FILSLAN
Filière de Santé Maladies Rares Sclérose Latérale Amyotrophique et Maladies du Neurone Moteur

MND-NET
German Network for Motor Neuron Diseases

ARSLA
Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres maladies du motoneurone

11TH ALS AND MND RESEARCH MEETING

FRENCH-GERMAN EDITION

October 21 and 22, 2025

ICM, Paris

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Tuesday, october 21, 2025

9:30 - 9:45	Opening: Philippe COURATIER (FILSLAN), Valérie GOUTINES (ARSLA), Débora LANZNASTER (ARSLA)
9:45-11:05 9:45 10:05 10:25 10:45	**ARSLA SESSION** (4 x 20 minutes) Moderators: Pierre-François PRADAT and Cédric RAOUL Hugo ALARCAN *iBrain Tours* Matthieu GILSON *Institut de Neurosciences de la Timone Marseille* Claire GUISSART *Laboratoire de Biochimie et Biologie Moléculaire CHU Nîmes* Raphaëlle CASSEL *INSERM 1118 Strasbourg*
11:05-11:50 11:05 11:20 11:35	**FILSLAN "TRAINING THROUGH RESEARCH" PROJECT AWARD 2024** (3 x 15 minutes) • Sibylle DE BERTIER • Alper ER • Marina HERNAN GODOY
11:50-13:30	Lunch buffet / First poster session
13:30-14:15	**SOMATIC MUTATIONS IN NEURODEGENERATION** Jochen WEISHAUPT *Ulm*
14:15-15:30 14:15 14:30 14:45 15:00 15:15	**SESSION 1** (5 x 15 minutes) Moderators: Aurore BERNARDIN and David BRENNER OC 1.1 - Johannes DORST *Ulm University* OC 1.2 - Nour HALABI *Imagine Institute Paris* OC 1.3 - Marcel NAUMANN *University Medical Center Rostock* OC 1.4 - Giorgia QUERIN *APHP Pitié-Salpêtrière Hospital Paris* OC 1.5 - Antonia DEMLEITNER *TUM University Hospital rechts der Isar*
15:30-16:00	Break (30 minutes)
16:00-17:00 16:00 16:15 16:30 16:45	**SESSION 1** (4 x 15 minutes) Moderators: Aurore BERNARDIN and David BRENNER OC 1.6 - Charlotte GAVARD *Institute for Neurosciences of Montpellier* OC 1.7 - Maximilian WIESENFARTH *Ulm University* OC 1.8 - Sylvie BANNWARTH *Reference Centre for Mitochondrial Diseases CHU de Nice / IRCAN* OC 1.9 - Thomas MEYER *Charité – Universitätsmedizin Berlin*
17:00-17:45	**CONFERENCE BICENTENARY OF THE BIRTH OF JEAN-MARTIN CHARCOT** Danielle SEILHEAN and Martin CATALA
17:45	Conclusion day 1
Welcoming 18:30 **Beginning 19:00**	ARSLA Awards Evening Institut Imagine, 24 Bd du Montparnasse, 75015 Paris

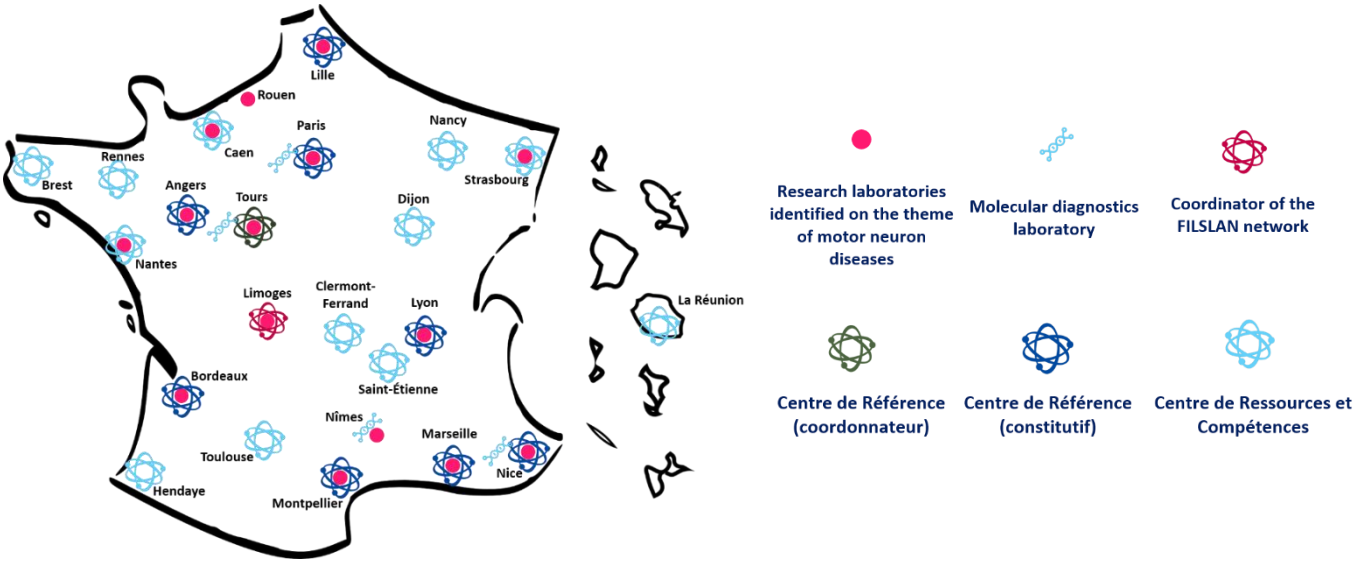
Wednesday, october 22, 2025

8:30-9:15	**CROSS-SPECIES MULTI-OMIC TO PRIORITIZE DISEASE MODIFIER AND NEW ALS GENES** Salim MEGAT *Strasbourg Translational Neuroscience & Psychiatry STEP*
9:15-10:30	**SESSION 2** (5 x 15 minutes) Moderators: Maximilian WIESENFARTH and Marina HERNAN-GODOY
9:15	OC 2.1 - Mohamed EL MENDILI *Sorbonne Université Paris*
9:30	OC 2.2 - Jochen WEISHAUPT *Heidelberg and Ulm University*
9:45	OC 2.3 - Sarah MERESSE and Killian GHIKH-MIMIETTE *Institut du Cerveau Paris*
10:00	OC 2.4 - Laura TZEPLAEFF *Rechts der Isar Hospital of the Technical University Munich*
10:15	OC 2.5 - Emilien BERNARD *Lyon ALS Center*
10:30-10:45	Break (15 minutes)
10:45-12:00	**SESSION 2** (5 x 15 minutes) Moderators: Maximilian WIESENFARTH and Marina HERNAN-GODOY
10:45	OC 2.6 - Philippe GOSSET *King's College London*
11:00	OC 2.7 - David BRENNER *University Hospital Ulm*
11:15	OC 2.8 - Christian LOBSIGER *Sorbonne Université, Paris Brain Institute, ICM, Inserm, CNRS, APHP*
11:30	OC 2.9 - Joachim SCHUSTER *Ulm University German Center for Neurodegenerative Diseases*
11:45	OC 2.10 - Anaëlle BURGARD *University of Strasbourg*
12:00-13:30	Lunch buffet / Second poster session
13:30-13:45	Announcement of ARSLA awards / Research support actions ARSLA scientific committee jury : Chantal Sellier, Claire Guissart, Emilien Bernard and David Devos
13:45-16:00	**ROUND TABLE: PRESYMPTOMATIC ALS GENE MUTATION CARRIERS** Moderators: Marie-Hélène SORIANI and Jochen WEISHAUPT • **30 years of experience with presymptomatic testing in late onset inherited neurodegeneration** Alexandra DURR *Paris Brain Institute* • **First learnings from the premodiALS study** Paul LINGOR *TUM University Hospital* • **Metabolic Alterations in presymptomatic ALS Gene Mutation Carriers** Johannes DORST *RKU – University and Rehabilitation Clinics Ulm* • **Preventing ALS, Myth or Reality, the US Experience** Senda AJROUD-DRISS *Northwestern University Chicago* • **Challenges of phenoconversion in routine clinical care** Maria Del Mar AMADOR *Pitie Salpetriere Hospital Paris*
16:00-16:15	General conclusion: Philippe COURATIER

FILSLAN

FILSLAN is the national network for rare diseases dedicated to Amyotrophic Lateral Sclerosis and motor neurone diseases. The network was created in 2014 by the Ministry of Social Affairs and Health as part of PNMR 2 and under the responsability of DGOS. Since January 2021, Professor Philippe COURATIER is the national coordinator of the FILSLAN network which is located at the Limoges University Hospital. In 2023, 22 ALS Centers have been labeled.

FILSLAN network



The FILSLAN team

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ACT4ALS-MND

National Network for Clinical Research in Amyotrophic Lateral Sclerosis - Motor Neurone Diseases

Gaëlle BRUNETEAU network coordinator, Amandine BORDET project manager, Alizé CHALANÇON project manager

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FILSLAN website

ARSLA

Created in 1985, ARSLA is the French National Association for research on ALS.

It works to discover treatments and a cure for ALS, also to serve and advocate for empower people affected by ALS.

It offers several services to help and support the patients and their families. For example, it provides for free, equipment that improve quality of life - such as communication devices that allows people with ALS to communicate despite all their limitations.

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- Projects for young researchers: research projects carried out by 4th year students' thesis on ALS.
- Biotech projects: research projects carried by start-ups to develop therapies in ALS.

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EDITORIAL

This eleventh research conference dedicated to motor neuron diseases is being held at the ICM in La Salpêtrière. This conference is unique. On the one hand, in 2025, the Filslan network and ARSLA sought to establish a close partnership with our German colleagues and, as you will see, the program brings together researchers from both sides of the Rhine. Filslan and MNDnet have collaborated to enable 19 researchers to present their latest findings. On the other hand, 2025 marks the bicentenary of the birth of Jean Martin Charcot, and we will have the immense pleasure of listening to Prof. Seilhean and Prof. Catala, who will put the seminal work of this great clinician into context. Finally, an international round table will address the difficult subject of monitoring individuals carrying pathogenic mutations. Take advantage of these two days to exchange ideas and foster new collaborations.We hope you enjoy this new edition demonstrating the growing interest in ALS and Motoneurone diseases research.

Pr P.Couratier

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SILVER

Effik est un laboratoire pharmaceutique français, filiale du groupe Italfarmaco, présent dans plus de vingt pays. Avec un ancrage local fort et une vision mondiale, Effik exerce son expertise dans deux domaines : la Neurologie et la Santé de la femme. Dans chacun d'eux, Effik développe des solutions pour répondre aux besoins des patients et des professionnels de santé, avec des exigences de qualité, de sécurité et de conformité réglementaire. La Neurologie constitue un axe majeur, centré sur la sclérose latérale amyotrophique (SLA). L'implication d'Effik s'inscrit dans une volonté de partenariat avec les cliniciens, les chercheurs et les associations. Le fait qu'Effik participe en 2025, pour la 9ème année consécutive aux Journées de la Recherche sur la SLA et les MNM témoigne de son implication au service de la recherche et des patients.

Zambon est une entreprise innovante dans les domaines de la chimie et la pharmacie, fondée sur l'histoire et les valeurs d'une entreprise familiale italienne, avec des projets ambitieux de croissance et de développement.

