza Garibaldi): prendere la Linea 1 in direzione Piscinola e scendere alla fermata Policlinico.
- Dall'Aeroporto di Napoli-Capodichino: è possibile raggiungere la sede direttamente in taxi **(aereoporto temporaneamente chiuso)**.

- By metro: take Metro Line 1 (direction Piscinola) and get off at Policlinico station. From there, CESTEV is approximately a 5-minute walk, at 95 Via Tommaso De Amicis.
- By taxi: ask the driver to take you to CESTEV – Department of Biotechnology, University of Naples Federico II, 95 Via Tommaso De Amicis (Policlinico area).
- From Naples Central Railway Station (Piazza Garibaldi): take Metro Line 1 towards Piscinola and get off at Policlinico station.
- From Naples International Airport (Capodichino): you can reach CESTEV directly by taxi **(airport temporarily closed)**.





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Al fine di garantire il regolare svolgimento dei lavori, si invitano i relatori a rispettare le seguenti indicazioni:

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2. Le presentazioni devono essere realizzate in formato PowerPoint (.ppt/.pptx).

3. Non è obbligatorio utilizzare il proprio computer portatile.

4. Si invitano i relatori a rispettare rigorosamente i tempi di presentazione assegnati. Sarà disponibile un sistema di conto alla rovescia per monitorare il tempo a disposizione.

Il personale tecnico sarà presente in aula per fornire assistenza.

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Gli autori che presentano un poster sono invitati a essere presenti durante le sessioni di discussione dei poster, secondo quanto previsto dal programma ufficiale.

- I poster devono essere preparati in lingua inglese.
- Dimensioni massime: 70 cm (larghezza) × 100 cm (altezza).
- I poster devono essere affissi sulla bacheca numerata assegnata.
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- I poster non rimossi entro l'orario previsto non saranno conservati dalla Segreteria Organizzativa.

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To ensure the smooth running of the programme, speakers are kindly requested to observe the following guidelines:

1. In accordance with CME regulations, specific medicinal product brand names may not be displayed during accredited sessions. Only generic names (active substances, instruments, devices) are permitted. Commercial brand names must not be mentioned, even when unrelated to the topic being presented. In addition, references to pharmaceutical companies are not allowed.

2. Presentations must be in PowerPoint format (.ppt/.pptx)

3. Personal laptops are not strictly required.

5. Speakers are kindly requested to adhere strictly to the allocated presentation time. A countdown

Technical staff will be available in the room to provide assistance.

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Presenting Authors are requested to be available during the poster discussion periods according to the official programme.

- Posters must be prepared in **English**.
- Maximum dimensions: **70 cm (W) × 100 cm (H)**.
- Posters must be displayed on the assigned numbered board.
- Posters must be removed at the end of the relevant poster session.
- Posters not removed within the scheduled time will not be stored by the Secretariat.

PROGRAMMA/PROGRAMME

08:45 – 09:30	**Welcome Addresses** Messaggio di saluto del Magnifico Rettore UNINA: Prof. Andrea Mazzucchi Presidente NBG: Prof. Ennio Del Giudice Direttore Dip. Neuroscienze UNINA: Prof. Ciro Costagliola/Prof. Maurizio Guida Direttore Dip. Med. Mol. e Biotecnologie Med.: Prof. Antonio Feliciello Direttore CESTEV
09:30 – 10:15	**Opening Lecture** Chair: Rosa Iodice, Irene Cantone **Keynote Speaker: Prof. Diego Centonze, Department of Systems Medicine, University of Rome "Tor Vergata"** *The future of multimodal biomarkers in neurological diseases*
10:15 – 10:45	**Coffee Break**
SESSION 1 **10:45 – 11:15**	**Omics and fluid biomarkers** Chair: Maria Pia Miano, Maurizio Taglialatela **Lecture** Prof. Ioannis Sotiropoulos, Institute of Biosciences and Applications, Athens *Exosomes as a novel diagnostic platform in the new era of Precision Medicine. Implications in Stress and Alzheimer's disease brain pathology*
11:15 – 12:00	**Short Talks** 1. Federica Carrillo: Circulating epilipids reveal a novel signature of oxidative lipid remodeling in Parkinson's disease. 2. Ilaria Iacobucci: Development of a comprehensive diagnostic pipeline integrating MALDI-MSI and Proteomics methodologies to map the molecular signature of epileptic FCDIIb lesions. 3. Federica Cieri: circRNAs as promising biomarkers in Amyotrophic Lateral Sclerosis.
SESSION 2 **12:00 – 12:30**	**Protein Aggregation and Structural Biomarkers in Neurodegenerative Diseases** Chair: Stefano Cinti, Giuseppina Mattace Raso **Lecture** Prof. Alfonso De Simone, Department of Pharmacy, University of Naples Federico II *Addressing the pathological aggregation of alpha-synuclein in synucleinopathies*
12:30 – 13:15	**Short Talks** 1. Carmen Biancaniello: Modulating α-Synuclein Amyloid Aggregation via Lipid Interactions: Insights from Wild-Type and Double-Mutant. 2. Natalia Abate: CSTB drives proteostasis and trafficking in neurodevelopment via TRiC/CCT: implications for EPM1 pathogenesis. 3. Andrea Castellaneta: Development of a UHPLC-APCI-HRMS Method for the Analysis of 21 Oxysterols in Plasma and SEC-Enriched Neuronal Extracellular Vesicles.

13:15 – 15:00	**Light Lunch and Poster Session**
SESSION 3 **15:00 – 15:30**	**Neurophysiology as a Tool for Biomarker Discovery** Chair: Fiore Manganelli, Vincenzo Barrese **Lecture** Prof. Vincenzo Di Lazzaro, Department of Medicine, University Campus Biomedico Roma *Modulating cortical excitability in Amyotrophic Lateral Sclerosis. Biomarkers and therapeutic implications*
15:30 – 16:15	**Short Talks** 1. Valentina Virginia Iuzzolino: Association of motor cortical metabolism with corticospinal physiology and neuroaxonal injury in amyotrophic lateral sclerosis: a Multimodal Study combining FDG-PET, TMS and plasma biomarkers. 2. Annarita Barone: Sensory-motor gating deficits across schizophrenia patient subgroups: a composite prepulse inhibition index analysis. 3. Dania Ioia: Precision-medicine approaches in severe epilepsies caused by gain-of-function variants in KCNT1.
SESSION 4 **16:15 – 16:45**	**Digital Biomarkers, Robotics and AI** Chair: Aniello Murano, Giovanna Sannino **Lecture** Prof. Fanny Ficuciello, Department of Electrical Engineering and Information Technology, University of Naples Federico II *Human-centred robotics and AI for neurodigital biomarkers*
16:45 – 17:30	**Short Talks** 1. Davide Ranucci: Dysarthria assessment in patients with Multiple Sclerosis. 2. Raffaella Mancino: GaitRef-MAE: Development of a Multimodal Transformer for Normative Gait Reference Generation in Amyotrophic Lateral Sclerosis. 3. Mariarosaria Meola: Force-Controlled Tactile Stimulation Using a Collaborative Robot to Study Attention.
17:30 – 18:00	**Best Presentation Award Ceremony and Closing Remarks** Chair: Ennio Del Giudice, Raffaele Dubbioso, Fabio Arturo Iannotti
18:00 – 18:30	**NBG Shareholders' Meeting**

Presidente NBG: Ennio Del Giudice
Comitato scientifico:
Raffaele Dubbioso
Fabio Arturo Iannotti
Rosa Iodice
Valentina Virginia Iuzzolino
Sirio Cocozza



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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°1

TITLE	**Modulation of NCX1 expression in monocytes associates with Multiple Sclerosis progression**
AUTHORS	M. Cammarota[1], V. Rubino[2], C. Criscuolo[1], A. Cianflone[3], M. De Martino[4], V. De Rosa[5], F. Esposito[6], G. Abbadessa[7], F. Carriero[8], G. Terrazzano[8], P. Chieffi[9], S. Bonavita[7], V. Bresciamorra[1], L. Annunziato[2], G. Ruggiero[2], F. Boscia[2]
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	Ionic imbalance and functional heterogeneity of monocytes play key roles in multiple sclerosis (MS) progression. A better understanding of monocyte response in the context of ionic dysregulation during MS course may have relevant implications for understanding of disease pathogenesis and treatments. The sodium calcium exchanger NCX1 influences monocyte-derived macrophages reactivity under inflammation; however little is known about its monocyte-specific expression during MS course. By means of RT-PCR, flow cytometry, and confocal analyses, we determined the expression profiling changes of NCX1 exchanger in monocytes of patients during relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) course. NCX1 expression was significantly upregulated in monocytes from transitional RRMS subjects. Conversely, NCX1 levels were significantly reduced in all monocyte subsets after conversion of RRMS to SPMS disease. Interestingly, NCX1 expression in monocytes significantly correlated with

	the percentage and growth ability of the regulatory T cell (Treg) subset, whose derangement underlies MS progression. Perturbation of transcripts encoding the isoform1 and 4 of the Ca2+-ATPase, the a1 subunit of the Na+/K+-ATPase, and the long non-coding RNA SLC8A1-AS1 associated with NCX1 changes in peripheral blood mononuclear cells (PBMC) during MS. Our findings demonstrated a stage-specific dysregulation of NCX1 exchanger in monocytes during MS progression and suggested that ionic imbalance in monocytes may influence not only their functional response but also the immune regulatory network during MS course. These data may be relevant for the identification of novel biomarkers and/or therapeutic targets in MS.
Contact	Mariarosaria Cammarota mariarocammarota@gmail.com

XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°2

TITLE	**Glucotoxicity modulates dopaminergic genes expression and G-quadruplexes content in SH-SY5Y cells**
AUTHORS	A. Croce[1], F. Zatterale[1], C. Bucciero[1], M. Longo[1], D. Conza[2], A. Nicolò[2], L. Ulianich[3], F. Beguinot[1], A. M. Malfitano[1] and F. Fiory[1]
AFFILIATION	[1]Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy; [2]Faculty of Medicine and Surgery, University of Naples Federico II; [3]Institute of Endotypes in Oncology, Metabolism and Immunology "G. Salvatore"(IEOMI), Naples, Italy
	Diabetes mellitus (DM) is associated with cognitive decline and dopaminergic dysregulation. Alterations of dopamine (DA) homeostasis may contribute to cognitive impairment in DM. Glucotoxicity resulting from chronic hyperglycemia leads to the accumulation of methylglyoxal (MGO), a reactive dicarbonyl. We previously demonstrated that, in SH-SY5Y cells, MGO reduces intracellular DA levels upregulating proteins able to decrease DA amount, including MAO-B (Monoamine oxidase B). Similarly, high glucose reduces DA levels in some brain regions in animal models, but the underlying molecular mechanisms are still unknown. To clarify these points, we treated SH-SY5Y cells with 50 mM glucose (HG) and evaluated by Western blot the expression of proteins involved in DA synthesis and degradation. We found that HG did not affect COMT (Catechol-O-methyltransferase), α-Syn (α-synuclein), MAO-B and DDC (DOPA decarboxylase) expression. In contrast tyrosine hydroxylase (TH) protein and mRNA levels evaluated by Western blot and RT-qPCR were decreased by 40% and 60% respectively upon HG exposure. Importantly, 50 mM xylose treatment did not significantly modify TH protein expression, supporting the specificity of HG effect. According to computational analysis, both TH and MAO-B promoters contain sequences potentially forming G-quadruplexes (G4s), DNA secondary structures able to regulate gene expression. Importantly, incubation of SH-SY5Y cells with G4s stabilizing agents such as BRACO-19 and PhenDC3 increased MAO-B expression, while decreasing TH expression, supporting a functional role for G4s in the regulation of these two genes. Since G4s are involved in neurological disorders, we hypothesized that glucotoxic insults such as MGO and HG could affect MAO-B and TH expression by modulating G4s. To investigate this possibility, SH-SY5Y cells were treated with 50 mM glucose for 48, 72, or 96 hours or with 400 μM MGO for 48 hours and intracellular G4s levels were quantified by flow cytometry using the G4s-specific BG4 antibody. We found that both MGO and HG increased the percentage of G4s-positive cells. Pretreatment with aminoguanidine, a MGO scavenger, almost completely abolished MGO effect on G4s and xylose treatment did not

	significantly affect cellular G4s content, indicating that the effects of HG and MGO on G4s are stimulus specific. Thus, we can conclude that HG decreases TH levels, MAO-B and TH expression is modulated by G4s and both MGO and HG increase cellular G4s content. Further studies are needed to identify the specific G4s regulated by HG and MGO in TH and MAO-B promoters. These results support a possible role of G4s in the regulation of DA homeostasis under glucotoxic conditions and identify the pharmacological modulation of G4s stability as a potential strategy to regulate TH and MAO-B levels in neuronal cells.
Contact	Alessandra Croce alessandracroce94@gmail.com

XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°3

TITLE	**Altered dendritic spine morphology and autophagy in Angelman syndrome models: involvement of serotonin receptor 7**
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	Background Angelman syndrome (AS) is a neurodevelopmental disorder caused by loss of maternal UBE3A expression, leading to impaired neuronal function and synaptic plasticity. Although UBE3A contributes to protein homeostasis, the involvement of autophagy in AS remains incompletely understood. Previous studies have shown that stimulation of the serotonin receptor 7 (5-HT7R) improves synaptic and behavioral deficits in AS mouse models. Here, we investigated dendritic spine abnormalities, early neuronal differentiation, and autophagy in mouse and human models, and assessed the effects of the selective 5-HT7R agonist LP-211. **Methods** Dendritic spine density and morphology were assessed in the cerebral cortex of adult AS and wild-type mice using DiIC18 labeling and visualization by confocal microscopy. Human neuronal progenitor cells, obtained from cerebral organoids generated from AS patient-derived induced pluripotent stem cells and controls, were differentiated for 8 days. UBE3A expression, proliferation and neuronal differentiation markers, and 5-HT7R levels were evaluated by western blot analysis. Autophagy was investigated by analyzing LC3B and p62/SQSTM1 under basal conditions and following LP-211 treatment, with or without bafilomycin A1. **Results** AS mice displayed increased cortical dendritic protrusion density, including a higher density of thin spines with reduced length, alongside smaller mushroom spine heads, suggesting altered spine maturation. In the human model, AS cells showed reduced 5-HT7R expression, as well as reduced Ki67 and increased MAP2 levels at day 8, indicating reduced proliferation and faster neuronal differentiation. At this early stage, AS cells also exhibited increased LC3B puncta and p62/SQSTM1 accumulation, compatible with altered autophagic turnover and potentially inefficient cargo degradation. LC3B accumulation following bafilomycin A1 exposure indicated that autophagosome formation remained at least partially preserved. When

	cells were treated with LP-211, control cells display reduced p62/SQSTM1 levels and promoted LC3B and p62 accumulation under lysosomal blockade, supporting enhanced autophagic flux. Conversely, AS cells showed an attenuated response, with no additional increase in LC3B puncta following combined LP-211 and bafilomycin A1 treatment compared with bafilomycin A1 alone.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°4

TITLE	**Plasma NfL, GFAP and pTau181 define distinct biological axes in amyotrophic lateral sclerosis**
AUTHORS	Rosanna Balzano[1]; Gianmaria Senerchia[1], Valentina Virginia Iuzzolino[1], Myriam Spisto[1-2], Fabiana Panico[1], Carmela Polito[3], Lucia Aruta[1], Mariano Fiorenza[3], Rosa Sirica[3], Daniela Terracciano[3], Raffaele Dubbioso[1]
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	Objectives Amyotrophic lateral sclerosis (ALS) shows marked clinical and biological heterogeneity. Plasma NfL, GFAP, and pTAU181 are promising blood biomarkers, but their biological meaning remains unclear. We defined their distinct roles and tested whether their combined use identifies biologically meaningful ALS subgroups. **Material and methods** We conducted a cross-sectional biomarker study in a deeply phenotyped ALS cohort with neurological and healthy controls. We measured plasma NfL, GFAP, and pTAU181 with automated immunoassays. We assessed upper motor neuron involvement with TMS and clinical scales, and lower motor neuron involvement with electromyography and strength testing. We adjusted all models for age, sex, and rate of progression. We used latent profile analysis to identify biomarker-based subgroups. **Results** ALS patients (n=123, 61 females, median age 64 years) showed higher NfL than neurological controls (median 73.96 pg/mL to 107.30 vs 17.02 pg/mL) and healthy controls (12.73 pg/mL), both $p<0.001$, and higher pTAU181 than neurological controls (2.67 pg/mL vs 1.75 pg/mL), $p=0.041$, and healthy controls (0.95 pg/mL), $p<0.001$, while GFAP differed only versus healthy controls (43.30 pg/mL vs 28.75 pg/mL), $p=0.001$. Plasma NfL was independently associated with UMN assessed by transcranial magnetic stimulation ($p=0.007$), and by clinical UMN scales, $p=0.022$, as well as with rate of progression, $p<0.001$. pTAU181 showed no association with UMN measures, all $p<0.30$, but increased with lower muscle strength, $p=0.001$, and with greater chronic LMN denervation on electromyography, $p=0.011$. GFAP was unrelated to motor neuron burden, all $p<0.90$, and was primarily associated with age, $p<0.001$, and behavioural lability, $p=0.002$. Latent profile analysis

	identified three reproducible biomarker profiles with a graded association with disease aggressiveness, $p<0.001$. **Conclusion** Plasma NfL, GFAP, and pTAU181 capture distinct biological processes in ALS. Their combined assessment supports biologically meaningful patient stratification.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°5

TITLE	**Targeting gut microbiota-endocannabinoidome axis to counteract muscular and neurocognitive impairments in Duchenne muscular disease**
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	Duchenne muscular dystrophy (DMD) is a devastating, X-linked progressive neuromuscular disorder caused by mutations in the DMD gene, affecting approximately 1 in 3,500–5,000 live male births. Although characteristically defined by myofiber fragility and muscle wasting, the systemic pathophysiology of DMD extends beyond the musculoskeletal system. In our previous study, analyzing the fecal samples of mdx mice, the gold standard preclinical model of DMD, we documented a profound alteration of the gut microbiota, characterized by a reduced abundance of specific bacterial strains producing essential molecules, including short-chain fatty acids (primarily acetate, propionate, and butyrate) compared to healthy age-matched mice. Remarkably, oral administration of sodium butyrate to mdx mice for three weeks recovered locomotor impairment, rescued muscle autophagy and counteracted inflammation (Kalkan H et al. EMBO Mol Med 2023). Besides skeletal muscle degeneration, dystrophin deficiency also affects cardiac, respiratory, and central nervous system (CNS) function. In particular, a substantial proportion of individuals with DMD exhibit cognitive, learning, language, behavioural, and neuropsychiatric abnormalities, with intellectual disability occurring more frequently than in the general population (Vaillend C et al. Nat Commun 2025). In this study, we shifted our focus from the periphery to the central nervous system, hypothesizing the existence of a functional gut–brain axis connection that could be fundamentally altered in dystrophic pathology and linked to its systemic and neurological manifestations. To this end, we treated mdx mice with an oral administration of a salt solution containing a mix of SCFAs or vehicle for 3 weeks. At the end of the treatment, mdx mice receiving vehicle (water) or SCFAs were subjected to neurological and neurocognitive tests. Downstream transcriptomic, nuclear magnetic resonance (NMR), and mass spectrometry-based analyses were conducted to profile and quantify the

	SCFA-related central effects and potential modifications to the endocannabinoid system. Notably, dysregulation of this complex signaling network has been previously shown to exacerbate DMD severity in the same mouse model. Our results demonstrate that, in addition to the protective effects documented in DMD skeletal muscles, SCFA supplementation is also effective in producing beneficial central effects by recovering the cognitive deficits observed in mdx mice compared to controls. Furthermore, we focused our attention on the bacterial family Bacteroides, given their well-known role in host health. Specifically, we found that the Bacteroides vulgatus strain was significantly downregulated by about 54% in mdx mice, and most importantly, by about 47% in patients with DMD compared to healthy individuals. In addition to SCFAs, these bacteria are known to produce an N-acyl amide called commendamide, whose biological properties remain largely unknown (Cohen, L. J. et al. Proc. Natl. Acad. Sci. U.S.A (2015)). We discovered that commendamide plays an essential role in preventing muscle ferroptosis, an iron-dependent form of regulated cell death. Remarkably, this beneficial effect was enhanced upon concomitant administration with SCFAs in cellular models of DMD (Di Muraglia N et al. J Transl Med. 2026). Moreover, commendamide was effective in preventing microglial reactivity triggered by IL-6 and TNF-α. Mechanistically, we found that commendamide acts through peroxisome proliferator-activated receptors alpha and gamma (PPARα and PPARγ), which are functionally integrated within the endocannabinoid system. Altogether, these findings establish the gut microbiota-endocannabinoidome axis as a critical pathological driver and therapeutic target in DMD. By simultaneously addressing both muscular dystrophy and neurocognitive impairment, this dual-action paradigm paves the way for a novel class of disease-modifying therapeutics.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°6

TITLE	**Regional Corticomotoneuronal Burden Reflects Disease Spread and Predicts Outcomes in Amyotrophic Lateral Sclerosis**
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	Objective: Reliable biomarkers of upper motor neuron (UMN) involvement in amyotrophic lateral sclerosis (ALS) remain limited, especially for corticobulbar pathways. Transcranial magnetic stimulation (TMS) detects corticospinal dysfunction, but its role in capturing multiregional corticomotoneuronal involvement and disease spread is unclear. We assessed whether a regional corticomotoneuronal burden derived from TMS, including cranial pathways, improves detection of UMN degeneration and predicts clinical outcomes. **Materials and Methods**: In this multicentre retrospective study, we analysed consecutive patients within the ALS spectrum who underwent TMS between 2010 and 2025 at three Italian referral centres. Motor evoked potentials (MEPs) were recorded from cranial, upper limb, and lower limb muscles. A regional corticomotoneuronal burden score was computed across districts. Associations with regional clinical involvement and functional King's stage were examined. Kaplan–Meier and Cox regression models assessed predictors of percutaneous endoscopic gastrostomy (PEG)-free and tracheostomy-free survival. **Results**: We included 390 patients. Corticomotoneuronal abnormalities showed region specific associations with clinical involvement across bulbar, upper limb, and lower limb domains, and with more advanced King's stage (all $p<0.001$). Central abnormalities were more frequent in the bulbar district (54.5%), followed by lower limbs (49.2%) and upper limbs (38.9%). Including cranial pathways increased detection of upper motor neuron dysfunction from 62.1% to 77.7%, with an absolute increase of 15.6% ($p<0.001$). Corticomotoneuronal impairment was present in patients without clinical involvement: 28.6% in bulbar, 18.6% in upper limb, and 29.5% in lower limb regions. Isolated corticobulbar abnormalities were observed in 40.7% of patients with normal spinal MEPs. Inexcitable cranial MEPs were associated with shorter PEG free survival and remained independently predictive (HR 1.89, 95% CI 1.01 to 3.52, $p=0.03$). Higher corticomotoneuronal burden was associated with faster disease progression and independently predicted shorter PEG free survival (HR 1.37, 95% CI 1.04 to 1.79, $p=0.023$) and tracheostomy free survival (HR 1.23, 95% CI 1.02 to 1.48, $p=0.030$).