Zambon France déploie son activité dans trois domaines : L'automédication responsable, la médecine de prescription en ville et la médecine de spécialités (neurologie, maladies respiratoires sévères).

Dans le domaine des spécialités hospitalières, Zambon est particulièrement impliquée en neurologie, dans la maladie de Parkinson et dans la sclérose latérale amyotrophique.

BRONZE

Biogen est une entreprise de biotechnologie, pionnière dans l'innovation scientifique, qui développe et met à disposition des nouveaux médicaments qui transformant la vie des patients et créent de la valeur pour nos parties prenantes.

Nous nous appuyons sur une compréhension approfondie de la biologie humaine et nous mobilisons différentes approches pour développer des traitements là où il n'y a pas de solutions ou des thérapies présentant des bénéfices supérieurs pour les patients. Notre approche consiste à prendre des risques audacieux et mesurés pour garantir un retour sur investissement au service d'une croissance durable.

SUMMARY

ARSLA SESSION

Organisation/Moderation: Cedric RAOUL and Pierre-François PRADAT (Chairmen of the ARSLA Scientific Council)

OC A1 - Evaluation of blood-brain barrier integrity during the evolution of Amyotrophic Lateral Sclerosis

Alarcan H (1,2), Al Ojaimi (2), Masse F (3), Osman S (2), Eymieux S (4,5), Gonzalez L (6), Paget C (6), Trovero F (3), Emond P (2,7), Dufour D (2,7), Lefèvre A (2), Corcia P (2,8), Andres C (1,2), Veyrat-Durebex C (1,2), Blasco H (1,2)

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The blood-brain barrier (BBB) protects the central nervous system from the entry of toxic molecules but also limits the passage of many brain-targeted drugs. An alteration of this barrier has previously been reported in ALS, including by our team [1], but this aspect has been little studied in this pathology. In this context, the aim of this project is to characterize the integrity of the BBB in ALS to evaluate the impact of its alteration on the pathophysiology of the disease as well as on the pharmacokinetics of therapeutic candidate drugs. Using the prospective cohort METABALS (ClinicalTrials.gov: NCT01962311), we related albumin quotient (QAlb) and other markers of BBB integrity (NSE and S100B proteins) to the metabolomic and inflammatory profiles of patients to provide mechanistic insights into their potential modifications. We identified an association between NSE protein and the inflammatory profiles of patients, while QAlb was mainly associated with metabolites, its elevation being particularly linked to a disturbance in the purinergic system. Then, we characterized the state of BBB integrity during the evolution of the disease in the mouse model TAR DNA-binding protein 43 (TDP-43) A315T. We observed an increase in BBB permeability, reflected by the sodium fluorescein permeability index, at the pre-symptomatic stage in the brain, as well as at the late stage of the disease in the brain and spinal cord. We also observed elevated serum concentrations of NSE at the late stage of the disease. These results, combined with recent literature data [2], suggest that these alterations could be independent of the disease progression stage and related to a loss of physiological function of TDP-43. In conclusion, our results highlight the importance of the BBB in the pathophysiology of ALS and encourage further studies aiming to continue the characterization of this barrier in this disease.

References :

1. Alarcan H, Vourc'h P, Berton L, et al. Implication of Central Nervous System Barrier Impairment in Amyotrophic Lateral Sclerosis: Gender-Related Difference in Patients. *Int J Mol Sci*. 2023;24(13):11196. doi:10.3390/ijms241311196
2. Arribas V, Onetti Y, Ramiro-Pareta M, et al. Endothelial TDP-43 controls sprouting angiogenesis and vascular barrier integrity, and its deletion triggers neuroinflammation. *JCI Insight*. 2024;9(5):e177819. doi:10.1172/jci.insight.177819

Keywords : TDP-43, blood-brain barrier, ALS

Funding : This work was funded by *Association pour la recherche sur la SLA* (ARSLA), the fundation *Patrick de Brou de Laurière*, and *AOI jeune chercheur du CHRU de Tours*.

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OC A2 - Multimodal MRI prognosis for ALS evolution

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1 Institute de Neurosciences de la Timone ; 2 Centre de Résonance Magnétique Biologique et Médicale; 3 Assistance Publique - Hôpitaux de Marseille

The early diagnosis of patients suffering from amyotrophic lateral sclerosis (ALS) remains a difficult problem, especially concerning the prediction of fast versus slow disease progression. Solving this challenge would greatly help personalizing the treatments and monitoring of patients. Our project has developed and tested an automated prediction pipeline for ALS progression. We rely on several modalities of magnetic resonance imaging (MRI) like the classical structural and diffusion MRI, but also sodium MRI that captures metabolic dysfunctions. We show that several MRI multimodalities can be combined to improve the prediction accuracy. We also identify how informative these modalities are for the prediction, as well as the concerned brain regions that points to the design of a biomarker. Our results underlie the relevance of sodium MRI and diffusion MRI for predicting the disease progression.

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OC A3 - Development of a targeted RNA-Seq approach for the molecular diagnosis of ALS

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Molecular diagnosis of ALS is essential for patient care, guiding both genetic counseling and access to targeted therapies. A major challenge remains the interpretation of splicing variants, which account for approximately 11% of variants of uncertain significance identified during ALS gene testing. Although their impact can be predicted using in silico tools, only RNA analysis from patient samples can confirm their pathogenic nature. To address this, we implemented a targeted RNA-Seq strategy (NCT06083584).

To date, 391 patients have been enrolled, and RNA-Seq has been performed in 74 of them. 37 carried variants predicted to affect splicing, which were prioritized for RNA-Seq analysis; 9 of these were confirmed to be deleterious.

To process these data, we developed SpliceVariantRNA, a reproducible and modular workflow implemented with Snakemake. From raw FASTQ files, it performs quality control, optional trimming, and read alignment using STAR. Splice junctions are identified and statistically assessed using SpliceLauncher, which applies gamma or negative binomial models depending on read depth; junctions with insufficient statistical power are retained for expert review to ensure rare but clinically relevant events are not missed.

Two previously unreported pathogenic variants were identified: *HNRNPA1*(NM_031157.4):c.1064-1G>C, in a 51-year-old man with slowly progressive distal asymmetric quadriparesis affecting predominantly the upper limbs, with low serum neurofilament levels (19 pg/mL), resulted in three distinct anomalies: exon 10 skipping, activation of a cryptic acceptor site within exon 10, and retention of intron 9; and *CHMP2B*(NM_014043.4):c.531+1G>A, in a 79-year-old woman with rapidly progressive

ALS/FTD and a family history of psychiatric disease, led to retention of intron 5, with the mutated allele present in 100% of RNA-Seq reads versus 39% of DNA-Seq reads.

In conclusion, this approach paves the way for more accurate genetic counseling and broader access to gene-targeted therapies in ALS. Future work will focus on enhancing blind detection of splicing defects, particularly in familial cases without a detectable DNA variant.

References: [1] Leman R, et al. SpliceLauncher: a tool for detection, annotation and relative quantification of alternative junctions from RNAseq data. *Bioinformatics*. 2020;36(5):1634–1636. [2] Mölder F, et al. Sustainable data analysis with Snakemake. *F1000Research*. 2021;10:33.

Keywords: Splicing, RNA-seq, Bioinformatics

Acknowledgements/Funding : This study (ROSA) received funding from NIMAO 2023-1 (€50,000) and from the *Association pour la Recherche sur la Sclérose Latérale Amyotrophique et autres maladies du motoneurone* (ARSLA 2023, €55,806), for a total budget of €105,806.

We thank the patients and clinical teams involved in the ROSA project, as well as the laboratory technicians whose careful work made RNA extraction, library preparation, and sequencing possible.

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OC A4 - Involvement of inhibitory neurons in Amyotrophic Lateral Sclerosis and frontotemporal dementia linked to Fused in Sarcoma protein

Lorenc F(1), Kan V (2), Dupuis L (1), Liebscher S (2), Cassel R (1)

(1) University of Strasbourg, INSERM, STEP lab U1329, team 3 ALS-FDT, Biomedical research centre, Strasbourg, France; (2) Institute of Clinical Neuroimmunology, Klinikum der Universität München, Ludwig-Maximilians-University Munich, Munich, Germany

Multiple evidence suggests that inhibitory neurons are involved in ALS. Indeed, patients show impaired intracortical inhibition prior to motor symptoms onset, and post-mortem studies highlighted molecular alterations of cortical and spinal inhibitory circuits. Recently, our laboratory and collaborators identified inhibitory defects in an ALS-FTD mouse model linked to Fused in Sarcoma (FUS). Mutations in *FUS* cause severe forms of ALS, particularly when *FUS* nuclear localisation signal (NLS) is truncated. This leads to the cytoplasmic mislocalisation of the protein, which is also observed in ALS and FTD patients devoid of mutations. In mice, the ubiquitous NLS deletion led to cortical hyperactivity associated with molecular and ultrastructural alterations of GABAergic synapses, ALS-like motor impairments and FTD-like behavioural dysfunctions. To characterise the contribution of inhibitory neurons to these phenotypes, we created a mouse model displaying a constitutive NLS deletion specifically in GABAergic neurons. Interestingly, when both copies of *Fus* were mutated, we observed a progressive alteration of the post-natal body development, illustrated by reduced weight and limb strength. Furthermore, half of the homozygous pups did not survive weaning and we are currently investigating the cause of death. When only one copy of *Fus* was mutated, mice were able to grow old and males showed FTD-like sociable abnormalities. We are now investigating the underlying mechanisms. In particular, our collaborators observed an increased spontaneous neuronal activity in the frontal cortex of anaesthetised animals. In a complementary strategy, we created a mouse model displaying *Fus* truncation in every cell type except inhibitory neurons. This showed to be sufficient to delay ALS-like motor defects in females. Ultimately, with this study, we will determine if *Fus* mutation in inhibitory neurons is sufficient and/or necessary to induce ALS and FTD-like symptoms.

Keywords: ALS-FUS, inhibitory neurons

Acknowledgements and Funding: The authors declare no conflict of interest and thank the University of Strasbourg for funding the project. U1329-U1118 CASSEL IDEX, DGG UNISTRA CASSEL, CASSEL FUS VGAT ARSLA R23085 MM

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- **Novel genetic causes elucidated several large French ALS Families**

Sibylle de Bertier1, Maria-Del-Mar Amador1,2,3, Tomoko Miki1,4, Coline Jost-Mousseau1, Séverine Boillée1, Christian Lobsiger1, Delphine Bohl1, Danielle Seilhean1,3,4, Stéphanie Millecamps1 and the FILSLAN research consortium

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The study of familial forms of ALS (fALS), which represent about 10% of patients, has led to the identification of more than forty genes causing the disease but, as one-third of fALS cases are still unresolved, new genetic causes remain to be identified. We analysed whole exome sequencing data from 300 French fALS patients and identified novel genetic mutations in MAPT and ARPP21 genes, both encoding neuronal proteins. Variants were selected based on familial segregation and recurrence across multiple families, showing either (i) high or low penetrance, and (ii) predominantly respiratory or spinal upper-limb onset in the case of MAPT and ARPP21 mutations, respectively.

These results expand the clinical spectrum of MAPT mutations, which are usually unrelated to ALS but are rather associated with tauopathies, for which new targeted therapeutic strategies, using antisense oligonucleotides (ASO) and immunotherapies, are currently being developed. For ARPP21, as it shares structural similarities with TDP-43 (the main neuropathological marker of ALS), including RNA-binding (suggesting transcriptional regulation role) and prion-like domains (conferring aggregation propensity), this implies convergent pathological mechanisms between both proteins.