	Discussion and Conclusion: Regional corticomotoneuronal burden captures disease spread and improves detection of upper motor neuron degeneration in ALS. This multiregional approach provides independent prognostic information and supports integration of district-based TMS assessment into routine evaluation and future diagnostic frameworks.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°7

TITLE	**Mass spectrometry and biochemical characterization of recombinant human CDKL5: phosphorylation, soluble aggregation and catalytic activity**
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	hCDKL5 is a serine/threonine protein kinase playing a central role in neuronal development and function through the phosphorylation of multiple cellular substrates[1]. Mutations in its coding sequence are associated with CDKL5 Deficiency Disorder (CDD)[2, 3], a severe neurodevelopmental disease for which no curative treatment is currently available. Enzyme replacement therapy has emerged as a promising therapeutic strategy, but its development requires a reliable recombinant production platform for catalytically active CDKL5. Although Pseudoalteromonas haloplanktis TAC125 is the only prokaryotic host reported to produce full-length human CDKL5, protein yield and product quality remain limited[4, 5]. In particular, recombinant hCDKL5 is recovered with moderate purity due to the co-purification of bacterial proteins, while biochemical analyses indicate the presence of soluble aggregated forms, suggesting that different hCDKL5 populations may coexist in the recombinant preparation. Previous studies on bacterially produced hCDKL5 catalytic domain highlighted the relationship between phosphorylation, aggregation and catalytic activity[6]. To further investigate these aspects, mass spectrometry was used to characterize its phosphorylation status under different culture conditions. The analysis revealed condition-dependent, site-specific phosphorylation profiles, providing information relevant to the functional characterization of the recombinant protein. In parallel, mass spectrometry identified co-purifying bacterial proteins, helping to characterize the composition of recombinant preparations and inform purification strategies. Expression of the catalytic domain was also investigated to assess whether removal of the largely disordered C-terminal region could improve protein stability and activity, with preliminary results supporting this possibility.

	To investigate the intracellular distribution of the recombinant protein, in vivo fluorescence microscopy was used to monitor an eGFP-tagged hCDKL5 kinase domain in P. haloplanktis TAC125. The fusion protein accumulated in distinct intracellular foci with a defined spatial distribution and a time-dependent increase. Based on these observations, cell extracts were fractionated by sucrose density-gradient centrifugation to resolve hCDKL5 populations, and selected fractions were subsequently purified and evaluated by functional assays. This approach enabled the recovery of a soluble hCDKL5 catalytic-domain preparation with reduced levels of co-purifying bacterial proteins while retaining catalytic activity toward the EB2 substrate in vitro. Fractions exhibited different levels of autophosphorylation associated with their capacity to phosphorylate EB2, with low-density fractions retaining both activities. Together, these findings demonstrate the potential of P. haloplanktis TAC125 as a production platform for human CDKL5 and support sucrose-gradient fractionation as a strategy to resolve and recover distinct soluble hCDKL5 populations while preserving enzymatic activity. Mass spectrometry contributes to this workflow by characterizing phosphorylation patterns relevant to kinase function and identifying co-purifying bacterial proteins. Further optimization of both production and purification will be required to increase the overall yield and quality of active, soluble hCDKL5, providing a basis for the development of more efficient and scalable production processes for future therapeutic applications in CDD. **References** 1. doi:10.1016/j.celrep.2017.12.083. 2. doi: 10.1371/journal.pone.0157758. 3. doi: 10.1002/humu.23263. 4. doi: 10.1186/s12934-022-01939-6. 5. doi:10.3390/md24050151. 6. doi.org/10.3390/ijms25168891.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°8

TITLE	**Structure-based identification and characterization of novel inhibitors of KNa1.1 potassium channels**
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	Background KNa1.1 (KCNT1) channels are sodium-activated potassium (K^+) channels widely expressed in neurons, where they regulate excitability. Pathogenic variants in *KCNT1* cause a range of epileptic syndromes associated with intellectual disability and drug-resistant seizures, and functional studies have shown that most of them increase KNa1.1 currents. Quinidine, a well-known antiarrhythmic drug that also blocks KNa1.1, has been used as a personalized treatment for these patients. However, it is only partially effective in controlling seizures, and its clinical use is limited by its poor selectivity, as it also blocks several other ion channels. To overcome these limitations, novel KNa1.1 blockers have been identified in recent years, including CPK18 and CPK20, two potent compounds recently described by our group (Iraci et al., *J. Med. Chem.*, 2024). Building on these findings, we aimed to increase the number of chemically diverse KNa1.1 inhibitors and to gain further structure–activity relationship (SAR) insights. **Methods** Starting from the results of previous screenings, a new library of 48 compounds was designed and synthesized to increase the number of active molecules on this channel. All compounds were tested at 10 μM using a thallium (Tl^+)-based fluorescent assay (FluxOR™) in CHO cells stably expressing KNa1.1 (CHO-KNa1.1), in which the channel was activated by loxapine, a selective KNa1.1activator. Inhibitory efficacy was quantified as the reduction of the slope of the fluorescence curve relative to loxapine alone. Statistical significance was assessed by ordinary one-way ANOVA followed by Dunnett's multiple comparisons test. Concentration–response analyses were then performed on the active compounds to determine their IC_{50} values and compare them with that of the lead compound CPK20. The blocking activity of selected compounds was further validated by whole-cell patch-clamp electrophysiology in CHO-KNa1.1 cells.

	Results Of the 48 compounds tested, 16 produced a statistically significant reduction in the fluorescence slope, indicating inhibition of KNa1.1. Concentration–response analysis of these 16 compounds showed that several were more potent than CPK20 (IC_{50} = 6.40 ± 1.61 µM). Three representative compounds were selected for further characterization: CPK56, structurally similar to CPK20, and CPK26 and CPK37,which belong to distinct chemotypes. CPK37 was the most potent, with an IC_{50} of 0.40 ± 0.10 µM, a 16-fold improvement over CPK20, while CPK26 and CPK56 showed IC_{50} values of 2.28 ± 0.68 µM and 3.66 ± 0.94 µM, respectively. Whole- cell patch-clamp recordings confirmed the blocking activity of all three compounds. **Conclusions** The identification of novel KNa1.1 blockers addresses a critical need in drug- resistant KCNT1-related epilepsies, for which effective therapies are lacking. In this study, we identified several inhibitors more potent than the published lead, including CPK37, a highly potent compound structurally distinct from CPK20. These findings expand the chemical toolbox for KCNT1 modulation and provide a solid basis for continued lead optimization, including selectivity profiling.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°9

TITLE	**Targeting PPAR receptors to counteract statin-induced muscle degeneration and neurotoxicity**
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	Statins, including simvastatin and atorvastatin, are among the most widely prescribed drugs worldwide for lowering LDL cholesterol through HMG-CoA reductase inhibition (1). Although generally well tolerated, statins can cause muscle-related adverse effects and may affect neuromuscular function, with underlying mechanisms remaining incompletely understood. Statin-induced muscle toxicity has been linked to mitochondrial dysfunction, reduced ATP production, and increased ROS generation, potentially related to altered CoQ10 availability (2). Moreover, atorvastatin has been shown to induce mitochondria-dependent ferroptosis in skeletal muscle cells through disruption of the Nrf2–xCT/GPx4 axis (3). Peroxisome proliferator-activated receptors (PPARα, PPARγ, and PPARδ) are ligand-activated transcription factors involved in lipid and energy metabolism, oxidative homeostasis, and mitochondrial function (4). We therefore hypothesized that PPAR activation may counteract statin-induced mitochondrial dysfunction and oxidative stress, thereby protecting against statin-associated muscle and neuronal toxicity. We investigated the effects of statins and PPAR activation in murine C2C12 myoblasts, as a model of skeletal muscle cells, and HT22 hippocampal neuronal cells. In C2C12 myoblasts, individual PPAR agonists partially rescued simvastatin-induced loss of viability, with combined PPARα and PPARδ activation producing the strongest protective effect. In atorvastatin-treated cells, significant rescue was observed predominantly with combinations including the PPARδ agonist. Remarkably, combined activation of PPARα, PPARγ, and PPARδ fully restored cell viability in statin-treated HT22 cells. The protective effect of combined PPAR activation was further supported by a comprehensive assessment of mitochondrial bioenergetics using Seahorse extracellular flux analysis, which revealed preservation of basal and maximal respiration, ATP production, and spare respiratory capacity in statin-treated cells. PPAR agonist treatment also attenuated statin-induced ROS accumulation and restored the altered GSH/GSSG ratio. Finally, western blot analysis showed that statins altered the expression of key regulators of mitochondrial function and oxidative stress, including OPA1, TFAM, mitofusin 2, GPX4, and NRF1, while increasing cleaved caspase-3. These molecular alterations were largely

	reversed by combined PPAR activation, including the restoration of GPX4 expression in C2C12 cells. Overall, our findings identify PPAR activation as a potential strategy to counteract statin-induced mitochondrial dysfunction, oxidative stress, and cell damage in muscle and neuronal cells. These results support further investigation of PPAR signaling as a protective mechanism against statin-associated toxicity. <u>REFERENCES</u> 1. Kalkan H, Panza E, Pagano E, Ercolano G, Moriello C, Piscitelli F, Sztretye M, Capasso R, Di Marzo V, Iannotti FA. Dysfunctional endocannabinoid CB1 receptor expression and signaling contribute to skeletal muscle cell toxicity induced by simvastatin. Cell Death Dis. 2023 Aug 23;14(8):544. PMID: 37612317; PMCID: PMC10447569. 2. Kovacic, S., Habicht, S. D., & Eckert, G. P. (2025). Effects of coenzyme Q10 supplementation on myopathy in statin-treated patients: a systematic review and meta-analysis. Journal of nutritional science, 14, e72. 3. Zhang, Q., Qu, H., Chen, Y., Luo, X., Chen, C., Xiao, B., Ding, X., Zhao, P., Lu, Y., Chen, A. F., & Yu, Y. (2022). Atorvastatin Induces Mitochondria-Dependent Ferroptosis via the Modulation of Nrf2-xCT/GPx4 Axis. Frontiers in cell and developmental biology, 10, 806081. 4. Montaigne, D., Butruille, L., & Staels, B. (2021). PPAR control of metabolism and cardiovascular functions. Nature reviews. Cardiology, 18(12), 809–823.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°10

TITLE	**Effects of CBGA in a mouse model of Traumatic Brain Injury**
AUTHORS	Limongelli Rebecca[1], Michela Perrone[1], Viviana Iodice[1], Andrea Maria Morace[1], Federica Ricciardi[1], Emanuele di Martino[1], Francesca Guida[1], Livio Luongo[1], Sabatino Maione[1].
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	Traumatic brain injury (TBI) is a major cause of long-term neurological disability, characterized by neuroinflammation, neuronal loss, and cognitive decline. The TRPM7 ion channel, involved in neurodegenerative diseases, has emerged as a potential therapeutic target. Recent evidence shows that cannabigerolic acid (CBGA), a natural compound from Cannabis Sativa plant, inhibits TRPM7 activity, suggesting that its pharmacological blockade may reduce secondary damage after TBI. Previous studies in an Alzheimer's model showed increased TRPM7 expression in diseased mice, which was significantly reduced by CBGA treatment. This supports the idea that TRPM7 modulation contributes to the neuroprotective effects of CBGA and that targeting this pathway could be an effective strategy for TBI. In the present pilot study, we investigated the effects of CBGA in a mouse model of severe TBI (sTBI). Brain injury was induced under general anesthesia using a weight-drop device, in which a 250 g weight was released from a height of 2 cm onto the skull, causing a reproducible severe traumatic insult. The VER155008, a synthetic antagonist of TRPM7 channel, was used as referred compound. Pharmacological treatments were performed intraperitoneally starting 5 h after sTBI induction and daily for 30 days. Animals received CBGA (5 mg/kg), VER155008 (5 mg/kg), or vehicle (1:9 DMSO/saline). Behavioral assessments were performed at different time points to evaluate sensory and cognitive alterations associated with the injury. Mechanical sensitivity was assessed using the von Frey test for four weeks following trauma. The administration of both compounds significantly increases the mechanical withdrawal threshold, compared with vehicle in TBI animals. Moreover, using the novel object recognition (NOR) and forced Y-maze we found that cognitive performance and short memory were ameliorated by pharmacological treatment in TBI mice. These findings support the potential involvement of stress-response pathways and cannabinoid-related signaling in the modulation of post-traumatic neurological dysfunction. Molecular investigations are currently ongoing to better understand the underlying mechanisms of the behavioral effects. In particular, gene and protein expressions will be performed to evaluate the potential modulations of molecular pathways associated with neuroinflammation, cellular stress responses, and ion channel regulation.

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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°11

TITLE	**Baseline Cortical Excitability as a Predictor of 5-Year Cognitive Outcomes in Neuromyelitis Optica Spectrum Disorders: A Prospective Study**
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	Introduction: Cognitive impairment is increasingly recognized as a clinically relevant feature of neuromyelitis optica spectrum disorder (NMOSD), yet its mechanisms and early predictors remain poorly understood. Changes in cortical excitability, measurable with transcranial magnetic stimulation (TMS), may reflect subclinical cortical dysfunction and could serve as a biomarker of subsequent cognitive decline. Methods: Forty-eight patients with newly diagnosed NMOSD and 25 matched healthy controls underwent baseline TMS assessment, including resting motor threshold (RMT), short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF). Patients completed a comprehensive neuropsychological battery at baseline and after 5 years. Cognitive impairment was defined as performance ≥1.5 SD below control means in at least two cognitive domains. Multivariable regression analyses were used to identify baseline predictors of cognitive decline, adjusting for age, education, disease duration, and annualized relapse rate. Results: At diagnosis, patients showed significantly reduced SICI and increased ICF compared with controls ($p < 0.01$), consistent with early cortical disinhibition. At 5 years, 18 of 48 patients (37.5%) had developed cognitive impairment, predominantly involving attention, executive function, and processing speed. Reduced baseline SICI independently predicted cognitive decline ($\beta = -0.42$, $p = 0.004$) after adjustment for demographic and clinical covariates. Neither relapse frequency nor EDSS progression was associated with cognitive outcome. Conclusion: Early alterations in cortical excitability, suggestive of GABAergic dysfunction, predict long-term cognitive deterioration in NMOSD. TMS-derived measures may help identify patients at higher risk of cognitive decline and inform early neuroprotective strategies.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°12

TITLE	**MR-39-mediated FPR2 activation regulates autophagy and metabolic stress adaptation pathways in glioblastoma**
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	Background: Glioblastoma (GBM) is an aggressive brain tumor characterized by therapeutic resistance and adaptive survival mechanisms, including hypoxia signaling and autophagy. Formyl peptide receptor 2 (FPR2) has emerged as a potential therapeutic target in GBM, but its involvement in autophagy regulation remains poorly understood. MR-39, a selective, blood–brain barrier-permeable FPR2 agonist, has shown antitumor effects by limiting mesenchymal features, angiogenesis, and hypoxic adaptation. Here, we investigated whether MR-39 modulates autophagic flux and stress-associated transcriptional programs in GBM cells. **Methods**: U87 glioblastoma cells were treated with MR-39 for 48 h or maintained as untreated controls. Autophagic flux was assessed by adding bafilomycin A1 during the final 4 h of treatment. Autophagy-related markers and transcriptional responses were evaluated using immunofluorescence, western blotting, quantitative reverse-transcription PCR, and RNA sequencing. **Results**: MR-39 treatment increased LC3B puncta formation and reduced p62/SQSTM1 protein levels. In the presence of bafilomycin A1 LC3B accumulation increased, indicating enhanced autophagic flux. RNA sequencing revealed changes in autophagy- and stress-related transcriptional programs, including downregulation of genes involved in hypoxia responses and mitophagy, such as EGLN1, HIF3A, and BNIP3. MR-39 also induced a transcriptional signature consistent with an ATF4-associated stress response, including increased expression of SESN2, TRIB3, and PPP1R15A (GADD34), alongside changes in genes associated with amino acid transport and MYC–mTOR signaling. Together, these

	findings suggest that enhanced autophagic flux is accompanied by remodeling of cellular stress adaptation and attenuation of selected hypoxia-associated transcriptional responses. **Conclusions**: MR-39 enhances autophagic flux and reshapes stress-associated transcriptional programs in U87 glioblastoma cells. These findings extend the biological effects of MR-39 and support further investigation of FPR2 stimulation as a strategy to modulate GBM adaptive responses. Establishing whether these changes contribute to MR-39 antitumor activity will require further functional studies.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°13

TITLE	**Oral sodium butyrate supplementation acts on intestinal dysbiosis and resolves spinal cord neuroinflammation and nociceptive neuron sensitization**
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	Background Gut microbiota dysbiosis is a key pathological feature closely linked to metabolic disorders and neuroinflammation. It is typically characterized by reduced levels of beneficial microbial metabolites, particularly short-chain fatty acids (SCFAs) such as butyrate, and by increased production of pro-inflammatory molecules. In this study, we investigated the therapeutic potential of butyrate in a mouse model of antibiotic-induced gut dysbiosis, which is characterized by disruption of the normal gut microbiota and associated intestinal inflammation. **Results** We found that oral administration of sodium butyrate significantly reduced gut inflammation, as evidenced by decreased levels of the pro-inflammatory biomarkers calprotectin and lipocalin-2 in fecal samples compared with untreated dysbiotic mice. Furthermore, antibiotic treatment led to a marked reduction in specific butyrate-producing bacterial species, including Faecalibacterium prausnitzii and Roseburia spp. Notably, the abundance of these species, was partially restored following exogenous butyrate administration. Finally, butyrate administration significantly attenuated neuronal hyperexcitability

	in response to intracolonic distension and reduced pro-inflammatory factor levels in the spinal cord. **Conclusions** These results highlight the role of butyrate in directly reducing gut inflammation and spinal neuroinflammation, while also promoting the restoration of some butyrate-producing bacteria. Our study underscores the potential of butyrate as a therapeutic agent for treating dysbiosis-associated gut inflammation and neuroinflammatory disorders, offering new insights into microbiota-targeted therapies for gut-brain axis regulation.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°14

TITLE	**Profiling Inflammatory Biomarkers in West African Patients with Ischemic Stroke: Links to Disease Severity and Functional Outcomes**
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	Stroke is a major global health burden, particularly in Africa. Cardiometabolic risk factors and inflammatory pathways contribute to atherosclerosis and may influence stroke onset and prognosis. However, the contribution of inflammatory proteins to ischemic stroke in indigenous African populations remains insufficiently explored. This study aimed to characterise inflammation-related protein patterns in acute ischemic stroke and assess their relationships with disease severity and clinical outcomes. We examined 90 ischemic stroke cases and 90 controls matched for age, sex, and ethnicity from the prospective SIREN cohort. Plasma concentrations of 368 proteins were measured

	using the Olink® Explore 384 Inflammation panel. Generalised linear models were used to compare protein levels between groups, while logistic regression examined associations with stroke severity (NIHSS >15 or SLS ≤5) and 30-day disability assessed by the modified Rankin Scale (mRS). Associations with neuroimaging lesion volume and mortality were also evaluated. Compared with controls, stroke cases showed 23 increased and 14 decreased proteins. Agouti-related protein (AgRP) and tumour necrosis factor receptor superfamily member 11A (TNFRSF11A) exhibited the largest increases, whereas interleukin-1 beta (IL-1β) and integrin alpha-11 (ITGA11) showed the greatest reductions. Severe stroke was present in 19/80 participants (23.8%) according to NIHSS and 28/85 (32.9%) according to SLS. Mean 30-day mRS was 2.5 (SD 1.9). After adjustment for age, sex, hypertension, diabetes, and dyslipidaemia, 70 proteins were associated with stroke severity, with complement C1q subcomponent subunit A (C1qa) showing the strongest association. Nine proteins, including C-C motif chemokine 23 (CCL23), were associated with poor functional outcomes at 30 days. No significant associations were found with lesion volume or mortality. These findings connect altered inflammatory protein profiles with stroke severity and early disability in indigenous West Africans, suggesting that immune dysregulation and neuroinflammation may contribute to clinical prognosis. The identified proteins merit further investigation as potential prognostic biomarkers and therapeutic targets.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°15

TITLE	**Crocin Preserves BBB-Related Endothelial Functions and Attenuates Systemic Inflammation in Experimental Rheumatoid Arthritis**
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	Systemic inflammation is a major contributor to blood-brain barrier (BBB) dysfunction, promoting endothelial activation, oxidative stress, and alterations of tight-junction organization that may facilitate neuroinflammatory processes. In chronic inflammatory disorders such as rheumatoid arthritis (RA), sustained peripheral inflammation has been associated with BBB impairment and an increased risk of neurological comorbidities. Therefore, identifying bioactive compounds able to attenuate systemic inflammation while supporting BBB integrity may represent a promising strategy for limiting inflammation-associated neurovascular alterations. Crocin, a carotenoid glycoside derived from *Crocus sativus* L., was investigated using complementary in vitro and in vivo models to evaluate its potential protective effects under inflammatory conditions. In BBB-relevant endothelial cell models (BEND.3 and HBEC5i cell lines), crocin showed no cytotoxicity at the tested concentrations and exerted significant antioxidant and anti-inflammatory activities. In addition, crocin preserved endothelial monolayer integrity and favorably modulated the expression of tight-junction proteins involved in BBB maintenance, supporting its potential role in preserving endothelial barrier function. The anti-inflammatory activity of crocin was further evaluated in adjuvant-induced arthritis (AA), a well-established experimental model of RA. Crocin significantly attenuated disease progression, reducing arthritis severity and circulating levels of IL-1β. The most pronounced effects were observed when crocin was administered in combination with methotrexate (MTX), resulting in a marked reduction in hind paw swelling and significant decreases in MCP-1 and IL-17 levels. To explore potential brain-related effects in the context of chronic systemic inflammation, hippocampal sections from healthy control, AA,

	MTX-treated, crocin-treated, and crocin/MTX-treated animals were examined by hematoxylin and eosin staining. Preliminary histological observations revealed apparent differences in hippocampal architecture and cellular distribution among experimental groups. Notably, the crocin-treated group displayed a relatively preserved histological appearance compared with arthritic animals. Although these findings are exploratory and require confirmation through standardized histopathological scoring and quantitative analyses, they suggest that crocin treatment may be associated with reduced morphological alterations in the hippocampus under inflammatory conditions. Overall, the findings indicate that crocin exerts anti-inflammatory effects in experimental arthritis and preserves BBB-related endothelial functions in vitro. The preliminary hippocampal observations further support the rationale for investigating the potential impact of crocin on neurovascular and brain alterations associated with chronic systemic inflammation. Further mechanistic and translational studies are warranted to establish whether these endothelial, anti-inflammatory, and histological effects are functionally linked and to clarify their relevance for preventing neurological complications associated with RA.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°16

TITLE	**Exploring the neurotoxic effects of PET microplastics through the Gut-Brain axis in zebrafish**
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	The gut–brain axis (GBA) refers to a bidirectional communication network between the central nervous system and the gastrointestinal system, mediated by the convergence of the autonomic nervous system, the enteric nervous system and multiple pathways. Recent advancements in microbiology have highlighted the gut microbiota as a key mediator of gut–brain interactions. This complex system is now recognized for its profound influence on neuronal function, behavior, and social interactions across most animal species. Experimental evidence shows that gut dysbiosis, the alteration of the gut microbial community, can trigger systemic inflammation that extends to the brain, contributing to neurodegenerative diseases. As ubiquitous environmental contaminants, microplastics (MPs) are primarily ingested by aquatic organisms through their diet, making the intestine the primary site of damage. Notably, even larger particles that cannot directly cross the gastrointestinal and blood–brain barriers can still elicit a systemic inflammatory state. In our study, dietary exposure to polyethylene terephthalate microplastics (PET-MPs) for 10 and 20 days induced a condition of distress, manifested first at the behavioral level, with increased aggression at 10 days (T10) and an altered anxiety-like state at 20 days (T20) of exposure. Microbiota analysis revealed an increase in the relative abundance of *Cetobacterium* at T10; this increase may be interpreted as a preliminary indication of an early microbial response to the stressful condition induced by PET-MPs, followed by the restoration of a stable microbiota profile at T20. In contrast, enzymatic analysis of some cytoprotective defense systems showed a decreasing trend in glutathione reductase (GSR) activity in the brain at both T10 and T20, with no changes in glutathione S-transferase (GST) or glucose-6-phosphate dehydrogenase (G6PD) activity. Histological analysis showed an inflammatory profile in the intestine, supported by an increased number of the goblet cells, probably due to the mechanical damage associated with the passage of MPs, and a mild inflammatory condition in the brain, identified by hyperemia, probably due to the systemic effect of substances released from MPs, in both exposed groups. These

	findings are consistent with gene expression analysis of *il-1b*, *c-fos*, *ngn1*, *sox9b*, *fn1*, *gfap, gria*, *gabbr2*, *gata4*, and *hand2*. Overall, these results provide evidence that even short-term dietary exposure to PET- MPs induces alterations at multiple levels of the gut–brain axis, highlighting the vulnerability of this system to microplastics contamination in aquatic organisms.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°17

TITLE	**KLHL14 a pontential biomarker for CLN1 Batten Disease in human iPSC and NPC models**
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	Background: Recent studies identify Kelch-like protein 14 (KLHL14), a Cullin- RING ubiquitin ligase (CRL3) substrate adaptor, as an emerging regulator of neuronal homeostasis. KLHL14 localizes predominantly in the endoplasmic reticulum, interacts with TorsinA to modulate GABAergic synapses, and, in murine models, acts as a key developmental marker during corticospinal neuron specification. Despite these growing insights into neuronal physiology, its involment in inherited neurodegenerative conditions remain entirely unexplored, thus providing a compelling rationale to investigate its role in severe lysosomal storage disorders such as CLN1 Batten disease. This fatal inherited neurodegenerative condition is caused by mutations in the PPT1 gene, a Palmitoyl- Protein Thioesterase 1 involved in removing palmitate residues from S- palmitoylated proteins prior to lysosomal degradation. It triggers progressive accumulation of autofluorescent lipopigments, culminating in rapid neurodegeneration characterized by progressive blindness, motor disturbances, loss of speech, seizures, ataxia, and early childhood death. **Materials and methods:** We used neural progenitor cell (NPC) lines, generated from human induced pluripotent stem cells (iPSCs) obtained from the *European Collection of Authenticated Cell Cultures* (ECACC), originating from two distinct CLN1-mutated patient cell lines SOZW_2 (c.125-15T>G) and MENZ_4 (c.451C>T; p.Arg151Ter). Both CLN1-mutated and wild-type control iPSCs were differentiated into neural progenitor cell (NPC) populations using the *STEMdiff™ Neural Induction Medium* supplemented with *STEMdiff™ Neural Induction Supplement* (STEMCELL Technologies), with daily media change for 14 days. Real-time quantitative PCR (RT-qPCR) was employed to evaluate lineage commitment by analyzing a panel of both pluripotency and neurospecific markers as well as to measure total *KLHL14* transcript levels. KLHL14 protein expression levels were revealed by Western blot using a rabbit polyclonal anti-KLHL14 antibody, followed by densitometric analysis with normalization against GAPDH across undifferentiated iPSC and differentiated NPC stages. **Results**: Quantitative transcriptional analysis of pluripotency and differentiation markers confirmed neural commitment toward NPCs in

	all cell lines, while distinct expression trends were observed for *TUBB3* and *TBR1* in CLN1 models compared to the wild-type. Although cell lines exhibited highly different basal levels of *KLHL14* mRNA expression, our data revealed neural differentiation-dependent downregulation in all cell lines. Unlike mRNA, protein levels showed substantiallysimilar baseline levels of KLHL14 in the pathological cell lines and confirmed the neural differentiation-dependent downregulation of KLHL14, although this downregulation in CLN1 NPCs is quite modest compared to the wild-type. Interestingly, protein levels at both the iPSC and NPC stages in the CLN1-mediated Batten disease models were approximately double those of the wild-type, particularly in pathological NPCs compared to controls, highlighting a molecular alteration in the pathological cell lines. **Conclusions:** We show that KLHL14 expression is reduced in NPCs compared to undifferentiated iPSCs in all cell lines. Batten disease models exhibit higher KLHL14 protein levels than the wild-type, particularly in the NPC state, highlighting its potential as pathological biomarker. Further studies are needed to elucidate the mechanisms underlying the divergent expression profiles of *TUBB3* and *TBR1*, to validate these findings in additional CLN1 models and in other forms of Batten disease and to fully clarify the potential functional role of KLHL14 in the pathogenesis of the disease.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°18

TITLE	**Peripheral TSPO Expression Reflects ALS Progression and Mitochondrial Adaptation in Patients and SOD1-G93A Muscle**
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	INTRODUCTION Emerging evidence supports an active role of skeletal muscle in the pathogenesis of amyotrophic lateral sclerosis (ALS), involving inflammatory processes and mitochondrial dysfunction within muscle fibers. The translocator protein (TSPO) is an 18-kDa transmembrane protein primarily located on the outer mitochondrial membrane. It regulates critical mitochondrial functions, including cholesterol transport (steroidogenesis), bioenergetics (ATP production), reactive oxygen species (ROS) homeostasis, and apoptosis. TSPO acts as a biomarker for neuroinflammation and mitochondrial dysfunction. **AIMS** This study aimed to define the role of TSPO in ALS skeletal muscle and to assess its potential as a progression biomarker in ALS patients. **METHODS** TSPO expression was assessed by qPCR in both affected and unaffected skeletal muscles of SOD1-G93A mice at early and late disease stages and in surgically denervated mice at different stages of the muscle atrophy. These findings were validated by immunohistochemistry and confocal microscopy. Furthermore, mitochondrial biogenesis (NRF1) and dynamics (DRP1, MFN2) markers were evaluated in the skeletal muscles of SOD1-G93A and denervated mice and correlated with TSPO expression. In addition, cholesterol and cholesterol ester levels were assessed in the gastrocnemius muscle of SOD1-G93A mice at both early and late disease stages, using mass spectrometry. Finally, TSPO was evaluated in human muscle biopsies and serum thorough ELISA essay from ALS patients and healthy controls. **RESULTS** qPCR revealed a significant TSPO upregulation in denervated gastrocnemius atdifferent stage of muscular damage and in SOD1-G93A

	gastrocnemius from early stages, while soleus and triceps expression increased at late stages. Furthermore, qPCR showed an increase of mitochondrial markers in denervated gastrocnemius at 2 days and in SOD1-G93A gastrocnemius in both early and late stage. In addition, cholesterol significantly increased in the SOD1-G93A gastrocnemius at both early and late stages, while its esters increased significantly only at the late stage. Immunohistochemistry and confocal microscopy confirmed high colocalization of TSPO with mitochondrial markers, suggesting that TSPO regulates mitochondrial activity from early disease stages. Consistently, increased TSPO expression was observed in muscle biopsies from ALS patients. Interestingly, circulating TSPO levels were increased in the serum of ALS patients, particularly in early-stage compared to late-stage patients. Notably, this increase was positively correlated with cumulative electromyography denervation scores. **CONCLUSION** TSPO upregulation in ALS skeletal muscle and serum supports its potential as a non-invasive biomarker for monitoring of muscle pathology in ALS. Furthermore, its association with mitochondrial markers suggests a role in biogenesis and remodeling during disease progression.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°19

TITLE	**Task-Dependent Alterations in Saccadic Peak Velocity in Developmental Dyslexia: Toward an Oculomotor Index**
AUTHORS	Pagano Adriana[1], Capolongo Giovanni Mario[1], Pacelli Carmela[1], Pizzo Ciro[1], Buonocore Antimo[1]
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	Developmental dyslexia (DD) has been associated with atypical eye movement patterns during reading and visual exploration. The magnocellular hypothesis suggests that impaired processing of rapidly changing visual information may contribute to reading difficulties and potentially affect visuomotor control. However, whether these alterations extend to basic saccadic kinematics remains unclear. Here, we examined the main sequence, the relationship between saccadic amplitude and peak velocity, in young adults with and without DD across linguistic and non-linguistic tasks, to assess whether amplitude-adjusted peak velocity could provide a quantitative index of oculomotor functioning in DD. A total of 15 young adults with DD (mean age = 20.3 years) and 22 neurotypical readers (mean age = 20.7 years) completed three eye-tracking paradigms: a visually guided saccade task, a visual search task, and a reading task. A complementary neuropsychological assessment was administered to assess participants' reading performance and domain-specific cognitive functions. Task-specific linear mixed-effects models evaluated group differences in peak saccadic velocity while accounting for saccadic amplitude and experimental conditions. Across tasks, the main sequence remained broadly preserved in both groups. However, participants with DD exhibited significantly lower amplitude-adjusted peak velocities during visually guided saccades ($\beta = -0.19$, $p = .002$) and visual search ($\beta = -0.11$, $p = .002$). In contrast, no statistically reliable group difference in peak velocity emerged during reading ($\beta = -0.05$, $p = .199$), although participants with DD produced shorter saccades in both visual search ($\beta = -0.84$, $p = .02$) and reading ($\beta = -0.58$, $p < .001$). These findings suggest that developmental dyslexia is associated with task-dependent differences in saccadic peak velocity, despite broadly preserved amplitude–velocity scaling. The reduced peak velocity observed during non-linguistic tasks may reflect alterations in saccadic vigor, potentially related to differences in visuomotor control. We suggest that amplitude-adjusted saccadic peak velocity may represent a promising quantitative oculomotor index for characterizing the visuomotor profile associated with developmental dyslexia.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°20

TITLE	**Decoding Vulvodynia: from pelvic sensitivity to central pain processing**
AUTHORS	Michela Perrone [1], Serena Boccella [1], Antimo Fusco [1], Roozbe Bonsale [1], Rosmara Infantino [1], Silvia Nuzzo [2], Giovanni Pecoraro [2], Federica Ricciardi [1], Andrea Maria Morace [1], Gianluca Petrillo [3], Ilaria Leone [2], Monica Franzese [2], Francesca Guida [1], Marco Salvatore [2], Alfonso Papa [4], Sabatino Maione [1], Livio Luongo [1]
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	Introduction Vulvodynia is a chronic pain condition affecting the vulvar area associated with tactile allodynia and spontaneous pain. In patients a depressive behaviour is also observed. Current treatments for vulvodynia are limited and there is a need for more effective therapeutic options. Growing evidence suggests that maladaptive plasticity of the central nervous system and microglia-mediated neuroinflammatory processes play a crucial role in this condition. The identification of therapeutic strategies capable of simultaneously modulating neuronal activity and the microglial response represents an emerging priority. **Methods** A model of vestibulodynia induced by Freund's Complete Adjuvant (CFA) was used. Tactile allodynia, general well-being and depressive-like behaviour were performed as key behavioural markers. In vivo electrophysiological recordings were conducted to characterize sacral spinal neuronal activity in the L6-S1 dorsal horn of the spinal cord. Furthermore, microglial activation in the same region was examined using immunofluorescence. Therapeutic interventions included a phytotherapeutic approach (Acmella oleracea and Boswellia serrata, AO+BA) and clinically used pharmacological treatments (gabapentin, amitriptyline, and palmitoylethanolamide:polidatine, PEA:Pol). **Results** In this study were observed marked alterations in behavioural experiments, including increased vulvar hypersensitivity (tactile allodynia), spontaneous pain and depressive-like behaviour. These alterations were associated with a significant increase in neuronal activity in the L6-S1 segments of spinal cord and the presence of microglia with a hypertrophic phenotype, indicative of a state of

	neuroinflammation. Therapeutic interventions demonstrated consistent efficacy in modulating both behavioural and neurobiological aspects. Specifically, treatments with the combination of AO+BA and PEAPol resulted in a significant reduction in hypersensitivity with a decrease in microgliosis and neuronal hyperactivity.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°21

TITLE	**Sphingolipid metabolism dysregulation in pre-symptomatic *Mecp2*$^{-/y}$ and *Mecp2*$^{R306C/y}$ mouse models of Rett Syndrome provides potential early biomarkers of the disease**
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	Rett syndrome (RTT; OMIM 312750) is a severe neurodevelopmental disorder that primarily affects females and is caused by mutations in the X-linked gene *Methyl-CpG-binding protein 2* (*MECP2*). This condition is characterized by an initial period of apparently normal development, followed by progressive loss of motor and cognitive skills and severe neurological impairments. Despite significant advances in understanding its genetic basis, the underlying pathogenic mechanisms that contributes to the onset of the symptoms still remains poorly understood. While research has traditionally focused on neuronal and synaptic implications, emerging evidence links MeCP2 dysfunction to dysregulation of sphingolipid (SL) metabolism. Previous lipidomic analyses, performed using liquid chromatography mass spectrometry (LC-MS), revealed significant alterations in hippocampal SL profiles of symptomatic *Mecp2*$^{-/y}$ mice, compared with wild-type controls. These metabolic perturbations were also associated with transcriptional dysregulation of several genes encoding enzymes and regulatory factors involved in SL metabolism. These findings suggest that MeCP2 plays a key role in regulating SL metabolism, and that disruption of this process may contribute to RTT pathogenesis. However, whether these metabolic alterations emerge during the pre-symptomatic phase, before the onset of clinically detectable neurological decline, remains unclear. To address this point, we focused on pre-symptomatic male mice carrying two distinct genetic lesions: the null allele (*Mecp2*$^{-/y}$) and the recurrent missense mutation *Mecp2*^{R306C}, compared to a wild-type cohort. Our integrative approach revealed early, mutation-specific perturbations in SL metabolism in hippocampus. Indeed, quantitative PCR (qPCR) assays identified a dysregulation of genes encoding key biosynthetic and catabolic factors of SL metabolism in both models, while LC-MS analysis revealed significant alterations in the abundance of specific SL, pointing to early

	metabolic distress preceding clinical manifestation. Notably, both *Mecp2*$^{-/y}$ and *Mecp2*$^{R306C/y}$ mice exhibited significant downregulation of the gene encoding the ceramide synthase 1 (*Cers1)* together with up-regulation of the gene *Cert1*, encoding the ceramide transporter 1, and the gene which encodes the enzyme galactosylceramidase (*GalC)*, coherently with altered levels of ceramide and sphingomyelin species. These convergent alterations suggest an upstream disruption of ceramide homeostasis, potentially involving impaired biosynthesis and enhanced catabolic processes.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°22

TITLE	**The impact of SYNJ1 overexpression on neuronal homeostasis**
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	Synaptojanin 1 (SYNJ1) is a ubiquitous inositol phosphatase, expressed at high levels in neuronal cells. We have previously demonstrated that SYNJ1 overexpression, caused by trisomy of chromosome 21, contributes to the pathogenesis of Down syndrome (DS) by altering the homeostasis and functions of early endosomes, and impairing recycling trafficking. Nevertheless, the exact mechanisms through which SYNJ1 alterations exert their pathogenic activity and affects neuronal homeostasis have not been fully elucidated. By leveraging new technologies to differentiate induced pluripotent stem cells (iPSCs) into neural progenitor cells (NPCs) and using a cellular imaging approach combined with a "multi-omic" approach to assess the effects of SYNJ1 overexpression on the transcriptome, proteome, and lipidome of human SH-SY5Y neuronal cells, we examined the impact of the cross-talk between SYNJ1 and the endosomal pathway on neuronal homeostasis. We found that SYNJ1 overexpression perturbs endosomal homeostasis and dynamics in neural precursors, in association with alterations in the morphological characteristics typical of differentiated neurons. We identified several clusters of mRNAs and proteins whose expression is altered in SYNJ1-overexpressing cells. Interestingly, some of these clusters include key modulators of synaptic trafficking, neurogenesis, and dopamine transport and metabolism, highlighting the role of SYNJ1 in maintaining neuronal structure and function. Other clusters, however, revealed new potential functions of SYNJ1, including lipid metabolism. Consistent with this, lipidomic analysis revealed an increase in plasmalogens and monounsaturated phosphatidylcholines,

	along with a reduction in polyunsaturated fatty acids and a loss of endoplasmic reticulum-associated triglycerides, indicating a metabolic shift toward the accumulation of protective lipids when SYNJ1 is overexpressed. Overall, our data reveal new cellular processes in which SYNJ1 is involved and suggest new possible mechanisms through which this protein may contribute to neuronal homeostasis and the neuropathogenesis of Down syndrome.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°23

TITLE	**Loss-of-function effects prompted by epilepsy-causing KCNT2 variants can be counteracted by riluzole**
AUTHORS	Maglieri Katia[1], Mosca Ilaria[1], Ambrosino Paolo[2], Taglialatela Maurizio[3], Rubboli Guido[4], Whiley Margaret[5], Murali Chaya[6], Rump Patrick[7], Cioclu Maria Cristina[8,9], Maria Virginia Soldovieri[1]
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	BACKGROUND. KCNT2 channels (also known as Slo2.1 or "Slick", *Sequence like an intermediate conductance K+ channel*) belong to the Slo family of potassium (K+) channels, also including the analogous KCNT1 isoform.1,2 Only few KCNT2 variants have been reported in patients affected by Developmental and Epileptic Encephalopathies (DEE),3 sever forms of encephalopathy resistant to traditional anti-epileptic drugs. **AIMS**: To characterize functional properties of three newly-identified variants in KCNT2 (D391H, C769Y, V823M) channels and to test the efficacy of drugs already in clinical use to counteract mutation-induced functional effects. **MATERIALS AND METHOD**S. Each variant was introduced through Quick- change PCR in plasmids encoding the human isoform of KCNT2 channels. Wild- type or mutant channels were espressed by transiently transfection in HEK cells. Currents were recorded 24 h later using patch-clamp technique in the whole-cell configuration. **RESULTS**. Patch-clamp recordings revealed that all newly-identified variants prompt loss-of-function (LoF) effects on KCNT2 channels currents in terms of reduced current densities (for all mutant channels) and reduced instantaneously- activated currents (for channels carrying C769Y or V823M variants). To counteract mutation-induced functional effects, drug riluzole was tested, as its ability to potentiate KCNT currents has been recently described.4 Preliminarypatch-clamp recordings have

	shown that the exposure to 100 μM riluzole significantly counteracts variant-induced functional effects. **CONCLUSION**. Newly-identified D391H, C769Y, and V823M variants prompt LoF effects on KCNT2 currents. Riluzole is able to activate KCNT2 currents, also in the presence of epilepsy-causing variants,thus indicating its possible use as a personalized approach in these patients. References: 1. Aldrich *et al.*, 2021. ***IUPHARBPS Guide Pharmacol CITE 2021(3)***. 2. Salkoff *et al.*, 2006. ***Nat Rev Neurosci*** 7(12):921–931 3. Ambrosino *et al.*,2018. ***Ann Neurol*** 83(6):1198–1204. 9. 4. Cioclu *et al.*, 2023. ***Ann Neurol*** 94(2): 332-349
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°24

TITLE	**Integration of LIBS and LFIA for High-Sensitivity Quantification of Total and Neuronal Extracellular Vesicles in Alzheimer's Disease**
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	Alzheimer's disease (AD) is a neurodegenerative disorder characterized by a decline in progressive cognitive abilities in older adults, which significantly affects their daily lives. According to the World Alzheimer's Report 2023, the global prevalence of AD is expected to increase from 55 million in 2019 to 139 million by 2050. Alzheimer's disease (AD) is characterized by early cognitive decline, which often remains latent and overlooked until it progresses to an irreversible stage. For this reason, identifying biomarkers for early prediction of AD is crucial. It is known that in pathological conditions, circulating levels and contents of extracellular vesicles (EVs) change significantly with respect to health status. EVs are a heterogeneous group of vesicles, ranging in size from 30 to 200 nm, released by almost all cell types in response to various intra/extra cellular stimuli, which serve as key mediators in cellular communication through the transfer of their cargo (proteins, lipids, nucleic acids) to recipient cells. In addition, thanks to their capability to cross the blood -brain barrier (BBB) until reaching peripheral blood, the study of EVs offers a significant advantage, as they can serve as a 'liquid biopsy' of the brain, potentially replacing invasive techniques like CSF sampling. EVs exhibit high molecular heterogeneity, so according to the guidelines of the International Society for Extracellular Vesicles (ISEV), their recognition must be entrusted to the detection of at least two classes of trans-membrane proteins common to all EVs, such as the tetraspanins CD9 and CD63. Furthermore, from the literature, it is known that several research groups have succeeded in selectively isolating neuronal EVs by exploiting the L1CAM protein as a membrane marker (1). In this work, we developed a novel readout strategy based on integrating LFIA technology with Tag-based Laser-Induced Breakdown Spectroscopy (Tag-LIBS) to isolate and quantify both total and neuronal-derived EVs. This approach combines the simplicity, rapid turnaround time, and cost-effectiveness of LFIA with the high analytical sensitivity of LIBS. Specifically, EVs were isolated from plasma samples via Size Exclusion Chromatography (SEC) and subsequently detected using custom-designed LFIAs targeting total and neuronal EV markers. The LFIA strips loaded with samples from healthy controls (HC) and AD patients were digitized and processed using ImageJ to extract optical density profiles from both the Test Line (TL) and Control Line (CL) for total and neuronal EV populations. Subsequently, direct LIBS analysis was performed on the

	positive TL. These two parallel readout strategies allowed the quantification of both EV subpopulations across the study cohorts, highlighting the enhancement in sensitivity achieved by LIBS compared to conventional densitometric analysis. Ultimately, this study aims to evaluate whether systematic variations in EV membrane antigens exist between healthy individuals and AD patients, reflecting diagnostic alterations in circulating EV subpopulations. [1] Mustapic, M.; Eitan, E.; Werner, J. K., Jr.; Berkowitz, S. T.; Lazaropoulos, M. P.; Tran, J.; Goetzl, E. J.; Kapogiannis, D. Plasma Extracellular Vesicles Enriched for Neuronal Origin: A Potential Window into Brain Pathologic Processes, Methods 2017 May, 11, 278.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°25

TITLE	**Neurovascular Adora2a as a key determinant of the neurobehavioral phenotype in a mouse model of 22q11.2 deletion syndrome**
AUTHORS	Sara Cioffi * [1], Gemma Flore * [1], Maria De Risi * [2,3], Sara Sannino[2], Fabio Russo[2], Diletta Cavezza[3], Salvatore Arbucci[1], Elvira De Leonibus* [2,3], Elizabeth Illingworth * [4]
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	22q11.2 deletion syndrome (22q11.2DS, DiGeorge syndrome) is the strongest known genetic risk factor for schizophrenia. Although alterations in the mesocorticolimbic dopaminergic systems have been reported in humans and in animal models, many mechanisms linking gene haploinsufficiency to neuropsychiatric dysfunction remain poorly understood. *TBX1*, a dosage-sensitive transcription factor located within the deleted region, is highly expressed in endothelial cells and has been associated with neurodevelopmental abnormalities. $Tbx1^{+/-}$ mice display impaired prepulse inhibition (PPI), a measure of sensorimotor gating relevant to psychosis, but the underlying mechanisms remain unclear. Here, we show that $Tbx1$ haploinsufficiency leads to extensive remodeling of dopaminergic circuits, characterized by increased numbers of tyrosine hydroxylase-positive neurons in the substantia nigra and ventral tegmental area, increased striatal tyrosine hydroxylase expression, and selective upregulation of D2 receptors. In parallel, $Tbx1^{+/-}$ mice exhibit reduced $Adora2a$ expression in the striatum, decreased A2A receptor expression in striatal endothelial cells, and reduced A2A/D2 receptor co-expression within striatal circuits. Consistently, $Adora2a$ expression was reduced following $Tbx1$ silencing in cultured endothelial cells and in brain endothelial cells isolated from $Tbx1^{+/-}$ mice, identifying $Adora2a$ as a TBX1-sensitive endothelial target. Despite the marked dopaminergic alterations, pharmacological D2 receptor blockade failed to rescue PPI deficits. In contrast, activation of A2A receptors fully restored sensorimotor gating. These findings indicate that dopaminergic abnormalities alone are insufficient to explain the behavioral phenotype and point instead to disrupted adenosine-

	dopamine interactions as a critical mechanism underlying impaired sensorimotor gating. Together, our results identify TBX1-dependent regulation of $Adora2a$ as a novel mechanism linking 22q11.2DS-associated genetic variation to dysfunction of striatal circuits. They further highlight adenosine signaling, including its neurovascular component, as a promising therapeutic target for neuropsychiatric manifestations associated with 22q11.2 deletion syndrome.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°26