The pathogenicity of those new ALS genetic mutations were studied through neuropathological analysis and functional characterization in cellular models (plasmid transfection in various cell lines and iPSC-derived motor neurons). Our results helped to decipher cellular pathway disturbances at work with these disease mutations and contributed to the understanding of cellular pathways and mechanisms involved in motor neuron degeneration, including mitochondrial distress, stress granule formation, phosphorylation and protein aggregation. Our findings also hold significant implications for genetic counselling, not only for affected patients but also for their at-risk family members.

- **Phase amplitude coupling: A promising biomarker of cortical excitability in amyotrophic lateral sclerosis (ALS)**

Alper Er (1), Alexandra Lackmy-Vallée (1), Michel Le Van Quyen (1), Julien Dauget (1), Arnaud Preuilh (1), Giorgia Querin (1, 2), Pierre-Francois Pradat (1, 2), Guillaume Marrelec (1), Véronique Marchand-Pauvert (1)

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder that leads to progressive motor weakness, paralysis, and death. Approximately 200,000 new cases occur worldwide each year.

A key pathophysiological feature of ALS is cortical hyperexcitability, reflecting a disturbance in the balance between excitation and inhibition (E/I) within cortical networks. Paired-pulse transcranial magnetic stimulation (ppTMS) has been instrumental in demonstrating this abnormality, but its use becomes challenging as the disease progresses, due to rising stimulation thresholds and the motor cortex inexcitability.

Electroencephalography (EEG) offers a non-invasive alternative for probing cortical function by measuring neuronal oscillations. Interactions between slow and fast rhythms of EEG, known as cross-frequency coupling (CFC), are increasingly recognized as markers of brain network dynamics. One specific form, phase–amplitude coupling (PAC), captures how the amplitude of faster oscillations is modulated by the phase of slower rhythms. Importantly, PAC has been linked to E/I regulation and found to be altered in several neurological and psychiatric disorders where the E/I balance found to be disrupted. Early studies suggest that PAC may also differentiate ALS patients from healthy individuals, making it a promising biomarker candidate. However, direct evidence connecting PAC to cortical E/I balance is still limited, and methodological variability hampers its clinical adoption.
This doctoral work aims to advance the development of PAC as a biomarker in ALS. First, we examine the relationship between PAC and cortical E/I balance. Next, we assess methodological variability of PAC in a cohort of ALS patients and controls. We then propose standardized analytical approaches to improve the robustness and reproducibility of PAC measures. Finally, we present our prototype of a user-friendly, server-based platform designed to make EEG and PAC analyses more accessible for clinical and translational research. Together, these studies highlight PAC as a potential non-invasive biomarker of cortical dysfunction in ALS and lay the groundwork for its future applications.
Key words: ALS, EEG, excitation-inhibition balance, cortical hyperexcitability, phase-amplitude coupling (PAC).
Acknowledgments: ANR grant (ANR-21-CE37-0033-02-FREQUALS), FILSLAN 4th year PhD funding.

- **Neurodevelopmental epigenetic alterations prime cortical neurons to dysfunction and degeneration in ALS mouse models**

Hernan-Godoy M (1), Diebold A (1), Stuart-Lopez G (1), Gorin C (1), Devignot V (1), Grosch S (1), Dieterle S (1), Kessler P (2), Brouard N (3), Le Gras S (4), Jost B (4), Andry V (5), Goumon Y (5), Rouaux C (1)

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ALS mostly manifests during adulthood, implicitly suggesting that it hits the fully mature central nervous system. However, the evidence of a long prodromal phase, the existence of juvenile forms, and the developmental roles of genes implicated in familial cases suggest that ALS may take its root during development [1]. Of note, neurodevelopmental and neurodegenerative diseases share several mechanisms, including alterations in one-carbon metabolism (1Cmet). 1Cmet intertwines the folate and methionine cycles, is controlled by four key enzymes (DHFR, MTHFR, MAT2A and AHCY), and is central to purine synthesis and cellular proliferation, and to methylation and epigenetic regulation [2]. This project aims at investigating whether ALS might arise from neurodevelopmental 1Cmet impairments, focusing on the motor cortex and the upper motor neurons using various omics approaches in the genetically and phenotypically complementary *Sod1*^{G86R} and *Fus*$^{+/\Delta NLS}$ mouse models of ALS. Using RNAscope, we reveal that *Dhfr* expression is significantly increased in cortical progenitors of both ALS mouse models at the time when they generate upper motor neurons. Cellular proliferation was unaltered, as assessed by BrdU labelling, DNA content analysis and immunofluorescence, suggesting that increased *Dhfr* expression might affect other cellular mechanisms, such as epigenetic regulation of gene expression. Metabolomic analyses

revealed increased methylation index in developing cortex of *Sod1*^{G86R} mice. Epigenetic Cut&Tag analyses of cortical progenitors from *Sod1*^{G86R} and *Fus*$^{+/\Delta NLS}$ embryos using H3K4me3 and H3K27me3 epigenetic marks are ongoing. Preliminary data reveal altered synaptogenesis, DNA damage and neurodegeneration pathways, suggesting that, prior to their birth cortical neurons may already be primed to dysfunction and degeneration.

References:
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Key words: neurodevelopment, 1C metabolism, epigenetics

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C1 CONFERENCE

Somatic mutations in neurodegeneration

Jochen WEISHAUPT

Ulm

SESSION 1

Moderation: Aurore BERNARDIN and David BRENNER

- **Presentations selected from abstracts submitted**

OC 1.1 - Metabolic alterations in presymptomatic ALS gene carriers

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Background: The emergence of potentially effective new therapies for genetic forms of amyotrophic lateral sclerosis (ALS) necessitates the identification of biomarkers to facilitate early treatment, prior to the onset of motor symptoms. We sought to investigate whether metabolic alterations are detectable in presymptomatic ALS gene mutation carriers.

Methods: Between 02/2014 and 06/2025, we prospectively studied 250 presymptomatic ALS gene mutation and individuals from the same families without pathogenic mutations as controls. Bioimpedance analysis (BIA) and indirect calorimetry were performed, and Body Mass Index (BMI), Fat Mass (FM), Body Fat Percentage, Body Water (BW), Lean Body Mass (LBM), Extracellular Mass (ECM), Body Cell Mass (BCM), ECM/BCM ratio, Cells Percentage, Phase Angle, Resting Metabolic Rate (RMR), Metabolic Ratio (MR), and NfL were measured.

Findings: A subset of 133 individuals has been previously published[1], showing that presymptomatic ALS gene carriers showed reduced LBM ($p = 0.02$), BCM ($p = 0.004$), Cells Percentage ($p = 0.04$), BW ($p = 0.02$), Phase Angle ($p = 0.04$), and increased ECM/BCM ratio ($p = 0.04$), consistently indicating a loss of metabolically active body cells. While in C9orf72 mutation carriers all tissue masses were reduced, only metabolically active tissue was affected in SOD1 mutation carriers. Unexpectedly, RMR ($p = 0.009$) and MR ($p = 0.01$) were lower in presymptomatic ALS gene carriers compared to non-carriers. In addition to these data, new longitudinal data from a validation cohort (n=250) will be presented.

Interpretation: The observed metabolic phenomena might reflect reduced physical activity and/or preemptive, insufficient compensatory mechanisms to prepare for the later hypermetabolic state. As pre-symptomatic biomarkers we propose ECM/BCM ratio and Phase Angle for SOD1, and a 4-compartment affection in BIA for C9orf72 mutation carriers.

Funding: This work was an investigator-initiated trial without institutional or industrial funding.

1. Dorst J, Weydt P, Brenner D, et al. Metabolic alterations precede neurofilament changes in presymptomatic ALS gene carriers. *EBioMedicine* 2023; **90**(104521): 104521.

OC 1.2 - FUS orchestrates metabolic processes associated with ALS pathophysiology offering therapeutic approaches

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ABSTRACT

Mutations in the Fused in Sarcoma (FUS) gene are associated with a juvenile-onset form of Amyotrophic Lateral Sclerosis (FUS-ALS), characterized by rapid and severe motor neuron degeneration. In this study, we characterized a fus knockout zebrafish ***fus$^{-/-}$*** model that recapitulates key pathological features of ALS, including progressive paralysis, increased larval mortality, disrupted muscle fiber architecture, and compromised mitochondrial network integrity. To investigate the metabolic consequences of FUS loss, we adopted a multi-model approach encompassing ***fus$^{-/-}$*** zebrafish, ***Fus$^{\Delta NLS/+}$*** murine skeletal muscle, ***Fus*-**depleted myoblasts, and edited mutant ***FUS*** human motor neurons. Our comprehensive analyses revealed defects in carnitine-mediated fatty acid transport and a reduction in tricarboxylic acid (TCA) cycle intermediates. Mechanistically, we identified *FUS* as a key regulator of muscle metabolism, essential for activating the *PPAR-α* signaling pathway, including downstream targets such as *acsl4, acsl5, and apoa1a*. Importantly, treatment with acetyl-L-carnitine (ALC) in ***fus$^{-/-}$*** zebrafish significantly rescued motor function and survival, while fenofibrate, a PPAR-α agonist, improved motor phenotypes, supporting the therapeutic potential of targeting this pathway. To strengthen the clinical relevance of our findings, we analysed fibroblasts derived from a **juvenile ALS patient carrying the FUS_G504W*fs12 mutation. This** de novo mutation led to familial ALS (fALS) with an early onset at 11 years of age, presenting a severe paralytic phenotype. Early disease progression was characterized by significant weight loss and muscle atrophy. Biochemical analyses of cerebrospinal fluid (CSF) and blood samples revealed elevated glucose and lactate levels. Notably, we detected an early and consistent downregulation of key nucleotide metabolitessuggesting increased energy expenditure and/or impaired nucleotide biosynthesis. This **hypermetabolic signature** closely mirrored the metabolic phenotype observed in both our *fus*-deficient zebrafish and patient-derived motor neuron models. Together, these findings establish FUS as a key modulator of muscle metabolic homeostasis and identify promising metabolic targets for therapeutic intervention in FUS-ALS.

Key words: FUS-ALS; zebrafish model; mitochondrial dysfunction.

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OC 1.3 - Elevated Type I Interferon Signaling Is a Shared Feature of Genetic ALS and Is Attenuated by JAK Inhibition in FUS-Mutant iPSC-Derived Motor Neurons

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Abstract:
Aberrant activation of the innate immune system has been observed in genetic forms of amyotrophic lateral sclerosis (ALS), including those caused by mutations in SOD1, TARDBP, and C9orf72, often involving the TBK1-IRF3 signalling pathway (1-3). In this study, we examined whether similar immune-related mechanisms are present in ALS caused by FUS mutations. Using isogenic and non-isogenic FUS-mutant (FUSmut) iPSC-derived spinal motor neurons (sMNs), we found upregulation of interferon-stimulated genes (ISGs) and activation of the TBK1-IRF3 pathway. FUSmut sMNs showed accumulation of cytosolic double-stranded RNA (dsRNA) and its sensor RIG-I, with RIG-I knockdown reducing IFN type I signalling. In contrast, MDA5 was not altered. IFN treatment of FUS wild-type (FUSwt) sMNs mimicked axonal degeneration seen in FUSmut sMNs. Mitochondrial dsRNA, rather than cytosolic DNA damage, appeared to contribute to this response, with axonal RNA sequencing revealing upregulated mitochondrial transcription in FUSmut sMNs. Inhibiting mitochondrial transcription reduced ISG expression, and treatment with the JAK-STAT pathway inhibitor ruxolitinib both lowered ISG levels and alleviated neurodegeneration.