TITLE	**MicroRNA-mediated modulation of direct cell reprogramming into dopaminergic neurons: implications for Parkinson's disease**
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	Parkinson's disease (PD) is the second most common neurodegenerative disorder, characterized by progressive dopaminergic neuron (DAN) loss not addressed by current symptomatic treatments [1]. Direct reprogramming of somatic cells into DANs represents a promising strategy for cell replacement therapy. Fibroblasts can be converted into DANs through the overexpression of three key transcription factors, ASCL1, NURR1, and LMX1A (ANL) [2]. However, the process must be highly efficient to be clinically relevant, and additional factors may help. In this context, small non-coding RNAs, particularly microRNAs (miRNAs), have emerged as powerful regulators of cell identity and differentiation [3]. This study aimed to identify miRNAs involved in fibroblast-to-DAN conversion. To this end, TH-GFP mouse embryonic fibroblasts (MEFs) were reprogrammed through ANL overexpression, and a time-course transcriptomic analysis identified nine miRNA clusters with distinct expression profiles. Thereafter, miRNAs upregulated during differentiation, including miR-218, miR-204/211, and miR-375, were tested for their role in dopamine cell reprogramming. Thus, MEFs were reprogrammed with ANL alone or combined with each selected miRNA, and after 16 days, neuronal marker expression was assessed. All tested miRNAs increased β3-tubulin levels when combined with ANL, indicating enhanced neuronal induction. However, miR-218 and miR-204/211 showed the greatest effect in promoting dopaminergic features. Specifically, both miRNAs significantly upregulated tyrosine hydroxylase expression at both gene and protein levels, and increased the gene expression of additional dopaminergic markers, i.e., *Vmat2* and *Ddc*, compared to ANL alone. Notably, miR-218 and miR-204/211 also enhanced neurite length and branching complexity in the resulting DANs,

	indicating increased neuronal maturation, a key prerequisite for functional integration. Given their positive effect, the combined use of miR-218 and miR-204/211 together with ANL was also tested to assess their potential synergistic effects. However, their co-expression did not result in a further improvement compared to individual miRNAs. Our findings identify miR-218 and miR-204/211 as key enhancers of dopaminergic conversion and neuronal maturation during direct reprogramming, highlighting their potential as RNA-based tools to improve dopaminergic neuron generation for future cell replacement therapies in PD. [1] Poewe et al., 2017. doi: 10.1038/nrdp.2017.13. [2] Caiazzo et al., 2011. doi: 10.1038/nature10284. [3] Pascale et al., 2022. doi: 10.3390/cells11060940.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°27

TITLE	**Arachidonoyl-sn-glycerol-3-phosphate (2-AGP), a Lysophosphatidic Acid, Mediates High- Fat Diet–Induced Working Memory Impairment via Tau Hyperphosphorylation and Microglial Dysfunction**
AUTHORS	Marfella B[1], Nicois A[1,3],Forte N[1], Boccella S[9], Somma C[7], Maione S[9], De Leonibus E[7,8], Mottola I[10], Gianfrani C[10], Mollica MP[2], Palomba L[1,3], Di Marzo V[1,6], Cristino L[1]
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	Understanding why overeating in obesity becomes self-reinforcing requires looking beyond basic appetite regulation to examine executive function impairments, particularly working memory (WM) deficits. These memory impairments contribute to sustained overeating and reinforce the hypothesis that obesity is a major risk factor for neurodegenerative disorders. WM dysfunction stems from multiple converging mechanisms, including neuroinflammation and gliosis. Our previous studies show that: 1. Obese mice exhibit gliosis and endocannabinoid- mediated deficits in episodic memory (*Forte et al., Nat Comm.*); 2. The neuropeptide Orexin-A (OX-A) enhances the levels of the endocannabinoid 2-arachidonoylglycerol (2- AG) and its derivative 2-arachidonoyl-sn-glycerol-3-phosphate (2-AGP) in the hippocampus of obese mice and in CSF of both obese mice and humans (*Forte et al., Front Aging Neurosci.*); 3. At the neuronal level, 2-AGP activates the LPA1 receptor (LPA1R) eliciting Tau phosphorylation at residue 231 via Pyk2-GSK3β pathway *(Forte et al., Front Aging Neurosci*. and *Fernández et al., Mol Metab.)*. Altogether these data support that

	LPA1R activation may represent a mechanistic link between obesity-associated neuroinflammation and tau pathology, as well as synaptic and memory deficits *(Fernández et al., Mol Metab.)*. Of note, LPA1R activation in microglia directly promotes a pro- inflammatory phenotype and lipid droplet accumulation (LDA), as it was previously described in aging brain *(Marschallinger et al., Nat Neurosci.)*. Concurrently, pro- inflammatory microglia itself can sustain GSK3β activation and Tau phosphorylation at residue 231 via IL-1β secretion *(Ghosh et al.,2013)*. On this background we hypothesized that in obesity, WM alterations may result from a LPA1R-mediated dual pathogenic mechanism whereby neuronal p231Tau hyperphosphorylation occurs in parallel with a chronic pro-inflammatory microglial state, creating a feed-forward loop that further accelerates Tau pathology. Using an integrated approach combining immunohistochemical, biochemical, electrophysiological, and behavioural methods we compared adult male C57BL/6J obese mice with sex/age-matched lean littermates. Our preliminary data show that: • Obesity impairs memory load and hippocampal synaptic plasticity. Obese mice exhibit reduced WM under high memory-load conditions assessed with six different objects test (6-DOT) and impaired CA3–CA1 long-term potentiation (LTP). • Obese mice exhibit p231Tau accumulation in CA3–CA1 regions and increased LDA in microglia (LDAM) accompanied by impaired phagocytic activity, as revealed by reduction of p231Tau accumulation within LDAM. • In vitro treatment with the lipid droplets accumulation inhibitor (PF) lowered TNF-α, IL-6, and IL-1β production in microglial cells cultured in presence of palmitic acid, used as a model of lipotoxic stressor. • Pharmacological inhibition of LPA1R with AM095 rescued both WM performance and hippocampal synaptic plasticity in vivo. Our findings strengthen the link between altered energy homeostasis, neuroinflammation and memory decline, uncovering novel therapeutic targets to preserve cognitive function under metabolic stress.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°28

TITLE	**Plasma Extracellular Vesicles in Schizophrenia: Effects on Microglia and Perspectives for Targeted Drug Delivery**
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	Background Schizophrenia is increasingly conceptualized as a disorder of disrupted neurodevelopment and brain connectivity, in which microglia play a central regulatory role. Extracellular vesicles (EVs) have recently emerged as key mediators of intercellular communication between the periphery and the central nervous system, representing a potential mechanism for the propagation of glial dysfunction and neuroinflammatory signals in schizophrenia. Since EVs can cross biological barriers, they are also attractive candidates as carriers for targeted delivery of antipsychotics. These two perspectives require a clear understanding of the native biological activity of patient-derived EVs. **Aim** In this context, the present study aims to assess whether EVs isolated from patients with schizophrenia induce morphological changes in microglial cells, thereby providing insight into early pathogenic mechanisms linking peripheral signals to central neuroimmune alterations. **Methods** EVs were isolated from peripheral blood samples collected from patients with schizophrenia and matched healthy controls by differential ultracentrifugation. All patients were receiving antipsychotic treatment (risperidone, clozapine or aripiprazole). Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS) and the PANSS Autism Severity Score (PAUSS). Neurological vulnerability was evaluated using the Neurological Evaluation Scale (NES), while cognition was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS). The isolated EVs underwent comprehensive characterization of their biophysical and functional properties. Nanoparticle Tracking Analysis and zeta potential measurements were employed to assess particle size distribution, concentration, and surface charge. To evaluate the functional impact of EVs, BV2 microglial cells were monitored using the xCELLigence real-time cell analysis system, allowing for dynamic, label-free tracking of cell viability and morphological changes post-exposure. Then, BV2 microglial cells were exposed to two different EVs concentrations (20mM, 30mM)

	Results EVs were successfully isolated from both patients and healthy controls, showing biophysical profiles consistent with small EV populations (sEVs). In real-time growth assays, EVs from healthy controls (n=3) did not affect BV2 proliferation at either dose, with all conditions reaching ~90–95% confluence. In contrast, EVs from patients (n=6) produced heterogeneous effects. Three samples did not substantially alter growth. Two samples slowed the logarithmic phase and prolonged the lag phase, one of them showing a cytostatic, non-lethal growth inhibition. One sample was markedly cytotoxic, with a sharp decline in confluence after 65–70 h at both doses. **Conclusions** Schizophrenia-derived EVs actively modulate microglial behaviour, supporting their role as a mechanistic bridge between peripheral signals and central neuroimmune function. Determining whether schizophrenia-derived EVs carry a disease-specific signature may clarify their contribution to microglial alterations relevant to neurodevelopment, including synaptic pruning and network maturation. Their influence on microglia also suggests a potential interaction with the immunomodulatory effects of antipsychotics. Ongoing proteomic and transcriptomic analyses of EV cargo will help elucidate the pathways through which these vesicles contribute to neuroinflammatory signalling. Characterizing the cargo and baseline activity of native EVs is also a prerequisite for evaluating their potential as vehicles for precision antipsychotic delivery.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°29

TITLE	**CSTB deficiency drives impaired autophagy and endosomal remodeling in early EPM1 neurodevelopment**
AUTHORS	Immacolata Palmieri[1], Natalia Abate[1], Laura Canafoglia[2], Francesca Ragona[2], Silvia Cappello[3,4,5], Marianna Crispino[1], Rossella Di Giaimo[1,3]
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	Progressive myoclonus epilepsy type 1 (EPM1) is a rare neurodegenerative disorder caused by the partial loss of function of cystatin B (CSTB), a cysteine protease inhibitor of the cathepsin family with well-established neuroprotective roles. Previous studies in patient-derived cerebral organoids identified early alterations during neurodevelopment with defects in ventral progenitor cell-fate and differentiation. Proteomic analysis of day-40 ventral-patterned organoids revealed a significant downregulation of autophagy-related pathways in EPM1. Our aim was to investigate if defects in autophagy-related pathways could be behind the altered neuronal progenitor identity in EPM1 patients during the earliest stages of neuronal differentiation. We focused on neural progenitor cells after only three days of neuronal induction. EPM1 cells showed a significant reduction in the LC3-II/LC3-I ratio compared to control cells, accompanied by reduced p-AMPK/AMPK and increased phosphorylation of the mTORC1 targets 4EBP1 and P70S6K. Phosphorylation of ULK1 at Ser757 was also increased, supporting an early impairment of autophagy initiation. Together, these findings provide the first evidence of dysregulated autophagic signaling during early neuronal differentiation in EPM1. We then hypothesized that impaired autophagic clearance in EPM1 may be associated with remodeling of the endosomal compartment, eventually redirecting intracellular material toward multivesicular bodies (MVBs) and extracellular vesicle biogenesis. Consistent with this hypothesis, we found out that EPM1 cells showed intracellular accumulation of EV markers like RAB7 and ALIX, suggesting altered organization and/or clearance of the late endosomal/MVB compartment. These findings may reflect a redistribution of intracellular cargos toward the EV pathway in the context of impaired degradative homeostasis.

	Future studies will aim to determine whether CSTB deficiency contributes to the coordinated dysregulation of autophagic and endosomal homeostasis in EPM1.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°30

TITLE	**From receptor to brain: caulerpin, a marine dual PPARα/γ partial agonist, as a probe for neural and peripheral biomarkers of appetite and reproductive modulation in fish**
AUTHORS	Vitale, R.M.[1], D'Aniello, E.[1,2], Gorbi, S.[3], Schiano, V.[1,4], Cutignano, A.[1], Carbone, M.[1], Ciavatta, M.L.[1], Lucini, C.[4], Amodeo, P.[1], Mollo, E.[1]
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	Bioactive dietary compounds acting on nuclear receptors can reshape brain circuits controlling feeding and reproduction, yet markers linking exposure, target engagement and central effects remain scarce. Caulerpin (CAU) is a bisindole alkaloid abundant in *Caulerpa cylindracea*, an invasive seaweed now a major food item for Mediterranean fish species, and in related "sea grapes" (e.g., *C. lentillifera*) widely consumed by humans in the Indo-Pacific region. This contribution integrates and reinterprets, from a biomarker perspective, two published studies (Vitale et al. 2018; Schiano et al. 2022), tracing CAU action from its molecular target to brain signatures and organismal outcomes. *Target identification*. Docking and molecular dynamics predicted CAU binding to PPARα and PPARγ, and luciferase reporter assays confirmed dual partial agonism without RXRα activation. CAU upregulated hepatic PPARα in the white sea bream *Diplodus sargus* and induced PPARα target genes of fatty-acid β-oxidation (*ACADM* and *ACOX1* in *D. sargus* liver slices; *ACADM*, *ACOX1* and *CPT1A* in HepG2 cells). *Exposure*. Orally administered CAU was detected by LC-MS/MS in *D. sargus* and accumulated mainly in lipid-rich tissues (liver and brain), indicating that it crosses the blood–brain barrier. It was also found in gonads of wild fish from invaded areas, supporting tissue CAU levels as an exposure biomarker. *Central and reproductive signatures*. In three independent trials, the zebrafish *Danio rerio* fed a 0.1% CAU diet consumed their food in less than half the time taken by controls, especially in later sessions. After 21 days, their brains showed upregulation of *Pparα*, *Pparγ*, endocannabinoid (*Cnr1*, *Cnr2*), orexinergic (*Hcrt*) and serotonergic (*5-HT1A*) genes, and downregulation of *Pomca* and *Npy*. In the liver, *Pparα*, *Pparγ* and *Acadm* were also upregulated, mirroring the hepatic response

	observed in *D. sargus*. In the brain, CAU also upregulated HPG-axis genes (*Gnrh2*, *Cyp19a1b*, *Ar*, *Ahr1a*) in both sexes and *Fshb* and *Lhb* in females, while kisspeptin genes changed in opposite directions in the two sexes. CAU increased the gonadosomatic index, reduced egg degeneration, and improved hatching and larval viability. Dietary CAU was transferred from parents to embryos and was undetectable in offspring by 30 days post-fertilization. Together, these data from two fish species outline a multi-level biomarker panel for a PPAR-active dietary compound: tissue CAU levels as exposure markers, hepatic PPARα target genes as peripheral markers of target engagement, a PPAR-endocannabinoid-orexin brain signature as a candidate central marker of effect, and HPG-axis transcripts together with gonadosomatic index and hatching success as markers of reproductive outcome. Given the interest in PPAR ligands for metabolic and neurodegenerative disorders, CAU may serve as a natural-product probe of PPAR-dependent brain pathways regulating appetite and reproduction. References Vitale, R.M., D'Aniello, E., Gorbi, S., Martella, A., Silvestri, C., Giuliani, M.E., Fellous, T., Gentile, A., Carbone, M., Cutignano, A., Grauso, L., Magliozzi, L., Polese, G., D'Aniello, B., Defranoux, F., Felline, S., Terlizzi, A., Calignano, A., Regoli, F., Di Marzo, V., Amodeo, P., Mollo, E. *Marine Drugs* 16, 431, 2018. Schiano, V., Cutignano, A., Maiello, D., Carbone, M., Ciavatta, M.L., Polese, G., Fioretto, F., Attanasio, C., Palladino, A., Felline, S., Terlizzi, A., D'Angelo, L., de Girolamo, P., Turano, M., Lucini, C., Mollo, E. *Marine Drugs* 20, 513, 2022.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 31

TITLE	**Symptoms and functional testing in morphologically defined small fibers neuropathy (SFN).**
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	Small fibers neuropathy (SFN) refers to damage of somatic and autonomic C-fibers and A-delta fibers. The diagnostic gold standard is skin biopsy. The aim of this study was to evaluate the sensitivity of other clinical and neurophysiological tests. We observed 74 SFN patients (F/M=57/17) with sensory and autonomic symptoms and signs, normal nerve conduction studies and reduced intraepidermal-nerve-fibers-density (IENFD) at skin biopsy. All patients underwent Composite-Autonomic-Symptoms-Score (COMPASS-31), SFN- Symptoms-Inventory-Questionnaire (SFN-SiQ), Quantitative sensory testing (QST), cardiovascular reflexes, and Dynamic Sweat Test (DST). Considering abnormal at least two modalities at four sites tested, QST detected a SFN in 94% of cases. Considering abnormal one modality, at foot QST was altered in 94% with Cold detection threshold abnormal in 73%. Sweat output after pilocarpine stimulation, evaluated by DST, was reduced in 90% at leg and 88% at forearm. Considering abnormalities in at least two tests, cardiovascular reflexes were impaired in 33%. Considering a total score>/= 5, SFN-Siq sensitivity was 98%. COMPASS-31 total score correlated with severity of autonomic
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 32

TITLE	**The sphingosine-1 phosphate receptor modulator ozanimod attenuates symptoms and molecular defects in a mouse models of Rett Syndrome.**
AUTHORS	Aquino Assunta[1], Genserico Roberta[1], Asaro Antonino[2], Elena Cacciapuoti[1], Aiese-Cigliano Riccardo[3], Pisapia Laura[1], Barra Adriano[1], Mele Lucia[1], Pepe Giuseppe[4], Maglione Vittorio[4], D'angelo Giovanni[2], Fioriniello Salvatore[1#], and Della Ragione Floriana[1#]
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	Rett syndrome (RTT; OMIM 312750) is the second most common genetic cause of intellectual disability in girls, which manifest as a severe neurodevelopmental disorder with cognitive and motor impairments. RTT is mostly caused by mutations in the X-linked *Methyl-CpG-binding Protein 2* (*MECP2*) gene, encoding an epigenetic factor crucial for nervous system functioning. MeCP2 deficiency recapitulates the RTT phenotype in mice, which can be rescued by gene restoration. However, the pathogenic mechanisms are still poorly understood and effective therapeutic options are currently lacking. We found that MeCP2 dysfunctions lead to altered sphingolipid (SLs) content in the hippocampus of *Mecp2*$^{-/y}$ male and *Mecp2*$^{-/+}$ female mice through deregulation of genes encoding factors implicated in SL metabolism (sphingo-genes). These observations identify the SL metabolism as a novel druggable target that, when altered, might contribute to RTT pathogenesis. Building on these findings, we propose a drug repositioning-based therapeutic strategy with Ozanimod (RPC-1063), a next generation sphingosine 1-phosphate (S1P) receptor modulator, already approved for the treatment of other neuropathologies. Our data showed that Ozanimod prolongs the lifespan, decreases the RTT phenotypic score, and protects *Mecp2*$^{-/y}$ mice from weight loss. Moreover, the treatment restored the physiological expression of the neurotrophic and neuroprotective factors BDNF and IGF-1, recovered physiological levels of phopsho- ERK1/2, modulated the expression of

	several genes involved in neuronal functions and normalized the expression of multiple sphingo-genes in the *Mecp2*$^{-/y}$ hippocampus. Based on these observations, we extended the analysis of molecular effects of Ozanimod in cortex and cerebellum, which are other brain regions particularly affected by MeCP2 deficiency. Consistently, in both brain regions Ozanimod showed a beneficial impact on molecular pathways previously shown to be modulated in the hippocampus. The comparable effects of Ozanimod across all brain regions analyzed strengthen the rationale for further investigating its therapeutic potential in RTT, supporting its ability to modulate disease-associated molecular alterations across distinct brain areas. The effect of Ozanimod on altered sphingolipid levels in the hippocampus, cortex and cerebellum of *Mecp2*$^{-/y}$ mice is, currently, under investigation. In parallel, we are exploring the pharmacological impact on additional hallmarks of RTT, as neuroinflammation and increased permeability of the blood–brain barrier.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 33

TITLE	**Cuprizone alters autophagy, G-quadruplex signal, and survival in human neuronal SH-SY5Y cells.**
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	Demyelination is a hallmark of multiple sclerosis and other neurodegenerative diseases, in which impaired autophagy and altered interactions among central nervous system (CNS) cells may contribute to disease progression. Cuprizone (CPZ), a copper chelator widely used as an experimental demyelinating agent in animal models, has poorly characterized cell-specific effects. This study aimed to investigate the effects of CPZ on autophagy and G-quadruplex (G4) structures in human microglial (HMC3) and neuronal (SH-SY5Y) cells, and to explore the potential protective effects of quercetin and metformin as well as microglia-mediated neurotoxicity. Autophagy-related markers BECN1 and LC3 were evaluated in HMC3 and SH-SY5Y cells treated with CPZ (1, 10, and 100 μM) for 24 and 48 h. G4 signal was assessed in both cell lines following CPZ treatment by flow cytometry using the G4-specific BG4 antibody. In SH-SY5Y cells, the effects of quercetin (50 nM) and metformin (1 mM) on CPZ-induced alterations were investigated by evaluating G4 -positive cell frequency and LC3-related parameters following 48 h of treatment with CPZ (10 μM), alone or in combination with either compound. Cell viability following CPZ treatment was assessed in both cell lines using Trypan Blue exclusion. Microglial phenotype modulation was evaluated by flow cytometry using CD11b, HLA-ABC, CD86, CD80, CD206, and HLA-DR markers. Finally, the effects of conditioned medium (CM) from CPZ-treated HMC3 cells on SH-SY5Y cells were investigated by assessing cell viability using Trypan Blue exclusion, followed by flow cytometric analysis of apoptosis and necrosis using Annexin V/PI staining. CPZ altered autophagy-related parameters in SH-SY5Y cells, as indicated by reduced LC3-II levels and a decreased LC3-II/LC3-I ratio, without affecting BECN1 expression. No significant changes in BECN1 expression or LC3 -related parameters were detected in HMC3 cells. Regarding G4 structures, CPZ reduced the frequency of G4-positiveSH-SY5Y cells after 48 h, whereas no significant changes were observed in

	HMC3 cells. In SH-SY5Y cells, co-treatment with quercetin or metformin counteracted the CPZ-induced alterations in G4 frequency and LC3-related parameters. CPZ treatment did not significantly affect cell viability in either cell line under the tested conditions. However, CPZ treatment increased HLA-DR expression in HMC3 cells, suggesting modulation of the microglial phenotype. Furthermore, CM from CPZ-treated HMC3 cells caused a slight, non-significant reduction in SH-SY5Y cell viability and increased early apoptosis, suggesting a potential indirect microglia-mediated neurotoxic effect. Our findings indicate that CPZ selectively alters autophagy-related parameters and reduces G4 signal in SH-SY5Y cells. Quercetin and metformin counteract these alterations, supporting further investigation into the relationship between G4 structures and autophagy regulation. Although CPZ did not directly affect cell viability under the tested conditions, CM from CPZ-treated microglial cells increased early apoptosis in neuronal cells, suggesting a possible indirect neurotoxic effect. These findings provide new insights into the cellular effects of CPZ and may contribute to a better understanding of the mechanisms associated with neuronal dysfunction in demyelinating conditions.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N°34

TITLE	**Phenotyping thought disorder in treatment-resistant schizophrenia: a multidimensional analysis using the thought and language disorder scale and clinical correlates**
AUTHORS	Ceparano C.[1], Iannotta F.[2], Ricci C.[2], Pezzullo G.[2], Catino A.[2], Del Monaco W.[2], Iasevoli F.[2], de Bartolomeis A.[2]
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	Formal thought disorder (TD) represents a core clinical marker of schizophrenia, significantly impacting global functioning and social integration. Historically, psychiatric literature has distinguished between "fluent" and "non-fluent" thought disorders. The Thought and Language Disorder (TALD) scale has emerged as a pivotal instrument, enabling clinicians to integrate the evaluation of objective signs with the patient's own subjective experience of their cognitive and linguistic flow. In the clinical landscape, treatment-resistant schizophrenia (TRS) poses unique diagnostic and therapeutic challenges. The primary aim of this study was to characterize the specific profile of thought and language disorders in patients with TRS compared to treatment-responsive patients (SCZ). This observational study involved 117 patients, clinically categorized into two groups: SCZ = 61 and TRS = 56. The TALD scale was subdivided into four distinct domains: Objective-Positive (OP), Objective-Negative (ON), Subjective-Positive (SP), and Subjective-Negative (SN). Clinical psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). We employed Welch's t-tests for group comparisons to account for unequal variances. Relationship between variables was assessed via Pearson correlations. A multiple linear regression model was constructed, controlling for age, sex, education, duration of illness, and chlorpromazine equivalents. Finally, a causal mediation analysis and a Receiver Operating Characteristic (ROC) curve analysis (using the Youden Index) were conducted to identify the optimal diagnostic cut-off for resistance. All the participants underwent a clinical interview conducted by two trained psychiatrists. The interview was recorded with the Tascam DR-05X digital audio recorder. After the interview, the two clinicians completed the TALD (Thought and Language Disorder Scale) scoring. The recordings were also rated by a Large Language Model (LLM), which was trained for TALD scoring according to predefined metrics, and produced independent TALD ratings for each participant. The TRS group exhibited significantly higher total TALD scores compared

	to the SCZ group (p = 0.032). Specifically, a marked impairment was found in the Objective-Positive domain (p = 0.025), reflecting greater observable disorganization. Conversely, subjective dimensions showed no significant differences between groups (p > 0.30), resulting in a significantly larger "TALD Gap" (the discrepancy between objective signs and subjective awareness) in TRS patients (4.74 vs 2.55). Regression analysis revealed that education level significantly influences the detectability of thought disorders (p = 0.03), whereas duration of illness was not a significant predictor (p = 0.28). This supports the hypothesis that TD, as measured by the TALD, acts as a stable "trait" marker rather than a degenerative feature. A moderate correlation was confirmed between TALD scores and PANSS Negative symptoms (r = 0.40, p < 0.001). Causal mediation analysis demonstrated that negative symptoms act as a total mediator in the relationship between treatment resistance and communicative deficits. The ROC curve identified an optimal cut-off of 28.5 points (AUC 0.61), yielding a high specificity of 85.2% for the TRS profile. Our findings suggest that treatment resistance in schizophrenia is characterized by objective linguistic disorganization, primarily driven by the severity of the negative affective dimension. The TALD scale proves to be a sensitive tool for phenotyping these patients.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 35

TITLE	**Neurosteroids as potential biomarkers in autism: link with inflammation and pharmacological modulation**
AUTHORS	Cristiano C [1], Filogamo F[1], Liguori FM[1], Russo R[1]
AFFILIATION	[1] Department of Pharmacy; University of Federico II; Naples Italy
	Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental condition arising from a complex interplay of genetic and environmental factors. The lack of curative treatments and the substantial biological heterogeneity of ASD underscore the need for biomarkers that can improve disease characterization and guide therapeutic development. Lipid mediators and neurosteroids represent promising candidates because of their roles in neurodevelopment, neuronal function, and inflammatory regulation. Altered docosahexaenoic acid (DHA) levels have been reported in ASD, supporting its role as a potential biomarker. However, neurosteroid biosynthesis and its relationship with systemic and central inflammation remain poorly characterized in ASD. To our knowledge, this study provides the first integrated characterization of neurosteroid levels and their biosynthetic pathway in BTBR mice, a preclinical model of ASD, alongside systemic and central inflammatory profiles. We also investigated the effects of low-dose DHA combined with ultramicronized palmitoylethanolamide (PEA-um), an endogenous lipid mediator with anti-inflammatory and neuroprotective properties. Our results showed that BTBR mice exhibited impaired neurosteroidogenesis, characterized by an imbalance between pregnenolone and allopregnanolone and reduced expression of neurosteroidogenic enzymes. These abnormalities occurred alongside systemic and central inflammatory alterations, increased repetitive behaviors, and impaired social interactions, revealing a broader pattern of neurosteroid and immune dysregulation. Combined PEA-um and DHA treatment restored allopregnanolone levels and normalized neurosteroidogenic enzyme expression, while attenuating inflammatory alterations and improving behavioral outcomes. Overall, these findings highlight neurosteroids as potential biomarkers of neurosteroidogenic dysregulation and candidate indicators of pharmacological response in a preclinical model of ASD. Integrating circulating and cerebral neurosteroid measurements with inflammatory profiles provides a basis for further investigation of their relevance to biological characterization and treatment monitoring.

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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 4

TITLE	**Dysarthria assessment in patients with Multiple Sclerosis**
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	Background: Speech patterns in MS are inadequately characterized. Software such as Dysarthria Analyzer (DA) facilitates a detailed speech analysis and could be useful in clinical practice. **Methods**: All patients underwent clinical assessments through Expanded Disability Status Scale(EDSS) and Brief International Cognitive Assessment for MS(BICAMS) and speech evaluation using the DA.For speech analysis,each patient performed 6 tasks:phonation A,phonation I,reading,monologue,monosyllabic and trisyllabic repetition. The DA automatically extracted 28 speech features,adjusted for age,gender and education,resulting in z-scores. A principal component analysis was performed,retaining only components with eigenvalues >1. A linear regression analysis was performed to explore correlations between EDSS and dysarthria factors aswell as between EDSS subscores and dysarthria. Correlations between the components and clinic-demographic features were assessed through forward stepwise analysis, including age,gender,disease duration,disease course,smoking habits,EDSS and Cognitive Functional System(CFS) as covariates. **Results**: We enrolled 72 patients[50 females;mean age 48.1±10.9 years; median disease duration of 14(0 – 34)years and a median EDSS of 3(1.5 – 6.5)]. Exploratory factor analysis identified a 7-factor model:Voice intensity;Voice Intensity Variation;Motor coordination;Speech dyadokocinesis;Speech Speed;Voice strenght-susteined vocal;Speech Latency. Higher EDSS associated with worse Voice Intensity Variation(r=-0.23,p=0.05),worse Speech Speed (r=-0.40, p=0.001) and worse Speech Latency(r=-0.23, p=0.05). Pyramidal, Sensitive, Cerebellar and Bowel/Bladder EDSS

	subscores associated with worse Speech Speed(r=-0.33,p=0.007; r=-0.31,p=0.01; r=-0.29,p=0.03; r=-0.47,p<0.001, respectively). Higher Brainstem EDSS subscores associated with worse Speech Latency (r=-0.47,p<0.001). Stepwise analyses unveiled that progressive MS patients showed worse Voice Intensity Variation (coeff. -1.20;p=0.02).We also reported a correlation between higher CFS score and worse Speech Speed (coeff. -0.38;p=0.02). **Discussion**: Extensive speech analysis can identify different aspects of MS disability. Higher disability is likely to be related to the ability to control muscles and breathing involved in phonation and speech articulation while cognition could affect speech through slower information processing speed.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 36

TITLE	**The novel Kv7 activator c60 reduces pain in oxaliplatin-induced peripheral neuropathy**
AUTHORS	Flavia De Martino[1]; Ingride L. Gaspar[1,2]; Laura Micheli[3]; Elena Lucarini[3]; Clara Ciampi[3]; Vincenzo Barrese[1]; Francesco Miceli[1]; Carmine Ostacolo[4]; Carla Ghelardini[3]; Lorenzo Di Cesare Mannelli[3]; Maurizio Taglialatela[1]
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	INTRODUCTION: Neuropathic pain frequently arises because of nerve damage or as a side effect of pharmacological treatments. A particularly severe form is chemotherapy-induced neuropathy (CINP), such as that triggered by oxaliplatin (OXA), which often induces discontinuation of therapy. Activation of Kv7.2, Kv7.3, and Kv7.5 voltage-gated potassium channels expressed in the nervous system suppresses neuronal activity and represents a valid strategy in the treatment of diseases characterized by hyperexcitability, such as pain Indeed, the Kv7 activators flupirtine and retigabine alleviate pain symptoms. However, both drugs have been withdrawn from the market due to severe side effects. In this study, we investigated, the effects of compound 60 (C60), a novel Kv7 channel activator developed in our laboratory, in a mouse model of oxaliplatin-induced neuropathy. **METHODS**: CINP in mice was developed by injecting 2.4 mg/kg oxaliplatin daily for 15 days. To evaluate the acute effects of Kv7 activators, Retigabine or C60 (0.1-3 mg/kg) were administered with intra peritoneal (i.p.) injections 24 hours after the last oxaliplatin injection (day 15)**.** Behavioral tests were performed every 15 min (0'-75') after the administration of Kv7 openers. To evaluate the chronic effect, mice were treated daily with Kv7 activators (both at 1 mg/kg) along with oxaliplatin for 15 days. Behavioral tests were performed at day 1, 8 and 15. At the end of the treatment period, tissues from key pain-related regions were collected for Western blot and quantitative PCR analyses. **RESULTS:** Acute treatment with both RET and C60 reduced cold allodynia and mechanical hyperalgesia, with similar efficacy; the Kv7 blocker XE991 fully reversed the effects of RET and C60. Chronic administration of RET or C60 also prevented the development of OXA-induced mechanical allodynia and hyperalgesia, starting from day 8.

	Moreover, C60 prevented the increase of GFAP protein expression induced by oxaliplatin in periaqueductal gray (PAG). Western blot analyses also revealed a downregulation of specific Kv7 subunits in some regions involved in pain transmission (Kv7.2 in dorsal root ganglia; Kv7.3 and Kv7.5 in the spinal cord; Kv7.2, Kv7.3, and Kv7.5 in the PAG; Kv7.5 in the cortex). Kv7 protein downregulation was not paralleled by a decrease in mRNA levels in cortex and spinal cord, suggesting post-transcriptional regulation. Noteworthy, C60 also prevented Kv7.5-downregulation in the cortex and spinal cord. **CONCLUSION:** Overall, these findings demonstrate that C60 effectively alleviates CINP and counteracts Kv7 channel downregulation, supporting its potential use in the treatment of pain.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 1

TITLE	**Circulating epilipids reveal a novel signature of oxidative lipid remodeling in Parkinson's disease**
AUTHORS	Federica Carrillo[1], Marco Ghirimoldi[2], Giuseppe Giurin[1], Mariarca Marciano[3], Francesca D'Amato[1], Nicola Modugno[3], Sara Pietracupa[3], Marcello Manfredi[2], Teresa Esposito[1,3]
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	Parkinson's disease (PD) is a complex neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons. Alterations in lipid metabolism and oxidative stress have increasingly been recognized as important contributors to dopaminergic neuronal dysfunction and degeneration. Our group has previously reported alterations in lipid levels at both the cellular and systemic levels, in PD-derived neurons and plasma samples, respectively. However, the contribution of oxidatively modified phospholipids to PD-related lipid dysregulation remains poorly understood. In this study, we investigated the circulating epilipidome in PD to identify disease-associated alterations and explore their biological and clinical relevance. We applied a discovery-to-validation strategy integrating untargeted lipidomic profiling, lipid-specific computational prediction and targeted parallel reaction monitoring (PRM) mass spectrometry. Candidate epilipids were further characterized by tandem mass spectrometry and Paternò–Büchi derivatization, while their oxidative origin was investigated through controlled plasma oxidation experiments. Targeted PRM analysis in an independent cohort of 384 patients with PD and 122 healthy controls identified a coordinated signature of nine oxidatively modified phospholipids, predominantly characterized by reduced plasma abundance in PD. Eight of these species remained significantly associated with disease after adjustment for age and correction for multiple testing. Epilipid-to-native lipid ratios further supported selective alterations in oxidized phospholipid pools rather than changes solely reflecting precursor lipid abundance. In patients within five years of diagnosis, the nine-epilipid panel discriminated PD from healthy controls with an AUC of 0.840 (95% CI: 0.788–0.886). The signature was also detectable in newly diagnosed drug-naïve patients, with an exploratory AUC of 0.976 (95% CI: 0.940–0.999; n=20). Furthermore, lower levels of selected epilipids were associated with longer disease

	duration. Interestingly, sex-stratified correlation analyses revealed distinct clinical associations, involving cognitive performance predominantly in males and non-motor symptom burden in females. Finally, two selected epilipids, PC(O-16:0_20:3<OH>) and PE(P-18:1_20:3<OH>), were increased in both PD patients-derived dopaminergic neurons and their respective conditioned media. Overall, our findings identify a novel circulating epilipid signature associated with PD, revealing selective alterations in oxidative phospholipid remodeling across systemic and neuronal compartments. This signature provides new insights into lipid redox homeostasis and its relationship with clinical heterogeneity in PD, while highlighting circulating epilipids as promising candidates for further investigation in prospective studies.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 1

TITLE	**Development of a comprehensive diagnostic pipeline integrating MALDI-MSI and Proteomics methodologies to map the molecular signature of epileptic FCDIIb lesions**
AUTHORS	Ilaria Iacobucci[1,2],Antonella Altieri[1,2], Alessia Lubrano-Lobianco[1,2], Dalia De Santis[3], Michele Rizzi[4], Niccolò D'Agaro[5], Giulia Capitoli[5], Chiara Calabretta[3] Cinzia Cagnoli[3], Rita Garbelli[3], Maria Monti[1,2]
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	Epilepsy is a neurological disorder affecting about 1% of the population. Despite anti-seizure medications, nearly 30% of patients develop drug-resistant epilepsy (DRE), for whom surgery remains the effective treatment. Among the lesions associated with DRE, Focal Cortical Dysplasias (FCDs) represent a major cause, although diagnosis remains challenging1. Combining MALDI imaging and LC-MS/MS proteomic approaches, this study aimed to define the molecular signature of FCDIIb in Formalin-Fixed Paraffin-Embedded (FFPE) surgical specimens. An integrated workflow was applied to 11 FCDIIb FFPE tissues to identify lesion-associated molecular alterations by combining spatially resolved ion maps with protein-level characterization. MALDI-MSI data were processed to preserve spatial information and generate ion distribution maps of lesion-associated molecular alterations. Tissue segmentation was performed using a Spatial Shrunken Centroids (SSC) approach, enabling the identification of lesional and perilesional grey and white matter regions. Comparison of matched lesional and perilesional areas identified 110 differentially expressed m/z features associated with FCDIIb ($|log2FC| > 0.5$; $p < 0.05$), including 62 upregulated and 48 downregulated signals in lesions and consistently detected in at least 50% of cases. In parallel, proteomes from lesional and perilesional tissues were compared using a shotgun LC-MS/MS differential proteomic approach. Protein identification, quantification, and pathway analysis were performed to identify dysregulated proteins and potential biomarker candidates ($|log2FC| > 0.5$; $p <0.05$). Proteomic profiling from

	the same FFPE tissues revealed two related yet distinct molecular components based on 203 differentially expressed features: a dysmorphic neuron-associated signature, primarily linked to altered neuronal growth, synaptic organization, and cytoskeletal remodelling, and a balloon cell-associated signature characterized by mTOR-driven growth dysregulation, impaired proteostasis/autophagy, and cellular stress responses. Integration of MALDI-MSI and LC-MS/MS datasets identified 22 shared molecular features. In addition, 88 and 203 differentially expressed features were uniquely detected by MALDI-MSI and LC-MS/MS, respectively, highlighting the complementary contribution of spatially resolved and proteomic approaches in defining the molecular signature of FCDIIb.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 37

TITLE	**Myrcene as a potential natural treatment in mild Traumatic Brain Injury (mTBI)**
AUTHORS	Viviana Iodice[1], Roozbe Bonsale[1], Milena Melake Teweldemedhin[1], Rebecca Limongelli[1], Michela Perrone[1], Federica Ricciardi[1], Andrea Maria Morace[1], Ida Marabese[1], Fabiana Piscitelli[2,7], Carmela Belardo [3,7], Francesca Guida [1,7], Vincenzo Di Marzo[2,4,5,6,7], Sabatino Maione[1,7], Livio Luongo[1,7]
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	Background: Mild traumatic brain injury (mTBI) represents a significant public health concern, often resulting in long-term cognitive, emotional, and behavioral impairments. Despite its prevalence, effective therapeutic strategies for mitigating mTBI consequences remain limited. For the first time, this study seeks to explore the potential neuroprotective properties of myrcene, a natural compound with promising implications for intervention. Myrcene, a monoterpene abundant in various plant species, exhibits notable anti-inflammatory, antioxidant, and neuroprotective properties. Preclinical studies have shown its efficacy in mitigating neuroinflammation, reducing oxidative stress, and enhancing neuronal survival, suggesting its potential utility in ameliorating mTBI-induced neuronal damage. Among the various sequelae of mTBI, alterations in pain, motor coordination, general well-being, aggression, sociability behaviors, and depression are prominent, highlighting the urgent need for effective therapeutic strategies. Given the absence of options and the promising neuroprotective

	attributes of myrcene, this study investigated myrcene efficacy in reducing mTBI consequences in a mouse model through a multi-disciplinary approachs. **Methods**: The present study evaluated the effect of 30 days of chronic myrcene treatment in a mouse model (C57BL/6J, male mice) of mTBI using a multidisciplinary approach. In vivo behavioral tests were conducted to assess pain threshold, motor coordination, social interactions, and anxiety- and depression-like behaviors. Morphological analysis was performed using immunofluorescence techniques on hippocampal brain sections. Subsequently, microdialysis-based CSF extraction was employed to analyze endocannabinoid levels, including 2-AG and anandamide, as well as neurotransmitters such as glutamate (Glu), glycine (Gly), and GABA, from the prelimbic cortex. **Results**: The results showed that deficits in behaviors related to pain perception, motor coordination, and emotional regulation were attenuated following myrcene administration. These beneficial behavioral effects were further supported by morphological and neurochemical data. An increase in the expression of GABAergic neuronal markers was observed in the hippocampus of treated animals, suggesting a role in modulating neuronal excitability. Notably, treatment with myrcene also normalized extracellular levels of glutamate, GABA, and glycine, as well as rebalanced endocannabinoid levels in the prelimbic cortex. **Conclusions**: In conclusion, our findings point to myrcene as a versatile and effective treatment option for mitigating the complex behavioral and neurochemical consequences of brain trauma. This study provides a strong foundation for future investigations into the role as a neuroprotective agent in managing traumatic brain injuries.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 38

TITLE	**RNA-based therapeutic strategy to rescue KDM5C haploinsufficiency in neurodevelopmental disorders**
AUTHORS	Drongitis Denise[1], Pacifico Eugenia[1], Verrillo Lucia[1], Poeta Loredana[1], Salsano Mariagrazia[1], Fico Annalisa[1], Tabolacci Elisabetta[2], Leoni Chiara[2], Paladino Simona[3], Gustincich Stefano[4], Miano Maria Giuseppina[1]
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	Lysine-specific demethylase 5C (KDM5C) is a key chromatin-remodeling factor implicated in X-linked neurodevelopmental disorders (NDDs), including intellectual disability, autism spectrum disorder, epilepsy, and behavioral abnormalities. Located on chromosome Xp22, KDM5C encodes an H3K4me3/H3K4me2 histone demethylase that plays a crucial role in the regulation of gene expression during brain development, neuronal plasticity, dendritic growth, and synaptic function. Since disease pathogenesis in affected females is primarily driven by KDM5C haploinsufficiency, therapeutic strategies aimed at restoring physiological protein levels represent a promising avenue for treatment. Here, we present a novel RNA-based therapeutic approach exploiting SINEUP technology to counteract KDM5C haploinsufficiency. SINEUPs are a class of synthetic long non-coding RNAs that selectively enhance translation of a target mRNA without affecting its transcription, thereby increasing endogenous protein expression while preserving physiological regulatory mechanisms. To evaluate the therapeutic potential of this strategy, we generated synthetic SINEUP molecules targeting both human and murine KDM5C transcripts. Their efficacy was assessed in multiple cellular models, including human cell systems and murine primary neurons. Across all tested systems, SINEUP constructs induced a significant and dose-dependent increase in endogenous KDM5C protein levels, demonstrating robust translational enhancement and high target specificity. Indeed, in Arx-knockout primary cortical neurons, a disease-relevant model characterized by reduced KDM5C expression, SINEUP-mediated restoration of KDM5C levels rescued its transcriptional repressive activity on downstream target genes and significantly

	improved neurite network development. Importantly, SINEUP-mediated upregulation of KDM5C was successfully achieved in patient-derived lymphoblastoid cell lines from affected females carrying heterozygous loss-of-function KDM5C variants, resulting in a significant restoration of endogenous KDM5C protein levels. These findings highlight the translational relevance of this approach and support its potential applicability to patients with KDM5C-related neurodevelopmental disorders and other genetic conditions caused by haploinsufficiency.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 39

TITLE	**DEE1-mouse model shows spatiotemporal changes in microglia morphology and distribution**
AUTHORS	Verrillo Lucia[1], Salsano Mariagrazia[1], Staiano Rosa[1], Drongitis Denise[1], Pacifico Eugenia[1], Barra Adriano[1], Marra Lucia[1], Flore Gemma[1], Terrone Gaetano[2], Miano Maria Giuseppina[1]
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	Microglia, the resident immune cells of the central nervous system, play a key role in surveilling brain homeostasis, neuronal pruning and in mediating neuroinflammatory response. Being highly dynamic cells, they change morphology depending on their functional state: from a ramified surveilling form to an amoeboid in response to harmful or inflammatory stimuli. In epilepsy, microglial activation contributes to neuroinflammation, altered synaptic connectivity, and increased neuronal excitability, promoting seizure susceptibility. Our previous findings highlighted for the first time a microglial activation in symptomatic *Arx*$^{(GCG)7/Y}$-DEE1 mice. This is a model for developmental epileptic encephalopathy type 1 (DEE1) caused by GCN expanded repeats in the *ARX* gene, an X-chromosome gene encoding a bifunctional transcription factor with a key role in mammalian corticogenesis. Building on these observation, we are characterizing the microglial dynamics in the *Arx*$^{(GCG)7/Y}$-DEE1 mice, to define the temporal and spatial patterns of microglial activation and its potential role in DEE pathogenesis. An *in vivo* approach combining immunohistochemistry (IHC) and morphometric analysis of IBA1+ microglial cells is employed in *Arx*$^{(GCG)7/Y}$ mice and age-matched male controls. Analyses are conducted at key stages of cortical development—embryonic day 15.5 (E15.5), postnatal day 1 (PND1), and postnatal day 15 (PND15)—to investigate temporal changes in microglial morphology and its laminar distribution. Our preliminary data show that alterations in microglial density and morphology arise before symptom onset, pointing to an early role in epileptogenesis. Specifically, mutant neocortex displays a reduction in ramified microglia, whereas an increased number of IBA1+ cells is observed in the early postnatal cortex of *Arx*$^{(GCG)7/Y}$-DEE1 mice. By PND15, analysis across key epileptogenic regions—including cortex, hippocampus, and striatum—reveals marked microglial morphological alterations. Together, these findings define critical developmental windows for investigating pro-inflammatory pathways and support targeting microglia as a potential therapeutic strategy in DEEs.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 3

TITLE	**Sensory-motor gating deficits across schizophrenia patient subgroups: a composite prepulse inhibition index analysis**
AUTHORS	Annarita Barone[1], Licia Velucci[1], Daniele Formisano[1], Sabrina Lavacca[1], Sara Corritore[1], Mariateresa Ciccarelli[1], Felice Iasevoli[1], Andrea de Bartolomeis[*1]
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	Treatment-resistant schizophrenia (TRS) is a severe condition affecting almost one third of patients with schizophrenia and remains a major clinical challenge because its pathophysiology is still poorly understood. We investigated, for the first time, whether prepulse inhibition (PPI), a well-established measure of sensorimotor gating, could differentiate healthy controls (HCs), patients with treatment-responsive schizophrenia (non-TRS), and those with TRS. We assessed habituation, response latency, and %PPI across nine prepulse intensity (82/86/90 dB) × interstimulus-interval (ISI) (30/60/120 ms) conditions in 93 participants: 39 HCs, 32 patients with treatment-responsive schizophrenia (non-TRS), and 22 with TRS. Seventy-nine participants met the startle data quality criteria and were included in subsequent analyses. To reduce variability across individual conditions, we derived a composite gating score for each participant using a two-step procedure: values were first winsorized within each of the nine intensity × ISI conditions, followed by a linear mixed-effects model with empirical-Bayes shrinkage (best linear unbiased predictor) to estimate each participant's composite score. The results were further corroborated by 2,000-iteration permutation testing. Mean %PPI, averaged across conditions, differed across groups for amplitude ($H(2)=6.08$, $p=.048$) and magnitude ($H(2)=6.51$, $p=.039$), with both effects surviving false discovery rate (FDR) correction and reflecting lower (less inhibited) %PPI in non-TRS or TRS relative to HCs. Similarly, three-group comparisons of the composite score revealed significant overall differences for both amplitude ($H(2)=6.20$, $p=.045$) and magnitude ($H(2)=6.32$, $p=.042$), again surviving FDR correction and confirmed by 2,000-iteration permutation testing. However, direct non-TRS vs TRS comparisons were not significant for either measure. Among clinical correlates, peak latency was strongly and inversely associated with Positive and Negative Syndrome Scale (PANSS)-negative symptom severity ($\rho=-.51$, $p<.001$), surviving FDR correction across the full matrix.