To explore translational potential, we analysed blood samples from genetic ALS patients and found that 55.5% had elevated IFN scores, most prominently among C9orf72HRE carriers (78.9%) and a subset of FUS-ALS patients (45%). No significant IFN activation was detected in SOD1-ALS patients. Importantly, IFN scores in blood correlated with clinical progression, suggesting a link between innate immune activation and disease severity.

These findings support a role for RIG-I-mediated innate immune signalling in the pathophysiology of FUS-ALS and suggest that ISG expression, found both in vitro and in patient blood, may serve as a potential mechanistic biomarker. This pathway may offer opportunities for patient stratification and therapeutic intervention in genetically defined ALS subgroups.

Key words: IFN-1; cGAS-STING pathway**;** RIG-I/MAVS;

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OC 1.4 - Longitudinal changes at 36 months in the spinal cord of asymptomatic carriers of the *C9Orf72* pathogenic variant

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Background:
C9orf72-related disorders are a leading genetic cause of frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) [1]. Spinal cord (SC) involvement is increasingly recognized in disease progression, but early biomarkers remain elusive [2]. This study investigates structural changes using multiparametric SC MRI in asymptomatic *C9orf72* mutation carriers.

Methods:
A 36-month longitudinal study was conducted in 40 asymptomatic *C9orf72* carriers, 32 non-carrier first-degree relatives, and 30 healthy controls. MRI-based grey matter (GM) and white matter (WM) cross-sectional areas and diffusion tensor imaging (DTI) parameters were analyzed. Longitudinal changes were assessed using linear mixed-effects models (LMEM), and phenoconversion predictors were identified via Random Forest analysis.

Results:
At baseline, all subjects were asymptomatic. One individual phenoconverted to ALS/FTD at M36, while three were classified as prodromal. Progressive GM atrophy was observed in C9+ carriers at C4-C6 levels, extending to C7 at later stages. GM decline emerged as the strongest predictor of phenoconversion, indicating early lower motor neuron degeneration. WM degeneration and FA reduction in the corticospinal tracts were also detected, suggesting progressive motor system involvement.

Conclusion:
SC MRI is a valuable tool for tracking disease progression in *C9orf72* carriers, particularly for the prediction of phenoconversion. GM atrophy is a key marker of motor neuron degeneration, emphasizing the need for refined biomarkers to guide early interventions.

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Keywords: *C9orf72*, spinal cord MRI, asymptomatic carriers.

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OC 1.5 - Tear fluid production in motor neuron diseases – the multicentric TEAR-ALS study

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Tear fluid (TF) production is regulated by parasympathetic innervation originating in the brain stem, a region often affected in MND. Diminished TF production was previously shown to be present in different neurological diseases, including MND [1], and may represent an underreported non-motor feature in ALS. The TEAR-ALS study was a multicentric, prospective study collecting TF and clinical data from a total of 1020 individuals in Germany and Switzerland from January 2020 to January 2024. TF was collected using an unanaesthetised 5-minute Schirmer test and wetting length (WL) served as quantitative measure of TF production. Patients with ALS and other MND were included together with healthy control probands (HC). Multiple linear regression models correcting for age and sex as confounders were used to compare WL. A total of 588 ALS, 25 HSP, 61 SMA, 4 SBMA patients as well as 342 HC were included in the study. While most patients in the ALS subgroup were classified as "classical ALS" (n = 384), patients with flail-arm (35) or -leg syndrome (12) as well as PLS (30), PBP (42) or PMA (70) were also included. WL was significantly different between groups showing higher values in HC (27.8 ± 20.7 mm/5 min) and SMA (35.1 ± 22.5) compared to ALS (21.4 ± 17.9) and HSP (21.1 ± 16.3) groups. Within the ALS subgroup, PMA showed significantly higher TF production compared to all other subtypes. The site of onset was not significantly influencing WL. Taken together, TF production

is reduced in MNDs with upper motor neuron (ALS and HSP compared to HC) but not lower motor neuron (PMA compared to ALS, SMA compared to HC) involvement. This study provides additional evidence for autonomic involvement in MNDs with upper motor neuron involvement and raises the attention for a treatable non-motor symptom.

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Key words: Tear fluid, non-motor symptom, clinical phenotypes

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OC 1.6 - Contribution of neutrophils and extracellular DNA traps to Amyotrophic Lateral Sclerosis pathogenesis

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Purpose: Chronic inflammation of the central nervous system (CNS) associated with dysregulation of peripheral immunity has been identified as a hallmark of amyotrophic lateral sclerosis (ALS).[1] Among these alterations, an elevated neutrophil-to-lymphocyte ratio has been correlated with accelerated disease progression and reduced patient survival.[2] Despite their abundance in peripheral blood and central role in inflammation, the contribution of neutrophils to ALS pathophysiology remains insufficiently explored. Neutrophils are the first line of defense against invading pathogens and initiate the inflammatory response. NETosis is one of their defense mechanism that leads to the formation of « Neutrophil Extracellular Traps » (NETs), web-like chromatin structures attached with cytosolic granule enzymes and histones. NETs serve to trap, neutralize, and eliminate invading pathogens. Neutrophils and NETs have attracted more attention recently in the context of chronic inflammation including neurodegenerative disease.[3] This study aims to clarify the role of neutrophils and NETs in ALS progression.
Methods: Using flow cytometry, we analyzed circulating neutrophils in both ALS patients and the $SOD1^{G93A}$ mouse model. The presence of infiltrating neutrophils and NETs in the spinal cord was assessed via imaging and flow cytometry. NET formation and their potential cytotoxicity toward motoneurons were investigated in vitro using a Live-Cell Analysis System.
Results: ALS patients exhibited a significantly increased neutrophil-to-lymphocyte ratio and a higher frequency of immunosuppressive neutrophils ($CD16^{high}$ $CD62L^{dim}$). In the SOD1G93A mouse model, we observed spinal cord infiltration by neutrophils, lymphocytes, and NETs. Moreover, neutrophils isolated from terminal-stage ALS mice displayed an enhanced capacity to form NETs in vitro.
Conclusion: Our findings support a potential contribution of neutrophils and their extracellular traps to ALS pathology, highlighting them as possible players in disease progression.

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Keywords: amyotrophic lateral sclerosis, neuroimmunity, neutrophils.
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OC 1.7 - First results of a multicenter european cohort study to evaluate therapeutic and prognostic effects in *SOD1*-ALS patients treated with tofersen

Wiesenfarth M (1), Ludolph AC (1,2), Elmas Z (1), Günther K (1), Müller K (3), Regensburger M (4,5), Petri S (6), Grosskreutz J (7), Reilich P (8), Schöberl F (8), Hagenacker T (9), Weyen U (10), Günther R (11,12), Haarmeier T (13), Weydt P (14,15), Conrad J (16), Lingor P (17,18), Meyer T (19,20), Hermann A (21,22), Koritnik B (23,24), Löscher W (25), Cetin H (26,27), Caravaca-Puchades A (28), González-Mingot C (29), Carbonell-Corvillo P (30), Lorente Gómez L (31), Díaz Marín C (32), Navarrete MA (33), Brenner D (1,2), Schuster J (1,2), Tumani H (1,2), Weishaupt JH (1,2), Kuźma-Kozakiewicz M (34), Vázquez-Costa JF (33,35,36), Dorst J (1,2), MND-Net working group

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Pathogenic variants of the *SOD1* gene occur in approximately 2% of sporadic and 11% of familial [1] ALS cases in Europe with heterogeneous clinical phenotypes and differences in prevalence across regions. After the VALOR study and its open label extension [2] demonstrated a reduction of neurofilament light chain (NfL) levels through treatment with the antisense oligonucleotide (ASO) tofersen, tofersen was approved by the FDA in 2023 and by the EMA in 2024. In the German MND-Net, we have scientifically accompanied a large cohort (n = 24) of *SOD1*-ALS patients within the framework of the German Early Access Program and found a significant reduction of NfL serum levels, the phosphorylated neurofilament heavy chain (pNfH) in CSF, and in disease progression [3]. It can be assumed that the clinical effects follow a specific sequence starting with modification of mechanistic and degenerative biomarkers and, subsequently, functional outcomes. As a potential side effect a clinical silent autoimmune inflammation of the central nervous system was observed in the majority of patients [3]. However, despite of the huge evidence of positive therapeutic effects, there are still open questions that need to be answered in the near future, including the assessment of a long-term therapeutic effect, the kinetics of neurodegeneration biomarkers and the occurrence of adverse events. As a small subgroup does not respond in ALSFRS-R score and progression rate, it has to be discussed whether this group actually represents “non-responders” or whether the treatment duration was still too short to demonstrate a clinical effect. With the aim to answer these open questions, we

performed a observational multi-center cohort study to evaluate therapeutic and prognostic effects in *SOD1*-ALS patients under tofersen treatment. We will present first results of long-term effects in a European „real-world“ cohort, including disease progression, biomarkers and correlation analysis with clinical features and genotypes.

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Keywords: SOD1, tofersen, antisense oligonucleotide
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OC 1.8 - Amyotrophic Lateral Sclerosis: what impact of the mitochondrial genome?

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Recently, Cheng and colleagues identified a mitochondrial DNA (mtDNA) deletion in 20 out of the 40 patients with sporadic amyotrophic lateral sclerosis (ALS) (*Cheng et al., Nat. Neurosc. 2025*) [1]. This variant -affecting a gene encoding a subunit of complex IV (CIV)- was detected at 1% heteroplasmy in blood samples. Previously, we demonstrated that mutations in the ***CHCHD10*** gene cause a mitochondrial disease associated with familial ALS (*Bannwarth et al., Brain 2014*) [2]. The study by Cheng and colleagues confirms these findings by showing that complex IV deficiency in rat motor neurons leads to an ALS phenotype.

The starting point of their article is the identification of the “6692A deletion” in 20 of the 40 patients (50%) with sporadic ALS. This mtDNA variant, designated **m.6698delA** according to current nomenclature, is located in the ***MT-CO1*** gene, which encodes a subunit of complex IV [1]. The authors detected this variant at very low heteroplasmy levels (1–1.2%) in blood samples from affected individuals. Secondary mitochondrial abnormalities in ALS and other neurodegenerative diseases are well documented. However, this observation raises questions about the actual prevalence of this mitochondrial variant and its potential causal link to sporadic forms of ALS.

To address this, we screened for variants in the mitochondrial genes encoding complex IV subunits using next-generation sequencing (NGS) in a cohort of 1,914 patients referred to our reference center at Nice University Hospital for suspected mitochondrial disease. Our results show that such variants, including **m.6698delA,** are not associated with an ALS phenotype and are extremely rare in both muscle and blood (0.8%). In this cohort, patients presenting an ALS-like phenotype did not carry variants in the ***MT-CO*** genes.