	Overall, these findings suggest that sensorimotor gating deficits are broadly present in schizophrenia compared with HCs, but do not provide direct statistical evidence that PPI reliably distinguishes TRS from treatment-responsive illness. Nevertheless, the observed effect-size pattern suggests that gating deficits may be more pronounced in TRS and warrants further investigation.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 1

TITLE	**circRNAs as promising biomarkers in Amyotrophic Lateral Sclerosis**
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	Amyotrophic lateral sclerosis (ALS) is a devastating adult-onset neurodegenerative disease characterized by the progressive degeneration of motor neurons. Its clinical heterogeneity makes diagnosis, prognosis and treatment challenging. The diagnostic process mainly relies on clinical observations; prognosis varies widely among patients despite a short median survival of only a few years from symptom onset; and currently approved therapies, while not curative, only contribute to slow disease progression. Additionally, although the molecular mechanisms underlying ALS have been extensively studied, they are not yet fully elucidated. In this regard, there is a crucial need for biomarkers that can be adopted in clinical practice to improve differential diagnosis, prognosis and treatment-response monitoring. Circular RNAs (circRNAs) are a subclass of non-coding RNAs, with an emerging potential as biomarkers in neurodegenerative diseases. Increasing evidence indicates that they are dysregulated in ALS, yet they remain poorly explored. This, together with circRNAs' high stability, tissue specificity, specific expression patterns and role in RNA metabolism, makes them ideal and attractive candidates as biomarkers in ALS. We, therefore, hypothesized that dysregulation in ALS-associated genes may be mirrored by dysregulation of their derived circRNAs, which could be detected in blood. In this study, we aimed to identify a whole blood circRNA profile as a source of candidate biomarkers for ALS. We established a workflow tailored to the extraction and enrichment of circRNAs from whole blood, a minimally invasive matrix. Then, as a circRNA profile of ALS whole blood is lacking, we combined deposited whole-blood circRNA-seq data with ALS databases and circRNA annotations. Following this analysis, 38 circRNAs derived from ALS-associated host genes and expressed in blood were selected. These

	circRNAs could be putatively dysregulated in ALS patients and represent potential biomarkers. Gene Ontology analysis prioritized 18 candidates involved in pathways relevant to ALS-associated neurodegeneration, such as synaptic trafficking, RNA metabolism and axon guidance. Nine of these candidates were tested by quantitative PCR in whole blood from a small cohort of ALS patients and healthy controls. Interestingly, 5 out of the 9 circRNAs tested were significantly dysregulated in ALS patients compared with controls, delineating an initial profile of ALS-associated circRNAs with biomarker potential. These preliminary findings support the feasibility of the adopted strategy to prioritize candidates for biomarker discovery. Overall, circRNAs represent a promising and underexplored source of whole-blood biomarkers for ALS.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 2

TITLE	**Modulating α-Synuclein Amyloid Aggregation via Lipid Interactions: Insights from Wild-Type and Double-Mutant**
AUTHORS	Carmen Biancaniello[1], Silvia Arino[1], Giuliana Fusco[1], Alfonso De Simone[1]
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	α-synuclein (αS) is a 140-residue presynaptic protein that, under pathological condition, aggregates into amyloid fibrils linked to Parkinson's disease and other neurodegenerative disorders commonly known as synucleinopathies. Although its pathological relevance is well recognized, the physiological role of this protein is still not properly understood. A number of studies have indicated its involvement in neurotransmission by modulating synaptic vesicle interactions and assembly both in vivo and in vitro, underlying the ability of αS to bind cellular membranes to attain its biological function. Indeed, αS exists in equilibrium between a cytosolic monomeric, predominantly disordered form, and a highly helical state when bound to lipid surface. Because of its intrinsic structural variability, the characterization of the membrane-bound physiological state is a challenging task. Despite this, previous work of Fusco et al. investigated the structural and dynamic properties of αS at the surface of synaptic-like vesicles, revealing two regions (the N-terminal 25 residues and the central region comprising residues 65–97) with independent membrane binding properties. This allows a single αS molecule to bind two different synaptic vesicles in a double-anchor step, promoting their interaction and assembly. In support of this 'double anchor' mechanism, a mutational variant incorporating the E46K and K80E mutations was specifically designed to enhance vesicle interactions. While preserving an overall comparable binding affinity and the same aminoacidic composition as the wild type αS, the mutant revealed different binding properties due to the enhanced exposure of the central region, along with an increased ability to promote synaptic vesicle clustering. Deciphering the interaction of αS with membranes is not only crucial to understand its normal functions but also its pathological mechanisms. Recent studies have suggested the formation of lipid-protein coaggregates depending on the relative proportion of the two species, affecting protein aggregation, amyloid formation and morphology. In this context, we assessed the effect of lipids on the mechanism of αS conversion from its soluble to its aggregate state by performing in vitro aggregation kinetics of both wild-type and the mutant via ThT fluorescence assay at varying concentrations of phospholipid DMPS. Curve fitting was performed to parametrize and compare the kinetics profiles, revealing that while the nucleation phase occurs on

	similar timescales in both variants, the double mutant αS forms fibrils much faster than the wild-type protein, maintaining higher aggregation rates across a much broader range of lipid concentrations. Overall, these data can help us to derive mechanistic insight into the lipid-induced αS aggregation, offering a more global understanding of the effect of lipids on the kinetics of amyloid formation.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 2

TITLE	**Development of a UHPLC-APCI-HRMS Method for the Analysis of 21 Oxysterols in Plasma and SEC-Enriched Neuronal Extracellular Vesicles**
AUTHORS	Castellaneta A.[1], Giannone P.[1], Losito I.[1,2], Cataldi T.R.I[1,2], Zöldhegyi A.[3], Molnár I.[3], Palazzo G[1]., Calvano C.D.[1,2]
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	Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline and impairment of daily functioning. Since pathological changes may precede the onset of clinical symptoms by years, the early detection of suitable biomarkers is essential for improving disease characterization and monitoring its progression. Alterations in cholesterol metabolism have been associated with AD and healthy aging. Oxysterols (OS), *i.e.*, oxidized derivatives of cholesterol, play important roles in cholesterol homeostasis and several biological processes. Changes in their quantitative profile may provide useful insights into the biochemical alterations associated with AD. Since oxysterols typically occur in trace amounts within biological matrices, highly sensitive and selective mass spectrometry (MS) techniques are essential for their accurate characterization. Plasma OS levels may reflect multiple physiological processes, including cholesterol metabolism and bile acid biosynthesis, potentially limiting their specificity for brain-related alterations. Their investigation in extracellular vesicles (EV) released by brain tissue may provide a complementary analytical approach. EV are membrane-enclosed particles released by cells that mediate intercellular communication through the transfer of molecular cargo, including proteins, lipids, and nucleic acids. Their composition may reflect aspects of the physiological or pathological state of their cells of origin, making them promising candidates for biomarker research. However, their potential as a minimally invasive source of brain-related biomarkers depends on the reliable identification of tissue-specific EV populations. Consistently with the International Society for Extracellular Vesicles (ISEV) guidelines, comprehensive EV characterization requires complementary approaches to assess both EV-associated proteins and potential contaminants. Furthermore, identifying neuron-derived EV demands additional validation using specific neuronal markers. In this study, we developed a pre-analytical strategy to isolate EV-enriched fractions from human plasma using size-exclusion chromatography (SEC). The enrichment of putative neuronal EV was

	assessed by a novel developed lateral flow immunoassay (LFIA). Direct MS characterization of OS in these fractions was complicated by the multiple isomeric forms and the formation of isomeric ions from non-isomeric precursors due to extensive in-source fragmentation. To address this analytical challenge and enhance sensitivity in OS detection, we optimized a preliminary ultra-high-performance liquid chromatography (UHPLC) method with the support of DryLab® software. The method was subsequently applied to profile and compare OS in whole plasma *versus* SEC-enriched EV fractions, investigating whether this approach could offer deeper insights into the role of oxysterols in AD. *Acknowledgements: We acknowledge PN RIC 2021-2027 Azione 1.1.2 – Titolo Progetto: Omics and Medicine for New Intelligent Applications - Biomedical Research and Innovation from THE to Develop Growth and Excellence in the South CI: 2309_QIIR112_00059B99 CUP H26000500007*
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 40

TITLE	**Integrative blood transcriptomics identifies U1-snRNP gene repression and miRNA–mRNA regulatory hubs in pre-clinical Parkinson's Disease**
AUTHORS	Davide D'Angelo[1], Alfonso De Simone[2], Nunzio D'Agostino[3]
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	Parkinson's disease (PD) is a progressive neurodegenerative disorder characterised by the loss of dopaminergic neurons and the accumulation of intraneuronal misfolded α-synuclein aggregates. Despite advances in understanding the underlying molecular mechanisms of PD, diagnosis still relies largely on clinical symptoms that appear relatively late in disease progression. To advance both the mechanistic understanding of PD and the development of new diagnostic tools, we here performed a late integration analysis of matched whole-blood mRNA-seq and miRNA-seq data from 2,604 PPMI participants (Healthy n = 658; PD n = 1,946), stratified into pre-clinical (n = 561), mild, moderate, and severe stages. Differential expression (adjusted $p < 0.05$; $\|fold\ change\| > 0.58$) revealed maximal alterations in pre-clinical (7386 differential expressed genes; 156 differential expressed miRNAs) and severe PD. Pre-clinical signatures were dominated by widespread downregulation, notably involving multiple U1 snRNA genes, indicating early repression of U1-snRNP spliceosomal components. Integration of predicted targets with Spearman anti-correlation identified 251 miRNA–mRNA pairs, driven by hub miRNAs including miR-34a-5p, miR-1299, miR-3120-5p, and miR-412-3p.Taken together, these findings highlight the importance of early spliceosomal dysfunction and miRNA dysregulation in preclinical PD, supporting their potential as novel blood-based biomarkers.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 41

TITLE	**Lipids as Signals of Innate Immunity: From Synthetic Sulfoglycolipids to the Neuroimmune Landscape**
AUTHORS	Carmela Gallo[1], Emiliano Manzo[1], Mario Dell'Isola[1], Marcello Ziaco[1,2], Giuliana d'Ippolito[1], Genoveffa Nuzzo[1], Laura Fioretto[1], Dalila Carbone[1], Giusi Barra[1], Angelo Fontana[1,2]
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	Microglia play a central role in maintaining brain homeostasis and responding to amyloid pathology in Alzheimer's disease (AD). Their activity, however, cannot be simply described in terms of activation or suppression, but rather as a continuum of functional states shaped by the molecular signals encountered in the tissue microenvironment. Among the receptors involved in this process Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), provides an intriguing interface between lipid sensing, cellular metabolism and innate immune responses, has emerged as a key target for strategies aimed at promoting neuroprotection. Sulfavant A (SULF A), a synthetic sulfoglycolipid inspired by naturally occurring marine sulfolipids, has been identified as a TREM2 ligand with distinctive immunomodulatory properties1. In a recent study2, SULF A promoted a reparative microglial phenotype, enhanced amyloid-β phagocytosis and clearance, and reduced amyloid plaque burden in the Tg2576 mouse model of AD. These effects were accompanied by neuroprotection and improved cognitive performance. Rather than considering these findings only from a pharmacological perspective, we are using SULF A as a molecular probe to address a broader question: to what extent can lipid structures encode signals capable of shaping innate immune responses? This perspective challenges a simplified distinction between pro- and anti-inflammatory signals and suggests that the composition and spatial organization of the lipid environment may actively contribute to defining immune cell behaviour. We are therefore extending our investigation from synthetic sulfoglycolipids to endogenous brain lipids. Mass spectrometry imaging (MSI), combined with targeted tandem mass spectrometry (MS/MS), allows us to investigate changes in the spatial distribution of lipid species directly in brain tissue. Preliminary comparisons between healthy and diseased brains reveal disease-associated alterations in the brain lipid landscape. By integrating synthetic lipid probes, receptor biology and spatial lipid analysis, we aim to explore the possibility that endogenous lipids participate in a molecular language connecting tissue state to microglial function. In this view, lipid alterations in neurodegeneration

	may represent not only biomarkers of disease, but also signals contributing to the regulation or dysregulation of innate immunity. [1] Gallo C, Manzo E, Barra G, Fioretto L, et al. Sulfavant A as the first synthetic TREM2 ligand discloses a homeostatic response of dendritic cells after receptor engagement. Cell Mol Life Sci 2022; 79: 369-384 [2] Gallo C, Verrillo L, Manzo E, Caiuzzi E et al. Microglial clearance, neuroprotection and cognitive recovery via a novel synthetic sulfolipid in Alzheimer's disease. J Neuroinflammation 2025; 23: 20-38
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 42

TITLE	**Gαo upregulation in mesencephalic astrocytes promotes a neurotrophic state in the A53T-α-Synuclein mouse model of Parkinson's disease**
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	Background. The Gnao1 gene encodes the Gαo subunit of heterotrimeric G proteins, which is highly expressed in the central nervous system, where it couples with several G protein-coupled receptors (GPCRs), including those for dopamine, GABA, acetylcholine and opioids. Gαo regulates adenylyl cyclase activity and cyclic AMP (cAMP) production by controlling the availability of Gβγ subunits. In the dopaminergic system, Gαo is a key regulator of D1 and D2 receptor signalling in striatal medium spiny neurons, contributing to motor learning, coordination, balance and movement. In Parkinson's disease (PD), the loss of nigrostriatal dopamine deprives these neurons of their primary modulatory input, leading to structural, electrophysiological and molecular changes that underlie motor dysfunction. Pathogenic Gnao1 variants cause a broad clinical spectrum of epilepsy and movement disorders, from hyperkinetic phenotypes such as dystonia, chorea and ballism to milder or atypical presentations that include parkinsonian features. Notably, mutations in the N-terminal α-helix of Gαo have recently been shown to cause a hypokinetic phenotype with bradykinesia and rigidity, linked to impaired G-protein formation and GPCR coupling. These findings point to Gαo as a potential contributor to the mechanisms of nigrostriatal dysfunction in PD. However, while Gαo has been extensively studied in neurons, its role in astrocytes in the context of PD remains largely unexplored. **Aims.** Re-analysis of a published single-nucleus RNA-sequencing atlas from A53T-α-Synuclein transgenic mice, a model of familial PD, revealed

	that Gnao1 is selectively upregulated in mesencephalic astrocytes. We therefore aimed to: • Characterize the role of Gαo in mesencephalic astrocytes of this model. • Investigate whether Gαo upregulation represents a compensatory mechanism regulating astrocytic reactive states and phenotypes. • Determine whether astrocytic Gαo signalling promotes adaptive neuroprotective responses to dopaminergic neuronal loss. **Methods.** We used molecular and biochemical approaches in mice carrying the human A53T mutation of α-Synuclein, focusing on the midbrain and on the signalling pathways downstream of Gαo. **Results.** Gnao1 products were selectively upregulated in mesencephalic astrocytes of A53T-α-Syn mice. This upregulation was associated with engagement of the cAMP/PKA/pCREB pathway, consistent with a compensatory signalling response. Through this pathway, astrocytic Gαo promoted a neurotrophic astrocytic state, which supported the survival of dopaminergic neurons against α-Synuclein aggregation. **Conclusions.** Our data identify Gαo as a previously unrecognized regulator of astrocyte function in PD. The upregulation of Gαo in mesencephalic astrocytes seems to be an adaptive response. This response, mediated by cAMP/PKA/pCREB signalling, leads to a shift in astrocytes towards a neurotrophic and protective phenotype in response to α-Synuclein-induced dopaminergic degeneration. These findings redirect focus from neuronal to glial Gαo signalling in PD and suggest that astrocytic G-protein pathways may represent a novel target for increase endogenous neuroprotection. Future work will define the upstream GPCRs that engage astrocytic Gαo and test whether its modulation can slow dopaminergic neurodegeneration.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 43

TITLE	**Multi-domain network integration of peripheral GFAP, metabolic, and cytokine signatures in Treatment-Resistant Schizophrenia**
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	Introduction: Glial dysregulation and metabolic alterations are increasingly implicated in the pathophysiology of schizophrenia, yet their specific contribution to treatment-resistant schizophrenia(TRS) remains elusive. Glial Fibrillary Acidic Protein(GFAP) serves as a primary peripheral biomarker of astroglial reactivity, whereas Neurofilament Light Chain(NfL) indexes neuro-axonal damage. Recent evidence suggests that these markers follow distinct trajectories across levels of treatment resistance. However, in the absence of direct group comparisons across response phenotypes, it remains unclear whether such alterations mark true treatment resistance or shared spectrum features. Integrating GFAP and NfL within a multi-domain framework offers a promising strategy to refine TRS characterization. **Aims:** To investigate whether serum GFAP and NfL levels, integrated within a multi-domain framework, can define a specific biological signature of TRS independently of overall clinical severity. **Methods:** A comparative cross-sectional analysis was performed on 122 subjects(59 healthy controls [HC], 33 non-treatment-resistant schizophrenia [nTRS], and 30 TRS). Serum GFAP and NfL were evaluated via automated chemiluminescent immunoassay. Metabolic parameters (glucose, cholesterol, triglycerides), complete blood count(CBC) derived inflammatory ratios (neutrophil-to-lymphocyte ratio [NLR], monocyte-to- lymphocyte ratio [MLR], platelet-to-lymphocyte ratio [PLR]) were determined using standard automated clinical laboratory assays, alongside a 27-cytokine multiplex immunoassay panel. Psychopathology was assessed using the Positive and Negative Syndrome Scale(PANSS). Between-group comparisons utilized non- parametric tests, analysis of

	covariance(ANCOVA) adjusted for age, sex, and chlorpromazine(CPZ) equivalents, and receiver operating characteristic(ROC) curve analysis. Multivariable logistic regression via leave-one-out cross-validation(LOOCV), machine learning algorithms (Random Forest and XGBoost), and unsupervised K-means clustering(k=3) across multi-domain indicators (neuro-glial, metabolic, CBC ratios and cytokine axes) were implemented. **Results:** GFAP concentrations exhibited a progressive elevation across groups, peaking in TRS patients (medians: TRS 23.90 pg/mL, nTRS 18.50 pg/mL, HC 16.60 pg/mL). While unadjusted pairwise comparisons between nTRS and TRS did not survive false discovery rate correction (pFDR=0.457), ANCOVA adjusting for age, sex, and CPZ dose confirmed a significantly elevated GFAP profile in TRS (pFDR=0.005). ROC curve analysis (TRS vs. nTRS, AUC=0.606) established an optimal Youden index cut-off of ≥28.1 pg/mL (specificity 87.9%, positive predictive value 73.3%). In multivariable models, GFAP emerged as the strongest positive standardized predictor (β=+0.648), yielding consistent performance across LOOCV logistic regression (AUC=0.654, accuracy 64.9%), Random Forest (AUC=0.666) and XGBoost (AUC=0.644), while NfL levels showed no significant group-level variance (p=0.720). Beyond single-marker predictions, unsupervised K-means clustering revealed a specific glio-metabolic and immune multi-domain profile, combining high GFAP, glucose, lipids, and distinct cytokine signatures, heavily enriched in TRS patients (72% vs. 31% in the low-activation profile; permutation p=0.030, Cramér's V=0.34). Serum GFAP showed no association with PANSS scores (p>0.28). **Conclusions:** Elevated serum GFAP and a distinct glio-metabolic and immune multi-domain profile represent robust biological correlates of TRS. The absence of concurrent elevations in NfL indicates that astroglial reactivity reflects a pathophysiological mechanism intrinsic to treatment refractoriness rather than overt acute neuro-axonal destruction. The lack of association between GFAP and continuous PANSS severity scores demonstrates that peripheral glial reactivity is not merely a marker of overall clinical severity, but rather indexes a discrete biological feature of treatment resistance, supporting its utility in biomarker- informed stratification frameworks.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 3

TITLE	**Association of motor cortical metabolism with corticospinal physiology and neuroaxonal injury in amyotrophic lateral sclerosis: a Multimodal Study combining FDG-PET, TMS and plasma biomarkers.**
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	Background: Motor cortical metabolism is reduced in many patients with amyotrophic lateral sclerosis (ALS), but the extent of this reduction varies. We investigated whether these differences are associated with corticospinal excitability and neuroaxonal injury, and whether these associations persist after accounting for clinical upper motor neuron (UMN) burden. **Methods:** Eighty patients with ALS spectrum disorders, including nine with primary lateral sclerosis (PLS), underwent clinical assessment, transcranial magnetic stimulation, fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET), and blood sampling on the same day. Patients were classified as hypoexcitable, normoexcitable, or hyperexcitable using the motor evoked potential/compound muscle action potential (MEP/CMAP) ratio. Whole-brain voxel-wise analyses compared hypoexcitable and hyperexcitable patients with 20 controls and assessed associations with MEP/CMAP across all patients. Regional analyses examined mean normalized FDG uptake within areas showing lower metabolism in hypoexcitable patients than in controls or hyperexcitable patients. Multivariable linear regression models included age, sex, King's stage, PLS status, MEP/CMAP, and plasma neurofilament light chain (NfL), phosphorylated tau181 (p-tau181), and glial fibrillary acidic protein (GFAP). Additional models included the Penn Upper Motor Neuron Score (PUMNS). **Results:** Twenty-one patients were hypoexcitable, 11 normoexcitable, and 48 hyperexcitable. Hypoexcitable patients had greater clinical UMN burden and lower metabolism in bilateral motor and adjacent sensory regions than controls and hyperexcitable patients. Across the cohort, higher MEP/CMAP ratios were associated with higher metabolism in these regions. Separate regression models were fitted for the regions

	identified by each comparison. In both regional models, lower FDG uptake was associated with lower MEP/CMAP (P = 0.007 and 0.010), higher NfL (P = 0.032 and 0.039), and PLS status (P = 0.003 and 0.007). After PUMNS adjustment, regional associations persisted for MEP/CMAP (P = 0.005 and 0.009) and NfL (P = 0.025 and 0.043). However, the voxel-wise MEP/CMAP association no longer survived correction for multiple comparisons after this adjustment. Neither GFAP nor p-tau181 was independently associated with regional metabolism. **Conclusions:** Differences in motor cortical metabolism across the ALS spectrum are associated with corticospinal excitability and neuroaxonal injury indexed by NfL. Combining imaging, physiological, and fluid biomarkers may help explain metabolic heterogeneity beyond clinical assessment alone. Regional findings remain exploratory because the regions were selected within the same cohort. Independent validation and longitudinal studies are needed to establish clinical utility.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 44

TITLE	**Synaptic dysfunction as an early feature of 22q11.2 deletion syndrome: a longitudinal proteomic study of *Tbx1*+/- mice**
AUTHORS	Sabrina Bianco[1,2], Eduardo Penna[3], Federica Carbone[3], Marianna Caterino[2,4], Margherita Ruoppolo[2,4], Marianna Crispino[3], Sara Veneziano[5], Gemma Flore[5], Sara Cioffi[5], Michele Costanzo[2,4], Gabriella Lania[5]
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	22q11.2 deletion syndrome (DiGeorge syndrome) is the most common microdeletion syndrome and is associated with an increased risk of cognitive impairment, autism spectrum disorder, and schizophrenia. Recently, we demonstrated that TBX1 haploinsufficiency causes metabolic dysregulation accompanied by behavioral abnormalities in adult mice; however, the molecular mechanisms linking TBX1 deficiency to brain dysfunction remain poorly understood. To address this question, we employed an omics-driven, hypothesis-generating approach to investigate the molecular alterations underlying this biochemical phenotype. We first profiled the whole-brain proteomes of *Tbx1*$^{+/-}$ and wild-type (WT) mice at 2, 4, and 7 months of age using label-free LC-MS/MS. We found that samples clustered primarily according to age and that the *Tbx1*$^{+/-}$ proteomic signature changed dynamically over time. Pathway enrichment analysis revealed an age-dependent molecular trajectory. Longitudinal clustering further identified protein modules that were selectively dysregulated in *Tbx1*$^{+/-}$ mice at 7 months of age. Some of the early alterations regarded synaptic components, thus we used synaptosomes (an in vitro model of synaptic regions), isolated from *Tbx1*$^{+/-}$ and WT mice brain to test possible synaptic alterations. In synaptosomes from hippocampus of 2 months-old *Tbx1*$^{+/-}$ mice we observed a reduced levels of Shank3 compared to controls, while at 7 months of age, not only Shank3, but also synaptophysin levels were decreased. These findings indicated impaired synaptic density and altered neuronal plasticity in *Tbx1*$^{+/-}$

	mice. To characterize these alterations, we performed quantitative proteomics of hippocampal synaptosomes isolated from *Tbx1*$^{+/-}$ and WT mice at 2 and 7 months of age, allowing us to follow synaptic proteome changes across the same time window as a whole-brain analysis. At 7 months, we observed widespread remodeling of the synaptic proteome, with significant enrichment for synaptic proteins and altered pathways related to cytoskeletal organization, neurotransmission and synaptic vesicle dynamics, mitochondrial and energy metabolism. Altogether, these findings reveal a previously unrecognized synaptic phenotype driven by Tbx1 haploinsufficiency and establish TBX1 as a key contributor to neural dysfunction within the 22q11.2 deletion syndrome critical region. By linking haploinsufficiency of a single 22q11.2 gene to progressive metabolic and synaptic alterations, our study provides a mechanistic framework connecting TBX1 deficiency to the cognitive and neuropsychiatric manifestations of the syndrome. Moreover, our results, identifying early synaptic dysfunctions in this pathology, suggest a potential therapeutic target and define a temporal window for intervention before the onset of widespread neuronal impairment.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 45

TITLE	**Regional amyloid-β imaging and symptom dimensions correlate in young treatment-resistant schizophrenia patients with severe cognitive impairment**
AUTHORS	Mariateresa Ciccarelli[1], Valeria Gaudieri[2], Benedetta Mazza[1], Annarita Barone[1], Felice Iasevoli[1], Licia Vellucci[1], Federica Iannotta[1], Giuseppe De Simone[1], Alberto Cuocolo[2], Sabina Pappatà[3], Andrea de Bartolomeis[1]
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	Background: Treatment-resistant schizophrenia (TRS), affecting approximately 30% of patients with schizophrenia, has different neurobiological features compared to treatment-responsive schizophrenia, with more prominent and progressive cognitive decline. The association between cognitive impairment in schizophrenia and amyloid-β (Aβ) pathology is unclear. However, cognitive deficits reflect substantial neurodevelopmental and connectivity-based disruptions, possibly involving neuroinflammation or cerebral hypometabolism in TRS. Neuroimaging evidence shows that Aβ accumulation may precede cognitive impairment by years, emphasizing the need to study biomarkers of neurodegeneration in younger TRS populations. **Aim of the study**: This study investigated whether TRS patients with cognitive deficit showed brain Aβ pathology using ^{18}(F)-Flutemetamol Positron Emission Tomography (PET), examining potential associations between cortical Aβ load and clinical symptoms. **Methods**: TRS patients (n = 12) and amyloid-negative cognitively impaired patients (Aβ- CI) without psychiatric disorders (n = 12) underwent a PET scan. Neuroimaging data were analyzed using the Diagnosis ORIented ANalysis (DORIAN) software, which provides a single averaged composite score as a proxy of regional cortical Aβ load, based on three semi-quantitative parameters: Standardized Uptake Value ratio (SUVr), Effectively Linear Binding Affinity (ELBA), and Time Delayed ratio (TDr). Clinical rating scale evaluation included the Positive and Negative Syndrome Scale (PANSS) 5-factor model and the Brief Assessment of Cognition in Schizophrenia (BACS). Spearman's correlation analyses were performed to evaluate the association between the regional Aβ composite scores and the clinical features (P value < 0.05).

	Results: PET visual inspection and semi-quantitative analysis did not reveal increased Aβ cortical load in any TRS patients compared to Aβ- CI. Correlation analyses revealed an inverse relationship between Right Posterior Parietal Cortex Aβ composite scores and PANSS Positive, 5-factor POS and 5-factor DIS scores and a positive association with Cognitive Composite t-score. **Conclusions**: This study suggests that although increased cortical Aβ deposition is not evident in TRS patients, a correlation between regional (^{18}F)-Flutemetamol PET signal variation and psychotic and disorganization symptoms may still be inferred, with a potential compensatory mechanism in the associative parietal hub that may temporarily increase the brain's adaptation to cognitive demands, thus improving the management of disorganized thoughts, before neurodegeneration occurs.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 3

TITLE	**Precision-medicine approaches in severe epilepsies caused by gain-of-function variants in KCNT1**
AUTHORS	[1] Dania Ioia, [1] Ilaria Mosca, [1] Katia Maglieri, [1] Deborah Puzo, [3] Paolo Ambrosino, [2] Marina Trivisano, [4] Maurizio Taglialatela, [1] Maria Virginia Soldovieri.
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	BACKGROUND: KCNT1 is a voltage-gated potassium channel, which is highly expressed in central nervous system mainly in cerebellum, frontal cortex, and hippocampus, playing an important role in neuronal exitability. Pathogenic variants in KCNT1 channels have been identified in patients affected by a wide spectrum of developmental and epileptic disorders (DEE). Epileptic patients carrying gain-of-function (GOF) KCNT1 variants are often pharmacoresistant to traditional anti-epileptic drugs, thus requiring the identification of alternative treatments. Recently, KCNT1-blocking activities have been also reported for the anti-depressant drug fluoxetine (FLX) and the non psycho-active drug cannabidiol (CBD). **AIMS**: The aim of the present study has been to characterize functional properties of KCNT1 channels carrying each variant in study, and to evaluate the sensitivity to fluoxetine and/or cannabidiol of mutant KCNT1 currents. **MATERIALS AND METHODS**: To these aims, exome sequencing was performed in patients affected by DEE. Mutations were engineered by Quick-change mutagenesis in plasmids encoding the human isoform of KCNT1 channels. Wild-type or mutant channels were expressed by transient transfection in CHO cells. Currents were measured using *patch-clamp* technique in the *whole-cell* configuration, to characterize functional and pharmacological properties. **RESULTS**: Exome sequencing reveals three variants in KCNT1 (R474C, R928C, I834V). Electrophysiological recordings reveal that all variants in study showed GOF effects in terms of increased current density, leftwardly-shifted voltage dependence of activation and increased istantaneous component for all KCNT1 variants. Fluoxetine (10 μM) was able to block by ~90% currents expressed by KCNT1 channels carrying each variant in study. Cannabidiol (10 μM) was able to block by ~100% currents expressed by KCNT1 channels carrying each variant in study.

	According to these, add-on treatment with fluoxetine and cannabidiol in patients carrying KCNT1 R474C or R928C variants prompts significant seizures reduction, with largest effects in the presence of the R474C variant. Due to the possible side effects caused by fluoxetine and cannabidiol, future studies will focus on investigating a potential additive blocking effect resulting from the combined use of the two drugs at lower concentrations than those currently used. **CONCLUSIONS:** KCNT1 variants identified in pharmacoresistant patients with DEE prompt GOF effects on their respective wild-type channels. Unconventional antiepileptic drugs counteract GOF effects caused by these variants, suggesting their clinical use, even at low concentrations, as precision-medicine approaches.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 46

TITLE	**Therapeutic improvement with the combination of PEA and ceftriaxone for neuropathic pain: new evidence supporting the beneficial synchronous pharmacological targeting of GLT-1 and PPARα.**
AUTHORS	Milena Melake Teweldemedhin[1], Emanuele D Martino[1], Roozbe Bonsale [1], Viviana Iodice[1], Michela Perrone[1], Salvatore Pagano[1], Rebecca Limongelli[1], Carmela Belardo[1], Francesca Guida[1], Enza Palazzo[1], Livio Lungo[1], Sabatino Maione[1]
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	Background: Neuropathic pain is a chronic and debilitating condition characterized not only by sensory abnormalities but also by affective, cognitive, and motor impairments. Increasing evidence implicates neuroinflammation and dysregulation of glutamatergic signaling in its pathogenesis. The astrocytic glutamate transporter-1 (GLT-1), a major regulator of extracellular glutamate homeostasis, is altered following nerve injury, contributing to excitotoxicity, central sensitization, and neuronal dysfunction. This study investigated whether ceftriaxone (CEF), a GLT-1 activator, and ultramicronized palmitoylethanolamide (umPEA), a PPAR-α agonist with anti-inflammatory properties, exert complementary therapeutic effects in a mouse model of spared nerve injury (SNI)-induced neuropathic pain. **Methods**: Male mice (7–8 weeks old, 22–25 g) underwent SNI surgery and received daily intraperitoneal administration of umPEA (5 or 10 mg/kg), CEF (100 or 200 mg/kg), or a combination of subeffective doses (umPEA 5 mg/kg + CEF 100 mg/kg) for 30 days. Mechanical allodynia, thermal hyperalgesia, anxiety-like behavior, depression-like behavior, motor coordination, gait performance, and recognition memory were assessed. Neurochemical and molecular analyses included in vivo microdialysis for extracellular glutamate and GABA quantification in the CA1 and CA3 region of hippocampus , Western blotting, ELISA, immunohistochemistry, and double immunofluorescence to evaluate GLT-1 expression, glial activation, BDNF levels, and spinal and hippocampal alterations. In addition, gut microbiota composition was investigated by targeted PCR-based analysis of selected bacterial taxa on DNA extracted from fecal samples. **Results**: Low-dose PEA at 5 mg/kg and ceftriaxone at 100 mg/kg, when administered individually, did not significantly reduce SNI-induced mechanical allodynia, nor did they alleviate motor and cognitive

	impairments or anxiety- and depression-like behaviors. However, the combination of PEA (5 mg/kg) and ceftriaxone (100 mg/kg) resulted in a significant improvement in pain thresholds. Furthermore, this combination enhanced behavioral outcomes related to depression, motor coordination, and memory. Biochemically, the combination therapy notably affects amino acid balance, particularly in glutamate and GABA levels, GLT-1 expression, and reduced astrocytic activation. **Conclusion**: Combined administration of subeffective doses of umPEA and ceftriaxone exerts synergistic neuroprotective and analgesic effects in SNI-induced neuropathic pain. These benefits are associated with restoration of glutamatergic homeostasis, modulation of glial reactivity, and improvement of sensory, affective, cognitive, and motor dysfunctions. Targeting both neuroinflammatory and glutamatergic pathways may therefore represent a promising multimodal therapeutic strategy for neuropathic pain and its associated comorbidities.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 47

TITLE	**Probing the cortical and corticospinal contribution to inhibitory and facilitatory paired-pulse TMS effects via immediate TMS-evoked potentials**
AUTHORS	Gianmaria Senerchia[1], Leo Tomasevic[2], Raffaele Dubbioso[1]
AFFILIATION	[1] Department of Neurosciences, Reproductive Sciences and Odontostomatology, University of Naples 'Federico II', Naples 80131, Italy. [2]Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany.
	Background: Cortical contributions to inhibition and facilitation remains unresolved with conventional paired-pulse TMS-EMG paradigms. Immediate transcranial evoked potentials (i-TEPs), recorded with TMS-EEG, offer access to cortical responses within 2–6 ms of stimulation. **Objective**: To characterize cortical inhibition/excitation balance after cortical perturbation via i-TEP modulation during inhibitory (short- and long-interval intracortical inhibition, SICI and LICI) and facilitatory (intracortical facilitation, ICF) paired-pulse TMS protocols, and examine cortical vs. corticospinal output within and between participants. **Methods**: Twenty-five healthy adults underwent single-pulse TMS, SICI (2, 3 ms), LICI (100, 150 ms) and ICF (10, 15 ms), with simultaneous EEG and EMG. We measured the global mean field amplitude of the first three i-TEP peaks (P1–P3) and their peak-to-trough excursions, and tested scalp topographies with cluster-based permutation statistics. i-TEP-MEP associations were assessed within participants (8,120 matched trials) and across participants, with familywise correction. **Results**: SICI reduced P2 and P3 without a significant P1 reduction. P2 suppression persisted at 3 ms despite nonsignificant MEP inhibition. LICI produced the largest MEP reduction and decreased selected peak-to-trough differences without significant absolute peak-amplitude changes. LICI100 also delayed P2. Mean MEP amplitudes were approximately 60–70% larger during ICF, without significant increases in i-TEP measures. Eight within-participant associations survived familywise correction, with modest aggregate correlations (0.15–0.22), involving single-pulse, ICF10 and test-stimulus control responses. No between-participant association survived familywise correction. **Conclusions**: By resolving inhibition and facilitation at the cortical level, i-TEPs show that paired-pulse protocols engage distinct mechanisms that the MEP cannot separate: SICI mirrors late I-wave suppression, LICI reshapes the temporal structure of cortical output, and ICF may arise downstream of the cortex. i-TEPs may thus provide a more reliable

	measure of cortical excitation-inhibition balance than MEPs, this is even more relevant in disorders of the corticomotor pathway where MEPs can be affected by the pathology.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 2

TITLE	**CSTB drives proteostasis and trafficking in neurodevelopment via TRiC/CCT: implications for EPM1 pathogenesis**
AUTHORS	Natalia Abate[1], Sabrina Napoletano[2,3], Marta Ianni[4], Francesca Barracca[1], Eduardo Penna[1], Aldo Donizetti[1], Laura Canafoglia[5], Francesca Ragona[5], Veronica Pravata[4], Silvia Cappello[4,6,7], David Dannhauser[2,3], Marianna Crispino[1], Rossella Di Giaimo[1,4]
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	Progressive myoclonus epilepsy type 1 (EPM1) is a neurodegenerative disorder caused by loss of cystatin B (CSTB) function. Recent studies using patient-derived cerebral organoids revealed altered ventral neuronal specification and excitatory/inhibitory imbalance, associated with impaired extracellular vesicle (EV)- mediated Sonic Hedgehog (SHH) signaling. However, the intracellular mechanisms underlying CSTB function during neuronal differentiation remain unclear. To address this, we investigated the CSTB interactome in human iPSC-derived dorsal and ventral cerebral organoids. Co-immunoprecipitation and mass spectrometry revealed a preferential association between CSTB and the TRiC/CCT chaperonin complex in ventral organoids, suggesting a role for CSTB in TRiC/CCT- related cellular processes. In EPM1-derived ventral neural progenitor cells at only 3 days of neuronal differentiation (vNPCs-D3), we observed disrupted F-actin organization and perinuclear accumulation of the late endosomal marker RAB7, suggesting impaired endosomal trafficking and potentially defective EV secretion. Accordingly, following CSTB knockdown in SH-SY5Y cells, live-cell imaging revealed reduced motility and preferential centripetal trafficking of CD63-positive multivesicular bodies (MVBs). Nanoparticle tracking analysis confirmed reduced EV release in EPM1 vNPCs-D3, accompanied by alterations in EV size distribution. Moreover, silencing TCP1, a core TRiC/CCT subunit implicated in vesicular secretion, partially reproduced the EV phenotype observed in EPM1 cells.

	We further identified reduced protein synthesis in EPM1-derived differentiating progenitor cells and mature neurons. Importantly, CSTB re-expression restored protein synthesis in EPM1 vNPCs-D3, whereas TCP1 silencing abolished this rescue, demonstrating the functional involvement of TCP1 in CSTB-dependent protein synthesis.Together, these findings identify a novel functional relationship between CSTB and TRiC/CCT, linking CSTB deficiency to altered cytoskeletal organization, endosomal trafficking, EV secretion and protein synthesis during early human neuronal differentiation.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 48

TITLE	**Integrated proteomic strategies to evaluate the effect of a GABA-producing lactic acid bacterium in a mouse model of Alzheimer's disease**
AUTHORS	Pasquale Ferranti[1,2], Gianfranco Mamone[2], Chiara Nitride[1], Giovanni D'Auria[1], Inés Barraguirre[3], Juan Beauquis[3], Lucila Saavedra[4], Elvira Maria Hebert[4]
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	Introduction: According to the WHO, dementia is a syndrome that involves impairment of memory, intellect, behavior, and the ability to perform activities of daily living. Alzheimer's disease (AD) is the most common form of dementia (60-70% of cases), for which there is no curative treatment. In addition to pharmacological approaches, numerous nutritional interventions are being studied for prevention or to improve the quality of life of those affected. Preclinical evidence indicates that psycobiotic or probiotic lactic acid bacteria (LAB) can attenuate cognitive decline and reduce amyloid burden in rodent models of AD (Naomi et al., 2022; Abdelhamid et al., 2024). Some LAB produce neuroactive metabolites such as γ-aminobutyric acid (GABA) (Cataldo et al., 2020), which may act on the host through the microbiota-gut-brain (MGB) axis, but the molecular mechanisms involved remain poorly defined. **Methods:** In this study, we set up a strategy to explore the molecular mechanisms underlying interactions between LAB, which produce neuroactive compounds such as GABA, and their hosts through the MIC axis. We tested the strategy on a genetic model of AD in mice. The animals were administered with the psychobiotic strain *Levilactobacillus brevis* CRL 2013, an efficient GABA producer, isolated at CERELA-CONICET (Argentina). At the end of the trial, the mice were sacrified and hyppocampus and fluids were taken and analyzed. An approach was applied which integrated proteomics based on nHPLC-MSMS Orbitrap instrumentation with enzymatic, biochemical, and immunological analyses. The integrated data were processed using dedicated bioinformatics analysis protocols (Abdelhamid at al., 2024). **Results:** We identified significant changes induced in the proteome expressions in animals treated with the probiotic strain CRL2013, proteins significantly involved in the synthesis of neuromodulators, plaque formation/reduction, memory formation and consolidation, and

	enzymes involved in energy metabolism and in the assembly of neuronal structures. The administration of the probiotics positively modulated the proteome pattern. The results support of the ability of certain LAB probiotic strains to play a beneficial role in the disease by modulating key metabolites and inflammation, and inducing specific signaling pathways in the MIC axis. Conclusions: The proteomic strategy developed is a powerful innovative tool to explore MIC axis and the effects of metabolites produced by LAB on AD. Once correlated with the physiological and clinical status of the animals, proteomic data could provide fundamental information on the molecular mechanisms of AD, while also paving the way to potential applications in the development of functional foods and supplements containing genetically and functionally characterized LAB for non-pharmacological intervention in subjects with risk factors and/or as a complement to the treatment of subjects affected by neurodegenerative diseases such as AD. **References:** 1. Cataldo et al., (2020). Front in Microbiol **11**: 3176-3189. Naomi et al. (2021). Nutrients 14; 3. Abdelhamid at al. (2024) Nutrients 16, 538.
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XIV NEAPOLITAN BRAIN GROUP MEETING 2026

Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 49

TITLE	**Human Motor Neuron Modelling of SORD-Related Charcot–Marie–Tooth Disease: Aldose Reductase as a Potential Therapeutic Target**
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	SORD deficiency is a genetically defined neuropathy caused by biallelic mutations in the *SORD* gene. It represents one of the most common genetic causes of autosomal recessive Charcot–Marie–Tooth disease type 2 (CMT2) and distal hereditary motor neuropathy. *SORD* encodes sorbitol dehydrogenase, a key enzyme of the polyol pathway. Loss of SORD activity leads to intracellular sorbitol accumulation. However, the mechanisms linking this metabolic alteration to motor neuron dysfunction and degeneration remain poorly understood. In particular, the cellular consequences of SORD deficiency in human motor neurons have not been fully characterized. To investigate these mechanisms, we first characterized three fibroblast lines derived from distinct CMT2 patients carrying biallelic *SORD* mutations ($SORD^{-/-}$), two fibroblast lines derived from unaffected heterozygous carriers ($SORD^{+/-}$), and fibroblasts from healthy control ($SORD^{+/+}$). SORD-deficient fibroblasts showed severe mitochondrial dysfunction, characterized by alterations in mitochondrial structure and dysregulated expression of proteins involved in mitochondrial fission. We then established a human induced pluripotent stem cell (iPSC)-based model of SORD-associated neuronal disease. Patient-derived iPSCs ($SORD^{-/-}$) were differentiated into motor neuron progenitors (MNPs) and subsequently into mature motor neurons

	(MNs). SORD-deficient neural cells displayed marked abnormalities in mitochondrial morphology and metabolism, accompanied by early signs of cellular stress. Notably, SORD-deficient motor neurons exhibited prominent neuronal phenotypes, including impaired neurite branching and altered synaptic architecture. We next investigated whether sorbitol accumulation directly contributes to these phenotypes. Wild-type neural cells were exposed to high concentrations of sorbitol. Sorbitol overload reproduced several features observed in SORD-deficient cells, including mitochondrial abnormalities and increased susceptibility to apoptosis. Finally, we focused on Aldose Reductase (AR), the rate-limiting enzyme upstream of SORD in the polyol pathway, which may represent a promising therapeutic target for SORD-associated CMT. Notably, AR inhibition has already been explored as therapeutic strategy in diabetic neuropathy. SORD deficiency was associated with increased AR accumulation, suggesting that enhanced AR activity may promote further sorbitol production and contribute to a self-reinforcing cycle of sorbitol accumulation and cellular dysfunction. Importantly, pharmacological inhibition of AR significantly ameliorated mitochondrial abnormalities in SORD-deficient motor neurons. AR inhibition also rescued neuronal structural defects, including impaired neurite branching and altered synaptic organization. These findings provide functional evidence linking polyol pathway dysregulation to mitochondrial dysfunction and neuronal pathology. Overall, our results identify AR as a potential therapeutic target in SORD-associated CMT2 and suggest broader therapeutic implications for neuropathies involving dysregulation of the polyol pathway.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 50