Taken together, these data raise the question of the mitochondrial genome's involvement in ALS.
Keywords: ALS, mtDNA, mitochondrial complex IV
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OC 1.9 - Motor phenotypes of ALS – a classification based on the region of onset, propagation, and the degree of UMN and LMN dysfunction

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Background:

In amyotrophic lateral sclerosis (ALS), heterogeneity of motor phenotypes is a fundamental hallmark of the disease. Distinct ALS phenotypes were associated with a different progression and survival. Despite its relevance for clinical practice and research, there is no broader consensus on the classification of ALS phenotypes.

Methods:

An expert consensus process for the classification of ALS motor phenotypes was performed from May 2023 to December 2024. A three-determinant anatomical classification was proposed which is based on the 1) region of onset (O), 2) the propagation of motor symptoms (P), and 3) the degree of upper (UMN) and/or lower motor neuron (LMN) dysfunction (M). Data collected in clinical practice of three ALS centers will be obtained and aggregated.

Results:

Onset phenotypes differentiate the site of first motor symptoms: O1) head onset; O2d) distal arm onset; O2p) proximal arm onset; O3r) trunk respiratory onset; O3a) trunk axial onset; O4d) distal leg onset; O4p) proximal leg onset. Propagation phenotypes distinguish the temporal propagation of motor symptoms from the site of onset to another, vertically distant body region: PE) earlier propagation (within 12 months of symptom onset); PL) later propagation (without propagation within 12 months of symptom onset), including the established phenotypes of “progressive bulbar paralysis” (O1, PL), “flail-arm syndrome” (O2p, PL), and “flail-leg syndrome” (O4d, PL); PN) propagation not yet classifiable as time since symptom onset is less than 12 months. Phenotypes of motor neuron dysfunction differentiate the degree of UMN and/or LMN dysfunction: M0) balanced UMN and LMN dysfunction; M1d) dominant UMN dysfunction; M1p) pure UMN dysfunction (“primary lateral sclerosis”, PLS); M2d) dominant LMN dysfunction; M2p) pure LMN dysfunction (“progressive muscle atrophy”, PMA); M3) dissociated motor neuron dysfunction with dominant LMN and UMN dysfunction of the arms and legs (“brachial amyotrophic spastic paraparesis”), respectively. The frequency of OPM phenotypes, collected in clinical practice of three ALS centers, will be presented.

Conclusion: This “OPM classification” contributes to specifying the prognosis, to defining the inclusion or stratification criteria in clinical trials and to correlate phenotypes with the underlying disease mechanisms of ALS. First data from clinical practice demonstrate feasibility and acceptance.

C2 CONFERENCE

Conference bicentenary of the birth of Jean-Martin CHARCOT

Danielle SEILHEAN and *Martin CATALA*

Presentation code: C = conference, OC = oral communication, RT = round table, P = poster

C3 CONFERENCE

Cross-species multi-omic to prioritize disease modifier and new ALS genes

Salim MEGAT

Strasbourg Translational Neuroscience & Psychiatry STEP

SESSION 2

Moderation: Maximilian WIESENFARTH and Marina HERNAN-GODOY

- **Presentations selected from abstracts submitted**

OC 2.1 - Spinal cord atrophy contributes to disease aggressiveness in Amyotrophic Lateral Sclerosis

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Purpose: To investigate the link between cervical spinal cord levels atrophy and disease aggressiveness in amyotrophic lateral sclerosis (ALS).
Methods: 3D-T2w spinal cord MRI of 93 ALS patients and 78 age- and gender-matched healthy controls (HC) were selected from our local as well as from national (PULSE study; CATI) and international databases [1]. Spinal cord cross-sectional area (SC-CSA) was measured from C1 to T2 vertebral levels [2]. Site of onset, disease duration (DD, missing=2) and the Revised-ALS Functional Rating Scale (ALSFRS-R) were assessed. Patients were clinically differentiated into fast (n=29), intermediate (n=31) and slow progressors (n=31) according to their ALSFRS-R progression rate: (48 - ALSFRS- R)/DD.
Results: ALS patients showed significant cord atrophy compared to HC at all vertebral levels (*p-value* < 0.01). Slow progressors showed significant cord atrophy only at the upper-cervical levels (C1 to C4), while intermediate and fast progressors showed significant atrophy at all vertebral levels (all *p-values* < 0.05). SC-CSA at C6, C7 and T1 were correlated with the ALSFRS-R (*R/p* = 0.211/0.042, 0.275/0.007 and 0.241/0.019, respectively). SC-CSA at C7 was correlated with the ALSFRS-R progression rate (*R/p* = -0.208/0.046).
Conclusion: Our study suggests that spinal cord atrophy contributes to disease aggressiveness, specifically at spinal levels innervating the forearm and the hand muscles. These findings complement previous study [3], by show- ing that the combination of upper and lower motor neurone degeneration at specific CNS compartments are the primary driver of disease aggressiveness in ALS.
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Keywords: Spinal cord MRI, cord atrophy, disease aggressiveness.
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OC 2.2 - Somatic mutations in ALS genes in the motor cortex of sporadic ALS patients

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In the vast majority of patients the cause of sporadic ALS remains unclear. We hypothesized that mosaic mutations in the CNS could account for a subset of the sALS cases, which would escape detection by conventional blood genomic testing. Thus, we leveraged whole exome and targeted gene panel as well as single-cell sequencing data from ALS autopsy tissue, to explore the presence of somatic mutations in ALS. Whereas whole exome sequencing did not show an overall increase of mosaicism, deep targeted panel sequencing of known ALS disease genes from motor cortex tissue revealed enrichment of low allele frequency variants in sALS, but not in fALS with an identified monogenic cause. We found that the somatic FUS variant p.E516X, located in an established hot spot for germline ALS mutations, leads to nucleo-cytoplasmic mislocalization and aggregation typical for ALS FUS pathology. Additionally, we performed somatic variant calling on single-cell RNA-sequencing data from sALS tissue and detected an accumulation of somatic variants in excitatory neurons, suggesting a neuron-autonomous disease initiation. Collectively, using a multi-modal approach, our findings suggest that somatic mutations within the motor cortex, especially in excitatory neurons, may contribute to the development of sALS.

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OC 2.3 - In vitro modelization of ALS neuropathological signature and heterogeneity using human iPSC-derived NMJ assembloids

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Developing ALS treatments is challenging partly due to its heterogeneity and since models recapitulating all the major characteristics of the disease are missing. Most sporadic and familial cases share a common neuropathological signature, including neurofilament (NF) accumulation and TDP-43 mislocalization. ALS is also characterized by the dismantling of the neuromuscular junction (NMJ) due to the degeneration of motor neurons (MNs), leading to skeletal muscle denervation and atrophy.

Although 2D iPSC-derived MNs are already able to model some neuropathological ALS hallmarks like NF accumulations [1], our aim is to establish a more integrated 3D cellular ALS model, assembling a spinal cord organoid with a 3D muscle spheroid based on a previous protocol, using control conditions [2]. We used iPSCs from control subjects and ALS patients to generate 3D NMJ assembloids. In these NMJ assembloids, MNs interact with their cellular environment, especially with muscle cells, and thus could enable our goal of recapitulating the major disease hallmarks including MNs degeneration and muscle denervation, TDP-43 nuclear clearing and cytoplasmic protein aggregation.

Over four months of culture, we could obtain reproducible spinal cord organoids, with iPSC differentiated into MNs, interneurons, astrocytes, and oligodendrocytes. Additionally, we successfully produced iPSC-derived NMJ assembloids, which remained morphologically and functionally intact for at least three weeks post-fusion. We are currently exploring the feasibility of obtaining the main ALS hallmarks in our model and deciphering the contribution of different cellular components using matched and mismatched conditions. The purpose is to obtain a new human model to better study disease mechanisms of ALS allowing the discovery of novel pathways as targets for future therapies.

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Keywords: iPSCs, Assembloids, NMJ

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OC 2.4 - Neurodegeneration NULISA panels in ALS patients and presymptomatic subjects revealed potential diagnostic and prognostic biomarkers: a premodiALS study

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Fluid-based biomarkers show great promise for both diagnosis and prognosis of ALS disease. For example, neurofilaments are elevated in blood of ALS patients, but also prior phenoconversion in presymptomatic gene mutation carriers (PGMC) as well as in non-mutation carriers who were later diagnosed with ALS [1–3]. Aiming to identify further prognostic biomarkers across different biofluids, we performed a pilot study in 102 participants (36 early ALS, 32 presymptomatic subjects, 29 healthy controls and 5 ALS mimics) of the premodiALS study. We used the Nucleic-acid-Linked Immuno-Sandwich Assay (NULISA) technology on matched plasma, serum and CSF and analysed approximately 120 proteins from a neurodegeneration panel. We observed a moderate correlation between normalized protein quantification in serum and plasma ($R=0.68$, $p<2.2e-16$), suggesting some quite large difference between plasma and serum. We observed a stronger correlation between CSF and serum ($R= 0.16$) than between CSF and plasma ($R=0.051$). Comparing ALS patients to controls, we identified multiple regulated biomarkers, such as decreased BDNF in serum (padj=0.007) or CHIT1 in CSF (padj=0.021). NEFH, NEFL, GFAP, and pTau-217 (padj<0.05) were consistently upregulated in ALS in plasma, serum, and CSF, suggesting robust disease association. NEFH was also upregulated in the serum of PGMC (padj=0.044), mainly driven by C9ORF72 expansion carriers. In the plasma of PGMC, further proteins demonstrated trends for upregulation (pTau-217 padj=0.081, MAPT padj=0.086) or downregulation (VEGF padj=0.054) compared to controls. In the CSF the three top dysregulated proteins in PGMC vs. control were HTT (padj=0.030), TARDBP (padj=0.06) and SOD1 (padj=0.072). In

conclusion, NULISA analysis revealed characteristic signatures for ALS and PGMC in plasma, serum and CSF. These findings may help to determine which fluid-biomarkers would be more relevant for the identification of individuals at risk for ALS. We anticipate that the inclusion of data from a larger cohort will empower even more robust conclusions.

Key words: pre-symptomatic, fluid biomarker, proteins**.**

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OC 2.5 - Double-blind, placebo-controlled, exploratory randomized clinical trial to assess safety and efficacy of IFB-088 in patients with bulbar-onset ALS

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Background

IFB-088 is a multifunctional molecule targeting major cellular mechanisms implicated in amyotrophic lateral sclerosis (ALS): TDP-43 mislocalization, oxidative stress and neurodegeneration. A phase 1 study in healthy volunteers showed a favorable safety profile.

Methods

Randomized, double-blind, placebo-controlled study. Patients with bulbar-onset ALS were randomized 2:1 to IFB-088 50 mg/day plus riluzole 100 mg/day or placebo plus riluzole 100 mg/day and treated for 6 months. Primary outcome was safety. Secondary outcomes were efficacy (ALSFRS-R, ALS-MITOS, King's College (KCs) scores, slow vital capacity (SVC), quality of life, pharmacokinetics and plasma and

urine biomarker profile. Change in ALSFRS-R from baseline to 6 months was analyzed by ANCOVA model with treatment and baseline ALSFRS-R as covariates.

Results

Among 51 patients enrolled, 41 had available data at 6 months. At baseline, patients in IFB-088 arm showed higher median PR (0.5 vs 0.3), median ALSFRS-R score (43 vs 45) and mean neurofilament (NfL) levels (94.5 vs 73.4 pg/ml) compared to placebo arm. The percentage of patients with any adverse events (AEs) was 73.5% in the IFB-088 arm and 58.8% in the placebo arm. Most AEs were grade 1 or 2 (83% and 86%, respectively), while serious AEs were 23.5% in both arms. Primary analysis did not show significant differences between arms for ALSFRS-R, MITOS and KCs. *Post hoc* analysis in PP, adjusted for NfL on top of ALSFRS-R at baseline to compensate for unbalanced disease severity, showed a slower decline of both ALSFRS-R and SVC in IFB-088 arm, that reached the pre-specified 2-sided level of significance of 0.20 (p=0.11 and 0.13, respectively). TDP-43, BiP, p75ECD, neopterin, TGF-beta1, and oxidative stress marker levels were significantly lower in IFB-088 arm.

Conclusion

IFB-088 treatment was safe and well tolerated in bulbar-onset ALS patients. Encouraging signals of efficacy shown by clinical scores and biomarker assays warrant confirmatory phase 3 clinical trial.

Keywords: bulbar-onset ALS; biomarkers; icerguastat

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OC 2.6 - Discovery of a new pharmaceutical compound restoring endoplasmic reticulum and mitochondria contact via VAPB-PTPIP51 thethering

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Background: Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are clinically related neurodegenerative diseases. These pathologies are characterized by the presence of TAR DNA-binding protein 43 (TDP-43) accumulations and familial cases of ALS/FTD by mutation of the TDP-43 encoding gene. In addition, a wide range of physiological functions are altered in ALS/FTD, including many of which are regulated by signaling between the endoplasmic reticulum (ER) and mitochondria. Over the last decades, numerous studies have demonstrated that ER-mitochondria signaling is perturbed in neurodegenerative diseases and have shown that this may be a driving mechanism in the onset and progression of the disease. VAPB and PTPIP51 are ER-mitochondria tethering proteins, respectively enabling inter-organelle signaling. The VAPB-PTPIP51 interaction is disrupted in ALS /FTD, making it a key target to restore ER-mitochondria signaling. Our group identified a pharmaceutical compound as a strong candidate to act on this complex. **METHODS:** We have tested our pharmaceutical compound in *in vitro* models, neuronal cell line SH-SY5Y and primary culture of rat cortical neurons to assess its efficacy on the VAPB-PTPIP51 complex. **RESULTS:** Our preliminary data show that the compound is very well tolerated and promotes proliferation of SH-SY5Y cells. Using nanoBit technology assay, we demonstrated an increase in VAPB-PTPIP51 contact and, using proximity ligation assay, restoration of the VAPB-PTPIP51 complex in several ALS/FTD induced mutations. Moreover, preliminary results of the compound's effect on the functional test of synaptic connectivity showed an improvement in FTD/ALS condition. **CONCLUSION:** These results allow us to define the basis for a targeted intervention with our compound in ALS/FTD conditions *in vitro* and *in vivo*. Finally, they will provide new knowledge into the involvement of the ER-mitochondria in the development of the disease.

Keywords: Amyotrophic lateral sclerosis, VAPB, PTPIP51

Acknowledgments: ARUK, MRC

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OC 2.7 - A missense variant disrupting NEK1 kinase function is sufficient to cause ALS

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ABSTRACT

Heterozygous deleterious loss-of-function (LoF) variants in the *NEK1* gene encoding a pleiotropic kinase, represents a frequent genetic cause of amyotrophic lateral sclerosis (ALS). Missense variants in *NEK1* which cause ALS in a monogenic (Mendelian) fashion have not been reported yet. Here, we identified a rare missense variant in *NEK1* (p.N598S) which co-segregated in an ALS pedigree and is enriched in the ALS population. This variant showed preserved protein expression in autopsy CNS tissue, patient-derived fibroblasts and induced motor neurons and is predicted to alter post-translational glycosylation. We generated and examined isogenic hiPSC-derived motor neurons carrying the p.N598S variant, the known disease-causing LoF variant p.R812*, and wild-type NEK1 to dissect the downstream pathomechanisms that drive NEK1-ALS, which remained unclear. Both NEK1-mutant cell lines shared known phenotypes including increased DNA damage and apoptosis, and axonal and ciliary pathology. Both NEK1 variants also precipitated similar transcriptomic profiles and previously unreported features embracing autophagy impairment with p62 accumulation and mislocalization of TDP-43 which could be rescued by overexpression of wild-type NEK1 in both p.N598S- and p.R812*-mutant motor neurons indicating that physiologic localization of TDP-43 is directly linked to NEK1 kinase activity. Neuropathologic assessment of a p.N598S-mutant autopsy case confirmed abnormal TDP-43 and p62 inclusion pathologies. Since treatment with a NEK1 kinase inhibitor mimicked the aforesaid phenotypes in cultured motor neurons, we hypothesized that p.N598S may alter NEK1 kinase function. Indeed the mutant-NEK1 phosphoproteome showed pronounced dysregulation of several target proteins featuring synapsin1 and YAP1 in both p.N598S- and p.R812*-mutant motor neurons, confirming that the p.N598S disrupts the kinase function. Conclusively, a rare *NEK1* missense variant disrupting NEK1 kinase function is sufficient to cause familial ALS in monogenic fashion. Our results highlight NEK1 kinase dysfunction as the disease-causing mechanism in NEK1-ALS which informs the development of therapy strategies and functional evaluation of NEK1 missense variants of uncertain significance.

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OC 2.8 - ALS/FTD-linked TBK1 deficiency in microglia induces an aged-like microglial signature and drives social recognition deficits

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Dominant loss-of-function mutations in *TBK1* encoding for TANK-Binding-Kinase 1 have been linked to Amyotrophic Lateral Sclerosis (ALS), Fronto-Temporal Dementia (FTD) and ALS/FTD [1]. However, pathogenic mechanisms remain unclear, particularly the cell-type specific disease contributions of *TBK1* mutations. Since TBK1 is involved in autophagy and immune signaling here, we focused on cell-specific *Tbk1* deletion in motor neurons or microglial cells in mice. We found that motor neurons are remarkably resistant to TBK1 loss. Despite lifelong and increasing presence of $p62^{+}$ accumulations suggesting stalled autophagosomes, no signs of neurodegeneration or transcriptional stress responses were present, even at advanced ages. Conversely, *Tbk1* deletion in microglia strongly altered their homeostasis and reactive responses. In the spinal cord, microglial TBK1 defines homeostatic microglial density, and its deletion led to a pro-inflammatory microglial signature, but was not sufficient to induce or modify ALS-like motor neuron damage. In contrast, in the brain, microglial *Tbk1* deletion caused an early social memory defect with preserved spatial memory, indicating that microglial TBK1 deficiency drives FTD-like social recognition deficits. This phenotype is linked to an early shift to a primed microglial signature with features of ageing and neurodegeneration, indicating that TBK1 restricts aged-like microglial activation. Importantly, we found focal microglial activation in brain regions with high baseline microglial densities, including the substantia nigra *pars reticulata* and pallidum, both linked to social behavior. This microglial activation led to focal induction of the chemokine CXCL10 which was paralleled by CD8 T cell infiltration and signs of focal neuronal phagocytosis by *Tbk1* deficient microglia. Our results indicate that while microglial *Tbk1* loss is not sufficient to induce ALS-like defects and initial defects in motor neurons are likely necessary, microglial *Tbk1* loss is sufficient to lead to FTD-like behavioral defects. This reveals that microglial dysfunction alone could be responsible for part of *TBK1*-linked FTD disease.

[1] Freischmidt Axel, et al. ..., Jochen H. Weishaupt. Haploinsufficiency of TBK1 causes familial ALS and fronto-temporal dementia. Nature Neuroscience. 2015, 18(5):631-636.

Keywords: Microglia, Mouse-modeling, FTD

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OC 2.9 - In-depth Analysis of Three Randomized Controlled Trials of the German ALS/MND-Network

Joachim Schuster[1,2], Aya Dasan[1], Jens Dreyhaupt[3], Christine Herrmann[1], Kornelia Günther[1], David Brenner[1, 2], Johannes Dorst[1], Jochen Weishaupt[1, 2], and the German ALS/MND trial sites

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ABSTRACT

The clinical development of novel therapies relies on the evaluation of efficacy, safety and tolerability through phase 2 and 3 trials, conducted according to international standards. To date, riluzole, a neuroprotective drug that blocks glutamatergic neurotransmission in the CNS, is the only compound showing clinical efficacy on sporadic ALS during pivotal studies in the 1990´s. Since then, the majority of efficacy studies in ALS have failed to yield positive results, with the recent exception of tofersen, which has been approved for the treatment of SOD1-ALS in Europe. Among these negative studies are three investigator-initiated trials (IITs) conducted by the German network for ALS and motoneuron diseases between 2008 and 2017, investigating different treatment approaches: GERP-ALS (pioglitazone), RAS-ALS (rasagiline) and LIPCAL-ALS (high caloric fatty diet). Each trial used similar inclusion and exclusion criteria, aimed at creating a comparable study population, and focused on the same study endpoints. The comparative analysis of these trials aimed at identifying study parameters that can be implemented in future ALS studies to prevent methodological issues affecting the significance of the study.

The analyses of these studies revealed that A) the upper cap of slow vital capacity (SVC) at BL (inclusion criterion) does not impact the composition of study population enrolled in our RCTs. Omitting an upper limit for SVC at BL will improve and accelerate patient recruitment. B) Survival analysis in placebo patients showed differing survival probabilities between slower and faster progressing patients confirming progression rate at BL being a key stratification factor to align primary outcome parameter, observation period, and study population in future trials. C) Survival analysis of placebo patients stratified by BMI showed different survival probabilities in LIPCAL-ALS I recommend “BMI at BL” for stratification in studies aiming at improving survival by weight stabilization. D) The placebo patients in these RCTs show very similar survival probabilities qualifying for a shared placebo group and basis for digital twin approaches in future trial designs. The presentation will highlight key findings and will give an outlook on important parameters that may improve future ALS studies.

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OC 2.10 - Beneficial effect of environmental enrichment on transgenic mouse models of FTD-ALS (fusopathies): epigenetic and transcriptomic studies

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The Fused in Sarcoma (FUS) protein plays key roles in cellular functions. FUS aggregation are pathological hallmarks of neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Enriched environment (EE) can be a potential therapeutic approach for the loss of brain plasticity in ALS-FTD pathology, yet the underlying mechanisms are still unknown.

Five months transgenic mice (FUSΔNLS) expressing a truncated FUS lacking its nuclear localization signal, show memory impairments and abnormal synaptic gene responses [1,2]. We examined whether EE housing could ameliorate behavioral and molecular phenotypes in FUSΔNLS and wild-type (WT) mice. After weaning, mice were housed in either EE (Marlau cages) or standard environment (SE) for four months. Behavioral, transcriptomic, and epigenomic analyses were conducted.

EE-housed FUS mice of both sexes showed improved performance in the Morris water maze. In the Object-In-Place task, FUS EE males performed significantly better. Transcriptomic analysis revealed EE-induced activation of immediate early genes (e.g., *Arc*, *Fosb*) and *Bdnf* in the hippocampus of both genotypes. In FUS mice, EE influenced multiple pathways linked to synaptic plasticity. Epigenomic profiling done by Cut&Tag-seq for H3K4me3, a transcriptionally active marker, showed that in SE, FUS hippocampi presented with a main enrichment at genes (1493) among which synaptic-related ones, compared to WT. Yet, they were not associated with transcriptional changes, suggesting an epigenetic priming in pathological conditions. Strikingly, we found that EE induced a depletion of H3K4me3 at many genes, among which about 60% were primed in FUS mice. Interestingly, this EE-induced demethylation was also significant in WT hippocampi. These data show methylation dysfunctions in FUS pathology, partially restored by EE that induces specific demethylation of synaptic genes. They further highlight these mechanisms as a common feature of EE effect. We also describe the key methyltransferases *Kmt2a* and *Setd1b* as potential regulatory players.

[1] Scekic-Zahirovic J, et al., Toxic gain of function from mutant FUS protein is crucial to trigger cell autonomous motor neuron loss. EMBO J. 2016 May 17;35(10):1077-97. doi: 10.15252/embj.201592559.

[2] Tzeplaeff L, et al., Mutant FUS induces chromatin reorganization in the hippocampus and alters memory processes. Prog Neurobiol. 2023 Aug;227:102483. doi: 10.1016/j.pneurobio.2023.102483.

Keywords: Enriched environment, Behavior, transcriptomics & epigenomics

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ARSLA funding

ROUND TABLE: PRESYMPTOMATIC ALS GENE MUTATION CARRIERS

Moderation: Marie-Hélène SORIANI and Jochen WEISHAUPT

(3 x 15 minutes, questions integrated into the debate + 1 hour discussion)

- **RT 1: 30 years of experience with presymptomatic testing in late onset inherited neurodegeneration**
  Alexandra DURR
  Paris Brain Institute

- **RT 2: First learnings from the premodiALS study**
  Paul LINGOR
  TUM University Hospital

- **RT 3: Metabolic Alterations in presymptomatic ALS Gene Mutation Carriers**
  Johannes DORST
  RKU – University and Rehabilitation Clinics Ulm

- **RT 4: Preventing ALS, Myth or Reality, the US Experience**
  Senda AJROUD-DRISS
  Northwestern University Chicago

- **RT 5: Challenges of phenoconversion in routine clinical care**
  Maria Del Mar AMADOR
  Pitie Salpetriere Hospital Paris

POSTER SESSION

P1: In search of the temporal origin of ALS using pharmacology on a rodent model

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While ALS typically meets the criteria of late neurodegenerative diseases, evidence suggests that genetic cases might arise from infra clinical neurodevelopmental impairment. In accordance with this hypothesis, unpublished and serendipitous results obtained from a former PhD student in the $Sod1^{G86R}$ mouse model of ALS clearly show that a treatment with the antiparasitic drug ivermectin (IVM) during development fully abolishes ALS disease onset and neurodegeneration. IVM is an anthelmintic medication that antagonises an invertebrate-specific neuromuscular glutamate-gated Cl^- channel receptors, and displays allosteric modulator functions on vertebrate GABAergic, glycinergic, cholinergic and purinergic ionotropic receptors. However, these effects are limited by the low penetrance of IVM in the adult mammalian brain. Taking advantage of IVM as a tool, my PhD project aims at assessing a putative neurodevelopmental origin of genetic cases of ALS, here SOD1. To do so, I have developed paradigms to test the effects of different formulations, doses and administration windows of IVM, i.e. Prenatal, Perinatal, Early-Postnatal and Late-Postnatal, on the sensorimotor development of the $Sod1^{G86R}$ mice, along with disease onset and survival. Longitudinal weight measurements and sensorimotor assessment demonstrate early impairment of $Sod1^{G86R}$ mice compared to controls, in support of a neurodevelopmental contribution to disease pathogenesis. Survival assessment, combined with molecular measurements indicate that IVM is toxic to mouse pups in a dose-dependent manner, an effect that is likely linked to the temporal regulation of the expression of the gene encoding the P-glycoprotein that prevents IVM penetration into the central nervous system. Finally, while Prenatal and Perinatal administrations of IVM have no effect on survival, encouraging results were obtained with the Early Postnatal window. The Late Postnatal window is now being tested. This window corresponds to the so-called “critical period of brain development”, when the brain is particularly receptive to sensory stimuli, learning and experiences, and displays enhanced synaptic plasticity.

Keywords: Neurodevelopment; ALS; Critical period of brain development

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ARSLA funding

P2: *NEK1* variants in French patients with sporadic and familial Amyotrophic Lateral Sclerosis

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Background:

Variants in *NEK1* (NIMA-related kinase 1) are associated with amyotrophic lateral sclerosis (ALS) [1-2]. *NEK1* encodes a multifunctional serine/threonine kinase involved in key cellular processes, including DNA damage response, mitochondrial homeostasis, and microtubule dynamics. Identified in both sporadic and familial ALS cases, the precise contribution of *NEK1* variants as genetic risk factors or causal mutations remains to be fully elucidated [3]. In this study, we aimed to characterize the *NEK1* variants identified in a large French cohort of ALS patients.

Methods:
Blood samples were collected between 1994 and 2024 across 22 French ALS Reference Centers. The cohort comprised 450 ALS patients (200 familial index cases and 250 sporadic cases), all negative for *C9orf72* repeat expansions. Whole-exome sequencing (WES) was performed using standard protocols. WES data were screened for *NEK1* variants with a minor allele frequency (MAF) < 0.005% in dbSNP and gnomAD databases. Clinical data were retrieved from medical records.

Results:
We identified 18 rare *NEK1* variants in 21/450 patients (4.6%), including 7 females (33%). Five variants led to premature stop codons. Two patients carried an additional pathogenic variant (*SOD1* or *FUS respectively).* Age at onset ranged from 26 to 79 years (mean: 56 years). Sixteen patients (80%) exhibited spinal onset, with 10 of these cases initiating in the upper limbs. Four patients had bulbar onset (50% female; mean onset age: 45 years). Disease duration ranged from 11 months to 21 years, with most patients displaying typical survival patterns (mean: 58 months).

Conclusions:
Rare *NEK1* variants are present in the French ALS population at a frequency comparable to that reported in other cohorts [3]. Upper limb onset appears to be more frequently associated with *NEK1* variants. Further research is warranted to clarify the role of *NEK1* in the complex genetic landscape of ALS.

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3. Pensato V, Peverelli S, Tiloca C, et al. Exploring NEK1 genetic variability in Italian amyotrophic lateral sclerosis patients. J Neurol. 2025 Jun 19;272(7):469.

Keywords: NEK1, genetics, ALS

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P3: Predicting ALS survival and functional decline via metaheuristic feature optimisation

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Amyotrophic Lateral Sclerosis (ALS), a progressive neurodegenerative disease with no curative treatment and affecting motor neurons, leads to motor weakness, atrophy, spasticity and difficulties with speech, swallowing and breathing. Accurately predicting disease progression and survival is crucial for optimising patient care, intervention planning and informed decision-making. Methods: Data were gathered from the PRO-ACT database (4659 patients), clinical trial data from ExonHit Therapeutics (384 patients), and the PULSE multicentre cohort aimed at identifying predictive factors of disease progression (198 patients) [1]. Machine learning (ML) techniques including Logistic/Linear Regression (LR), K-Nearest Neighbours, Decision Tree, Random Forest and Light Gradient Boosting Machine (LGBM) were applied to forecast ALS progression using ALS Functional Rating Scale (ALSFRS) scores and patient survival over one year [2]. Models were validated using 10-fold cross-validation, while Kaplan-Meier estimates were employed to cluster patients according to their profiles. To enhance the predictive accuracy of our models, we performed feature selection using ANOVA and Differential Evolution (DE) [3]. Results: LR with DE achieved a balanced accuracy of 76.05% on validation (ranging from 68.6% to 79.8% per fold) and 76.33% on test data, with an AUC of 0.84. With Kaplan-Meier estimates, we identified five distinct patient clusters (C-Index = 0.8; log-rank test p-value ≤ 0.0001). Additionally, LGBM predictions for ALSFRS progression at 3 months yielded an RMSE of 3.14 and an adjusted R^2 of 0.764. Conclusion: This study showcases the potential of ML models to provide significant predictive insights in ALS, enhancing the understanding of disease dynamics and supporting patient care.

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Keywords: machine learning, feature selection, metaheuristics

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Conflicts of interest: None declared

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P4: Role of mutated FUS in nucleolar homeostasis

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Nucleolar homeostasis is crucial for numerous cellular processes and overall cell health. However, the key molecular regulators involved in maintaining this homeostasis remain largely unknown. Recently, our team identified a novel role for the Survival of Motor Neuron (SMN) protein in preserving nucleolar integrity following DNA repair [1]. Building on this finding, our current research focuses on identifying SMN-interacting partners that may contribute to nucleolar homeostasis, with the aim of elucidating their specific roles in this process. Among these candidates, FUS (Fused in Sarcoma) has emerged as a particularly interesting protein, as it is known to interact with SMN [2] and is mutated in cases of amyotrophic lateral sclerosis (ALS) [3].

Interestingly, we demonstrate that FUS is retained at the nucleolar periphery following DNA damage induced by UV irradiation, as well as upon transcriptional inhibition by RNA polymerase II. In order to verify that FUS is important for nucleolar homeostasis, we developed a doxycycline-inducible cell line that allows for the controlled reduction of FUS protein levels. In this cell line the depletion of FUS has an impact in the reorganization of the nucleolus after a cellular stress. However, in neurodegenerative diseases, the issue is typically not a loss of FUS, but rather mutations that lead to its mislocalization within the cell. This dysfunction is notably implicated in disorders such as amyotrophic lateral sclerosis (ALS). To investigate this, we transfected doxycycline-inducible shFUS cells with plasmids expressing various ALS-linked FUS mutants. As with FUS-deficient cells, we investigated the impact of FUS mutations on nucleolar reorganization, with a particular focus on the behavior of SMN and RNA polymerase I (Pol I) proteins.

Key words : FUS mutation, nucleolar homeostasis, damage

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P5: Role of mitophagy in CHCHD10-related motor neuron disease

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Keywords : Motor Neuron Disease, Mitochondria, Mitophagy

In neurons, complex mechanisms are required to transport and deliver mitochondria at regions of high metabolic demands such as neuromuscular junctions. The mitochondria must then be transported retrogradely to the soma for elimination, this process is called mitophagy. Mitophagy dysregulation, leading to accumulation of damaged mitochondria, is a key player in neurodegeneration. The identification of a point mutation (p.S59L) in the *CHCHD10* gene was the first genetic evidence that mitochondrial dysfunction can trigger motor neuron disease (MND) (Bannwarth et al., 2014). In drosophila, the expression of the p.S59L variant induces a chronic activation of the *PINK1*-mediated mitophagy (Nam Chul Kim et al., 2021). Furthermore, *PINK1* inactivation rescues mitochondrial network fragmentation and cristae abnormalities in *CHCHD10*$^{S59L/+}$ patient fibroblasts.

We generated *Chchd10*$^{S59L/+}$ mice that reproduce amyotrophic lateral sclerosis (ALS) features and other symptoms found in patients, including mitochondrial cardiomyopathy and myopathy. To understand the role of mitophagy in *CHCHD10*-related disease, these animals were crossed with MitoQC mice,

known to render visualizable the mitophagy process *in vivo* (Ganley et al., 2016). Interestingly, when we evaluated brain, heart and muscle of *Chchd10*$^{S59L/+}$ mice after crossing with MitoQC animals, mitophagy levels were highly increased in these energy-intensive tissues compared to control mice. But surprisingly, mitophagy levels in motor neurons (MNs) from lumbar spinal cord and in neuromuscular junctions of these mice were comparable to the control animals. To decipher if mitophagy levels could impact MN death, we analyzed *CHCHD10*$^{S59L/+}$ patients iPSCs-derived MNs. Mutant MNs seemed to be resistant to basal and induced mitophagy compared to control cells. The next stage of the project aims to determine why MNs expressing the p.S59L mutation appear "refractory" to *PINK1*-dependent induction of mitophagy and what the consequences are in terms of neurodegeneration.

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P6: Predicting ALS progression with AI: insights from clinical and biological markers

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The aim of this work is to predict the amyotrophic lateral sclerosis (ALS) progression in patients from clinical and biological data using artificial intelligence algorithms. We estimate patients' health state evolution three months ahead and identify the medical features most correlated with disease progression.

We draw our data from PROACT [1], the largest public database on the disease, which aggregates data from 23 international clinical trials and contains clinical and biological information, such as doctors assessment, urine and blood tests, on 11675 patients. Our predictions are based on the ALSFRS-R 48-level scale [2] (higher is better health), the reference scale for SLA assessment.

We trained "Random Forest" models, which are known to perform well with relatively small patient cohorts characterized by hundreds of variables. Their sensitiveness to missing data led us to design a time-interval grouping system, aggregating patient observations into 3-month periods, aligned with clinical follow-up recommendations. We trained three successive models using the first one, two, or three intervals to predict the next. Our results are compared to baseline regression methods (linear and non-linear).

Our Random Forest model consistently outperforms the regression methods tested, showing that AI can be effective in this context. In the worst of the three interval-based models, we achieved a mean absolute error (MAE) below 2.47 in predicting ALSFRS-R scores three months ahead. The coefficient of determination (R^2) exceeds 83%, meaning our model closely follows actual disease progression in most cases.

Beyond raw predictions, we use Random Forest to identify the most discriminating variables in the model's decision-making process, to enhance its interpretability and improve ALS clinical follow-up. Notably, biological markers such as "Creatinine", "Creatine kinase", and "Bicarbonate" emerge as relevant predictors of disease progression. Ongoing work focuses on further reducing prediction errors to better understand disease progression and strengthen confidence in the model's key predictors.

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Keywords**:** Amyotrophic lateral sclerosis, Artificial intelligence, Biomarkers

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P7: *CREB3*^{r119g} drives neuronal resilience in Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disorder characterized by the loss of glutamatergic corticospinal neurons (CSN) and cholinergic motoneurons (MN). It results in muscular weakness, fasciculations and atrophy that eventually lead to respiratory failure. ALS is mostly sporadic in 90% of cases, but genetics is expected to highly contribute to disease onset and progression. Indeed, genome wide association studies (GWAS) identified a few genetic disease modifiers, mostly associated with a negative outcome, and demonstrated that ALS is primarily a disease of excitatory glutamatergic neurons. We reasoned that at least a subpart of genetic disease modifiers may directly modulate the molecular pathways selectively activated in vulnerable neurons as the disease progresses, and concentrated on CSN for their selective vulnerability and glutamatergic identity.

Using comparative cross-species single cell transcriptomics from mouse models and human ALS patients, we showed that disease vulnerable neuronal populations undergo ER stress and altered mRNA translation. Importantly, we identified the transcription factor CREB3 and its regulatory network as a resilience marker of neuronal dysfunction in ALS [1]. Using genetic and epidemiologic analyses we further identified the rare variant *CREB3*^{R119G} (*rs11538707*) as a new disease modifier in ALS that decreases both the risk of developing ALS and the progression rate of ALS patients [1]. Our project now aims at determining the mechanisms of neuronal resilience activated by *CREB3*^{R119G}. To this end, we will seek to identify the impact of the R119G mutation on the CREB3 activity and the TDP-43 function in immortalized human cells and iPSC derived motor neurons. This study will characterize how the *CREB3*^{R119G} mutation protects motor neurons and tie these pathways to TDP-43.

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Keywords: ALS, CREB3, iPSC

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P8: A FUS-dependent gene network underlies cognitive and behavioral impairment in ALS

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Amyotrophic lateral sclerosis (ALS) is the most common adult-onset motor neuron disease, typically emerging in the 5th or 6th decade of life. It progresses rapidly, leading to fatal paralysis within two to three years. While ALS is primarily a motor disorder, up to 50% of patients also experience cognitive (ALS-ci) or behavioral (ALS-bi) impairments, with some developing frontotemporal dementia (ALS-FTD). This clinical continuum between ALS and FTD is supported by shared pathological features, particularly abnormal TDP-43 protein aggregation, as well as common genetic risk factors. However, the specific mechanisms underlying cognitive and behavioral involvement in ALS remain unclear.

In our study, we identified mislocalization of the RNA-binding protein FUS in cortical projection neurons (CPNs) of ALS-ci patients, but not in those without cognitive impairment. Importantly, using a novel mouse model, we demonstrated that this FUS mislocalization alone is sufficient to cause cognitive and behavioral deficits, without affecting motor function, even after one year. This suggests that FUS mislocalization in cortical neurons may be a key driver of cognitive impairment in ALS, occurring independently of the motor symptoms.

A second major finding of our study is that FUS mislocalization is linked to genetic risk factors for ALS-ci and ALS-bi. By using a cross-species approach, we identified a network of genes regulated by FUS, including FBXO16 and WWOX, whose variants are associated with ALS-related cognitive and behavioral impairments. Notably, individuals carrying protein-truncating variants of FBXO16 exhibit behavioral and neuroanatomical abnormalities consistent with ALS-bi, further reinforcing the role of these genes in the disease.

Overall, our results highlight that FUS mislocalization should be systematically considered in the pathological characterization of ALS-ci/bi patients, and more broadly, in neurodegenerative diseases involving cognitive and behavioral symptoms. This study provides new insights into the molecular mechanisms driving cognitive dysfunction in ALS and its genetic underpinnings.

Keywords: ALS-FUS, gene network, cognitive impairment

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P9: Molecular assessment of the developmental "GABA switch" in the cerebral cortex of the fus$^{\Delta NLS/+}$ mouse model of ALS

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With reported paediatric and juvenile cases, and the neurodevelopmental roles of several ALS-related genes [1], some genetic cases of ALS might have a neurodevelopmental origin. This is particularly true for *FUS*, whose mutations are responsible for juvenile cases in humans, perinatal lethality in *Fus$^{\Delta NLS/\Delta NLS}$* homozygous mice [1], and brain development defects in *Fus$^{\Delta NLS/+}$* heterozygous mice [2]. In addition,

adults, *Fus*$^{\Delta NLS/+}$ mice present with cortical hyperexcitability and impaired cortical GABAergic synapses [2]. Together, these are reminiscent of an alteration of the developmental "GABA switch", during which GABA signalling switches from depolarizing to hyperpolarizing, a crucial mechanism for proper brain development [3]. To test a putative contribution of impaired GABA switch to FusALS, I employed molecular analyses of the motor cortex of *Fus*$^{\Delta NLS/+}$ mice at different developmental time points. My results show altered gene and protein expression of the two main actors of the GABA switch: the chloride importer NKCC1 and the chloride extruder KCC2. In addition, they highlight altered gene and protein expression of key regulators of KCC2 transcription, such as MECP2 and EGR4, as well a key-partners of KCC2 protein network such as OXTR and NETO2, some of them being direct splicing targets of FUS protein. The subunit composition of the $GABA_A$ receptor, that evolves during development and is altered in ALS [2], was also assessed, but only discrete modifications were found. Taken together, my results indicate that early molecular and cellular alterations take place in the developing cerebral cortex of *Fus*$^{\Delta NLS/+}$ mice, more particularly at the time of birth, which coincides with the timing of the GABA switch, and suggest that this critical mechanism may be altered in the *Fus*$^{\Delta NLS/+}$ mouse model of ALS. They encourage broader and non-biased molecular and cellular approaches that I now develop as a PhD project.

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Key words: Neurodevelopment, Fus, GABA switch
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P10: Mass spectrometry-based strategy for detection and characterization of Cu/Zn superoxide dismutase (SOD1)

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Cu/Zn superoxide dismutase (SOD1) is a homodimeric protein responsible in the regulation of oxidative stress through the dismutation of superoxide radicals (O_2^-). SOD1 is involved in Amyotrophic Lateral Sclerosis (ALS), in particular through genetic mutations, metal-binding abnormalities and post-translational modification (PTMs) [1]. These alterations can modulate SOD1's stability, aggregation and toxicity. To address these issues, liquid chromatography-tandem mass spectrometry (LC-MSMS) is a powerful analytical technique thanks to its high sensitivity and specificity.

In this study, recombinant SOD1 protein is analyzed to define a standard peptide profile after digestion with trypsin enzyme. Assays are also performed with recombinant SOD1 protein that we have misfolded [2]. A global approach can be used to detect SOD1 in biological fluids, including mutated forms, but to characterized protein modifications and conformation, immunoaffinity enrichment method and a suitable database is required.

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Keywords: Amyotrophic lateral sclerosis, SOD1, mass spectrometry

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P11: Investigating Therapeutic Potential By Targeting Glycolytic Pathway In ALS

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Amyotrophic lateral sclerosis (ALS) is the most prevalent motor neuron degenerative disease which cause the death of the patients within 2 to 5 years after first diagnosis[1]. Due to fast disease progression, optimized modeling and investigating early disease mechanisms is needed to find more effective therapeutic targets for ALS[1]. Energy metabolic impairment, where defects in mitochondrial function have been demonstrated as an early-stage pathological feature and implicated in motor neuron degeneration in ALS[1]. Given the complexity of boosting mitochondrial energy metabolism, seeking an alternative energy supply could be a more feasible way to compensate for the unmet energy demand. As glycolysis is the major energy-generating process that can work independently from mitochondria, we hypothesis that targeting glycolytic pathway could be a potential therapeutic approach for ALS[2].

FUS is one of the most common disease-causing genes of ALS and accounts for the majority of juvenile onset cases. We have reported that *FUS* mutations, such as P525L, can cause mitochondrial dysfunction and cytoplasmic aggregation, potentially leads to energy metabolic impairment in human induced pluripotent stem cells (hiPSC) derived motor neurons[3]. In this pilot study, we investigated whether the FUS P525L mutation alters mitochondrial and glycolytic gene expression and enzymatic function in hiPSCs. Two hiPSC lines with SIGi001 background—wild-type (SIGi001-WT) and FUS-mutant (SIGi001-FRT-P525L)—were used. These cell lines have been characterized by their pluripotency, morphology, and capacity for motor neuron differentiation. RT-qPCR analysis based on hiPSCs revealed no significant changes in mitochondrial genes (PGC1α, COX1), but a specific downregulation of PGK1 mRNA expression in FUS P525L line. Consistently, enzymatic study also revealed a reduced enzymatic activity of PGK1 in FUS P525L hiPSC line. These initial findings highlighted PGK1 as a selectively dysregulated metabolic node in FUS-mutant iPSCs and support future assessment and exploration of glycolytic modulation in hiPSC derived motor neurons in FUS-ALS.

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Key Words: FUS, iPSC, Glycolysis
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P12: Epidemiological trends