TITLE	**The skin as a window into Systemic Amyloidosis: amyloid deposits and peripheral nerve damage**
AUTHORS	Dell'Aversana D.[1], Pinton S.[2], Vacchi E.[2], Saragosa F.[1], Ciccarelli G.[1], Vitale F.[1], Aiello A.[1], Castiglia M.[1], Manganelli F.[1], Tozza S.[1], Nolano M[1,3] & Melli G.[2]
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	Background: Systemic amyloidosis comprises rare and progressive disorders characterized by amyloid fibril deposition, including kappa and lambda light chain (AL), hereditary (ATTRv) and wild-type (ATTRwt) transthyretin amyloidosis, and inflammatory subtype with the deposition of serum amyloid A (AA amyloidosis). The diagnostic gold standard is Congo red (CR) staining on target tissue with apple-green specific birefringence to the polarized light. This study aimed to define the diagnostic sensitivity of CR staining on skin biopsies as surrogate tissue, evaluate the association between amyloid burden and peripheral denervation, and determine the accuracy of immunogold labeling for amyloid typing. Methods: Sixty-eight patients with a previous diagnosis of systemic amyloidosis (17 ATTRv, 31 ATTRwt, 3 AL kappa, 14 AL lambda, and 3 AA) across three referral centers underwent clinical evaluations and skin biopsies at the ankle and thigh. Samples were analyzed using indirect immunofluorescence to assess cutaneous innervation and denervation patterns, and CR staining to detect amyloid deposits. Amyloid burden was quantified as deposit density (number of deposits normalized for number of analysed sections). CR-positive sections underwent Transmission Electron Microscope (TEM) observation, and consecutive sections underwent immunogold staining to determine amyloid subtypes (ATTR, AL kappa or lambda, and AA). Results: Patients with ATTRwt were older and predominantly male than the other subtypes. Cutaneous denervation was identified in more than 80% of patients across all subtypes, displaying predominantly a non-length-dependent pattern in ATTRwt and AL, and a length-dependent pattern in ATTRv. The diagnostic sensitivity of CR staining on skin biopsies reached 82.3% in AL amyloidosis and 76.5% in ATTRv, whereas it was.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 51

TITLE	**Diagnostic Challenges in Chronic Autonomic Failure: The Contribution of Multimodal Biomarkers**
AUTHORS	Francesca Masciarelli [1,2], Maria Nolano [2]
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	Background The aetiological diagnosis of chronic autonomic failure can be challenging. Atypical presentations of pure autonomic failure (PAF) and unusual courses of immune-mediated autonomic disorders may produce overlapping clinical phenotypes, delaying diagnosis and potentially affecting therapeutic decisions. Three clinical observations illustrate the contribution of multimodal assessment to distinguishing these conditions. **Clinical observations** Two patients reported unilateral anhidrosis at symptom onset, subsequently progressing to generalized anhidrosis and involvement of multiple autonomic domains. Comprehensive assessment was performed approximately eight and twenty years after symptom onset, when sweating impairment was already generalized. Investigations included cardiovascular autonomic reflex testing, sympathetic skin responses, dynamic sweat testing, thermoregulatory sweat test, quantitative sensory testing and skin biopsy. A third patient presented with an approximately 16-year history of slowly progressive dysfunction involving multiple autonomic domains, without overt non-autonomic neurological manifestations. The prolonged course and predominantly autonomic phenotype suggested a possible underlying neurodegenerative process. **Diagnostic assessment and discussion** In the first two patients, genetic screening for hereditary transthyretin amyloidosis and ganglionic acetylcholine receptor antibody testing were negative. Skin biopsies demonstrated cutaneous nerve fibre loss and phosphorylated α-synuclein deposits, supporting an underlying synucleinopathy and, in the clinical context, a diagnosis of PAF.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 52

TITLE	**Repurposing Fluoxetine Restores Retinal and Brain Neuronal Function in Multiple Sulfatase Deficiency**
AUTHORS	Martina Sofia[1], Sandra Strollo[1], Emanuele Di Mambro[1], Martina Siviglia[1], Maria Cretella[1], Vincenzo Cacace[1], Nicola Brunetti-Pierri[1], Andrea Ballabio[1], Diego Luis Medina[1], Nicolina Cristina Sorrentino [1,2]
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	Multiple sulfatase deficiency (MSD) is an ultra-rare lysosomal storage disorder caused by mutations in SUMF1, resulting in the combined deficiency of all known sulfatases and leading to progressive neurodegeneration, retinal dysfunction, neuroinflammation, and severe multisystemic manifestations. Currently, no effective therapy is available to halt disease progression, and the major therapeutic challenge remains the correction of neuronal pathology. Increasing evidence indicates that impaired lysosomal function and defective autophagy are key drivers of neuronal dysfunction and cell death in lysosomal storage disorders, highlighting drug repurposing as a promising strategy to rapidly identify disease-modifying treatments.Using a cell-based high-content phenotypic screening platform, we identified Fluoxetine, an FDA-approved selective serotonin reuptake inhibitor (SSRI) with established blood-brain barrier permeability and neurotrophic properties, as a candidate compound capable of restoring lysosomal homeostasis. To evaluate its therapeutic potential, Fluoxetine was administered to the hypomorphic Sumf1 p.Ser153Pro mouse model, which closely recapitulates the clinical and pathological features of human MSD. Histopathological, molecular, and functional analyses were performed on retinal and brain tissues following systemic treatment. Fluoxetine administration significantly reduced lysosomal storage and attenuated neurodegenerative pathology in both retina and brain. These effects were associated with improved neuronal homeostasis, reduced neuroinflammation, and restoration of retinal and cerebral function. The observed therapeutic benefit is consistent with enhanced lysosomal activity and autophagic clearance, suggesting that Fluoxetine acts as a disease-modifying agent rather than providing only symptomatic improvement. Overall, our findings identify Fluoxetine as a promising repurposed therapeutic for MSD and provide preclinical evidence

	supporting its further development for neuronopathic lysosomal storage disorders. Given its well-established clinical safety profile and ability to efficiently penetrate the central nervous system, Fluoxetine represents an attractive translational candidate that could be rapidly advanced toward clinical evaluation, either as a standalone therapy or in combination with emerging gene-based approaches to maximize therapeutic efficacy.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 4

TITLE	**GaitRef-MAE: Development of a Multimodal Transformer for Normative Gait Reference Generation in Amyotrophic Lateral Sclerosis**
AUTHORS	Raffaella Mancino[1], Emanuele Gaudino[2], Giulia Saccone[2], Angela Cavallo[3], Giovanni Berselli[1], Raffaele Dubbioso[3], Fanny Ficuciello[2]
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	Preserving independent walking is a central goal in the clinical management of amyotrophic lateral sclerosis (ALS), a progressive neurodegenerative disease in which the gradual loss of motor neurons alters how muscles are activated and, consequently, how joints move. Gait analysis provides an objective description of these alterations, and combining surface electromyography (EMG) with joint kinematics allows muscle activation to be observed together with the movement it accompanies. However, a deviation can only be identified with respect to what is expected, and interpreting these recordings thus requires a meaningful normative reference. Such a reference is commonly obtained as a healthy population average, which, although robust, describes a generic healthy gait rather than the one expected for a specific person under specific walking and recording conditions. Deep learning could address this limitation by learning how muscle activity and joint motion co-vary across the gait cycle. Yet, its applications to gait analysis have mostly targeted disease classification or kinematic modeling, while the generation of combined normative muscle and movement profiles has received less attention. In this study, we developed GaitRef-MAE, a multimodal Transformer-based masked autoencoder that learns healthy gait patterns to generate normative EMG and kinematic profiles over the gait cycle, against which individual recordings can be compared. To this end, the framework integrated bilateral EMG envelopes of four lower-limb muscles with sagittal hip and knee angles from inertial measurement units, conditioning the generated references on cycle duration and, when available, walking speed. Missing measurements were explicitly handled without assuming that either limb was unaffected, and EMG references were kept in physical units, so that differences in amplitude, shape, and timing could be examined separately. Trained exclusively on healthy gait,

	the model was first evaluated through leave-one-subject-out validation on 11 healthy participants, including synthetic signal perturbations. The frozen model was then applied in an exploratory analysis on three individuals with ALS. Our results showed that GaitRef-MAE generated EMG references closer to the healthy signals than the population mean in peak amplitude, waveform shape, and peak timing, while the population mean remained more accurate for kinematic waveform similarity and range of motion. In participants with ALS, the framework revealed a consistent pattern: in all three cases, left gastrocnemius activity was lower than expected during left terminal stance (88–93% of the right gait cycle), when this muscle normally contributes to push-off. Two participants also showed a reduced bilateral knee range of motion. Such results suggest that learning multimodal normative references from healthy gait is a feasible route toward a phase-resolved description of muscle and movement alterations in ALS. Since these references derive from healthy recordings, the observed deviations cannot be directly interpreted as disease severity, and validation on larger independent cohorts will be required to establish their clinical relevance. In the longer term, knowing where and when muscle support is lacking during walking may inform exoskeleton control for rehabilitation and walking assistance.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 53

TITLE	**Deep Learning Reveals the Structural Hotspots in Amyloid Fibrils**
AUTHORS	[1] Chiara Elena Palmiero, [2] Carmen Biancaniello, [3] Angelina Lombardi, [2] Alfonso De Simone
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	Amyloid fibrils are highly ordered protein aggregates generally associated with neurodegenerative conditions, including Alzheimer's and Parkinson's diseases. Unlike native protein folding, the amyloid assembly does not obey the "one sequence, one fold" paradigm, as a single polypeptide sequence can adopt multiple structurally distinct fibrillar polymorphs. Although recent advances in cryo-electron microscopy and solid-state NMR have rapidly expanded the repertoire of experimentally resolved amyloid structures, deciphering the underlying determinants that stabilise diverse polymorphic folds has remained elusive. To address this fundamental question, we developed Amylo-Spotter, an amyloid-specific deep learning framework trained on a curated atlas of non-redundant experimentally resolved amyloid structures. The model integrates structural, evolutionary and sequence-derived features within a Bidirectional Long Short-Term Memory (BiLSTM) architecture coupled with an attention-pooling mechanism to identify structurally constrained residues within amyloid fibrils. By applying Amylo-Spotter to fibrils of α-synuclein and amyloid-β (Aβ), we identified key structural hotspots that stabilise their fibrillar cores, effectively disentangling polymorph-invariant energetic constraints from fold-specific regions of structural permissiveness. Importantly, the identified hotspots rationalise integrative mutagenesis data, highlighting the critical role of these structural nodes. Collectively, these results demonstrate that the amyloid folding does follow fundamental sequence-structure principles, while establishing a general framework for decoding the mechanisms of amyloid assembly, including a new approach to identify de novo amyloid sequences. Moreover, by pinpointing polymorph-invariant structural determinants, Amylo-Spotter provides a rational basis for the design of conformation-specific probes and the development of structural biomarkers for neurodegenerative diseases.

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Biomarkers in Neuroscience: progress, challenges, and perspectives

SHORT TALK SESSION 4

TITLE	**Force-Controlled Tactile Stimulation Using a Collaborative Robot to Study Attention**
AUTHORS	Mariarosaria Meola[1], Paolino De Risi[1], Aldo Smaldone[2], Giulia Torromini[3], Fanny Ficuciello[1]
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	The effects of gentle touch on attention can be investigated by controlling how the tactile stimulus is delivered during task performance. This pilot study evaluated a robotic system designed to deliver reproducible forearm stroking and compared behavioral performance and autonomic responses between participants who performed attention tasks with tactile stimulation and those who performed the same tasks with the robot active but without skin contact. A six-degree-of-freedom collaborative robot fitted with a soft brush delivered strokes along a 10 cm segment of the non-dominant forearm. Five calibration points were used to adapt the stroking trajectory to each participant's forearm contour. During stroking, an admittance-like controller with proportional–integral regulation used load-cell feedback to adjust brush height and regulate contact force around a target of 0.20 N. Eleven volunteers aged 23–45 years took part in the study. In the tactile stimulation group, the brush stroked the forearm. In the control group, the robot executed the same programmed movements without making contact. After an initial two-minute period in the assigned condition, participants in both groups completed four tasks in randomized order: Visual Search, Posner spatial cueing, Stroop, and the Sustained Attention to Response Task (SART). The robot remained active during task performance in both groups, with tactile stimulation delivered only to the stimulation group. Reaction times and errors were analyzed in both groups, together with heart rate, heart rate variability (RMSSD and SDNN), and electrodermal activity. The robot followed the forearm contour across successive passes, with a mean contact force of 0.18 N in each of the two representative recordings. Participants in the stimulation group responded faster across all four tasks. The largest differences were observed in Visual Search and

	incongruent Stroop trials (approximately 150 ms each), followed by invalid Posner trials (130 ms). The differences were smaller in valid Posner and congruent Stroop trials (50 ms each) and in SART (10 ms). Accuracy differences were generally small and varied across tasks, with near-ceiling accuracy in valid Posner trials in both groups. Heart rate and heart rate variability tended to increase after task performance, whereas tonic skin conductance and the number of phasic skin conductance responses tended to increase during task execution. Autonomic measures showed no consistent differences between groups. These findings support the feasibility of delivering force-controlled forearm stroking during computerized attention tasks. The shorter reaction times observed in the stimulation group warrant further investigation. Given the small sample, the higher mean age of the control group, and the descriptive nature of the comparisons, a larger, age-balanced study is needed to determine whether tactile stimulation accounts for the observed differences in response speed.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

POSTER BOARD N° 54

TITLE	**Elevated plasma sTREM2 reflects microglial activation but lacks diagnostic and clinical relevance in amyotrophic lateral sclerosis**
AUTHORS	Cavallo A[1], Senerchia G[1], Iuzzolino VV[1], Terracciano D[2], Dubbioso R[1].
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ABSTRACT	**Background:** Microglial activation contributes to the neuroinflammatory response in amyotrophic lateral sclerosis (ALS). Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) reflects microglial activity in several neurodegenerative disorders, but its role in ALS remains unclear. **Methods:** We evaluated plasma sTREM2 as a marker of microglial activation in ALS and compared its diagnostic performance with established blood biomarkers of neurodegeneration. Plasma sTREM2, neurofilament light chain (NfL), phosphorylated tau181 (Ptau181), and glial fibrillary acidic protein (GFAP) were measured in 100 patients with ALS, 30 healthy controls, and 30 disease mimics. Group differences were assessed using general linear models adjusted for age and sex. Associations with clinical variables and inflammatory markers were tested using Spearman correlation, and diagnostic performance was evaluated using receiver operating characteristic curves. **Results:** Plasma sTREM2 differed across groups ($p = 0.016$), with higher levels in ALS compared with healthy controls ($p = 0.013$) and in mimics compared with healthy controls ($p = 0.007$), but no difference between ALS and mimics ($p = 0.394$). Discrimination between ALS and healthy controls was modest (area under the curve 0.677), with no discrimination between ALS and mimics (area under the curve 0.512). No association was found between sTREM2 and disease severity or inflammatory markers (all $p > 0.10$). **Conclusions:** Plasma sTREM2 increases in ALS but lacks diagnostic specificity and clinical associations, supporting its role as a nonspecific marker of neuroimmune activation rather than a biomarker of disease-related neurodegeneration.
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POSTER BOARD N° 55

TITLE	**Impact of Epileptiform Abnormalities on Functional Phenotype in a Cohort of Autism Spectrum Disorder Patients With or Without Epilepsy: A Monocentric Retrospective Study**
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ABSTRACT	Autism spectrum disorder (ASD) and epilepsy frequently co-occur, pointing to shared neurobiological mechanisms. While no specific seizure type or epileptic syndrome is consistently linked to ASD, epileptiform abnormalities (EAs) are common in affected individuals, though their precise clinical significance remains unclear. This study investigated the impact of EAs and epilepsy on the functional phenotype of 338 individuals with ASD, evaluated using video-electroencephalography (v-EEG) and standardized psychometric batteries (ADOS-2, Leiter-R, WISC-IV, and VABS). Patients with both ASD and epilepsy demonstrated significantly lower cognitive performance than those with ASD alone or ASD with EAs only. Notably, the ASD+EA cohort exhibited greater core symptom severity. However, no significant group differences emerged regarding adaptive functioning or language skills. These findings underscore the potential influence of subclinical epileptiform activity on cognitive and behavioral trajectories in ASD. Longitudinal studies are warranted to clarify the prognostic value of EAs and to better delineate their role in functional outcomes.
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POSTER BOARD N° 56

TITLE	**From raw EMG–IMU signals to digital biomarkers in ALS: a quality-controlled, multi-method analysis of upper-limb effort and passive exoskeleton assistance**
AUTHORS	Narges Sadat Hosseini[1], Raffaella Mancino[2], Giulia Vannucci[1], Raffaele Dubbioso[3], Fanny Ficuciello[1], Roberta Siciliano[1]
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ABSTRACT	Background: Upper-limb function in ALS is mostly followed with examiner-dependent scales, which say little about what the muscles do during a movement. Surface EMG and inertial sensors (IMUs) can record this during daily tasks, but clinical samples are small and very variable, and the effect of passive exoskeletons in ALS is poorly known. Methods: In the EXODAI 4.0 protocol, 15 ALS patients and 8 healthy controls performed drinking, lifting and pick-and-place (0.5 kg and 1 kg), with and without a passive shoulder exoskeleton, with EMG and IMU recorded from eight muscles. We built the whole chain from raw files: quality control at every stage, EMG band-pass filtering (20-450 Hz) and envelope extraction, IMU-based movement segmentation, windowing, feature extraction, and subject-level KPIs (twenty indicators of effort and movement) chosen before looking at the diagnosis. Shapiro-Wilk tests rejected normality, so groups were compared with Mann-Whitney U tests on subject-level medians (rank-biserial correlation as effect size, BenjaminiHochberg false-discovery-rate correction) and tasks with the Friedman test. A linear mixed-effects model with a subject random intercept handled repeated trials, within-subject antagonist ratios tested selective involvement, a sensitivity power analysis set the limits of inference, and the low-power exoskeleton contrast was re-estimated in a Bayesian model with a sceptical prior. Ward hierarchical clustering (1,000 bootstrap resamples, Jaccard index; Fisher's exact and permutation tests) looked for subgroups without labels. Logistic regression, RBF-SVM and random forest were evaluated with leave-one-subject-out crossvalidation, fixed hyperparameters and training-only standardisation, and SHAP values explained the forest. One patient with a confirmed device artefact was excluded (14 ALS, 8 controls). Results: Patients used far more muscle activity for a similar movement. Absolute RMS amplitude was about five times higher in ALS at the distal forearm ($p = 0.001$) and about four times higher across muscles ($p = 0.004$), while angular velocity, smoothness and

	duration did not differ (all p > 0.66). The increase grew from proximal to distal, largest at the wrist extensor (3.7 times) and smaller at the biceps (1.6) and triceps (1.8), with no shift in antagonist ratios. The intraclass correlation was near 0.80, so trials are not independent. Clustering found a patient subgroup with marked hyperactivation, while others were indistinguishable from controls. Balanced accuracy was 0.76-0.77 (AUC up to 0.83), and SHAP assigned about three quarters of the weight to the two forearm muscles. The exoskeleton lowered effort in proximal muscles (pooled cohort: deltoid -58% in drinking and pick-and-place) but changed little in the distal forearm. In patients alone no per-task reduction was significant, yet the posterior probability of a deltoid reduction during drinking was about 99% (-31%, 95% credible interval -48% to -6%). Conclusions: Methods built on different assumptions describe the same pattern, making a small set of interpretable indicators a candidate digital biomarker and a possible target for adaptive assistance. Passive shoulder support helps where it acts but does not reach the distal forearm. Limits are the small crosssectional sample and the use of absolute, not MVC-normalised, amplitudes.
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POSTER BOARD N° 57

TITLE	**Reshaping Muscle Coordination with Passive Shoulder Exoskeletons in Amyotrophic Lateral Sclerosis: A Riemannian Analysis**
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ABSTRACT	The ability to use the arms in everyday tasks, from eating and drinking to personal care, is a cornerstone of independent living, and its progressive loss is among the most disabling consequences of amyotrophic lateral sclerosis (ALS). This is particularly evident in the flail-arm phenotype, in which weakness predominantly affects the proximal upper limbs and makes even lifting the arms increasingly difficult. Passive shoulder exoskeletons represent a promising solution, as they can support residual motor function by partially compensating for arm weight without powered actuation. Establishing whether such assistance is truly beneficial, however, is not straightforward. A task may be successfully completed, or a muscle less activated, while the assistance redistributes muscular demand across other muscles or reinforces compensatory strategies. Assessing the effects of an exoskeleton thus requires looking not only at how much muscles are activated, but also at how they are coordinated. Conventional electromyographic (EMG) amplitude measures address only the first aspect, while multivariate approaches such as muscle synergy analysis require selecting and matching components across conditions, which is challenging in small and heterogeneous clinical cohorts. Riemannian geometry offers a complementary approach: by treating the covariance structure of multichannel EMG as a single geometric object, it characterizes the relationships among muscle activation patterns without decomposing them into components. In this study, we combined Riemannian analysis of EMG covariance with conventional amplitude measures to investigate the effects of a passive shoulder exoskeleton in 12 individuals with flail-arm ALS, providing a component-free assessment of how assistance reshapes multi-muscle coordination. Participants performed two upper-limb tasks adapted from the Brooke Scale, lifting arms and simulated drinking, with and without maximum assistance, while EMG was recorded from six shoulder, arm, and

	forearm muscles. Five age-matched healthy controls followed the same protocol, so that each ALS coordination pattern could be compared with a healthy reference obtained under the same task and condition. The distance from this reference quantified how far coordination deviated from healthy behavior, and its change with assistance was taken as the primary outcome. Our results showed that the response to assistance was strongly task-dependent. During arm lifting, coordination was closer to the condition-matched healthy reference with assistance in 10 of 12 participants, even though muscle activation remained almost unchanged. During drinking, the opposite occurred: coordination was further from the condition-matched healthy reference with assistance in 10 of 12 participants, while activation slightly increased in the shoulder muscles and decreased in the arm and forearm muscles. This pattern suggests a task-dependent redistribution of muscular demand, potentially reflecting an altered movement strategy under assistance. These effects were robust to alternative distance metrics and matrix representations. Although limited to two tasks and to a device primarily supporting shoulder elevation, such results suggest that coordination measures capture effects of assistance that muscle activation alone would miss. Considering both may therefore support a task-specific evaluation and selection of upper-limb exoskeletons for people with ALS.
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Biomarkers in Neuroscience: progress, challenges, and perspectives

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TITLE	**GATA6/TET3-mediated DNA hydroxymethylation of the NCX1 heart promoter contributes to preconditioning-induced neuroprotection**
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ABSTRACT	The Na+/Ca2+ exchanger 1 (NCX1) is a key regulator of calcium and sodium homeostasis and contributes to neuroprotection induced by ischemic preconditioning (PC). In neurons, NCX1 expression is controlled by two promoters, NCX1-Br (brain-specific) and NCX1-Ht (heart-specific). While DNA methylation represses NCX1-Ht activity, hydroxymethylation mediated by ten-eleven translocation (TET) enzymes is associated with transcriptional activation. In this study, we investigated the epigenetic mechanisms regulating NCX1 expression in neuronal cells. In ascorbic acid–treated SH-SY5Y cells, TET3 selectively increased 5-hydroxymethylcytosine (5hmC) levels at the NCX1-Ht promoter, leading to enhanced NCX1 mRNA and protein expression. This effect was not observed at the NCX1-Br promoter. Mechanistically, TET3 physically interacted with the transcription factor GATA6, whereas no interaction was detected with REST. Importantly, mutagenesis of GATA binding sites within the NCX1-Ht promoter abolished both GATA6 and TET3 recruitment, demonstrating the requirement of GATA6 for TET3-mediated epigenetic activation. Furthermore, cortical neurons exposed to hypoxic preconditioning followed by oxygen-glucose deprivation/reoxygenation (OGD/Rx) showed increased GATA6 and TET3 protein levels together with enhanced DNA hydroxymethylation at the NCX1-Ht promoter. These changes were absent in neurons subjected to OGD/Rx alone. Overall, our findings identify a novel neuroprotective mechanism in which the GATA6/TET3 complex epigenetically activates NCX1 transcription during ischemic preconditioning. Targeting this pathway may represent a promising therapeutic strategy for stroke and ischemic brain injury.
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Con il contributo non condizionante di:











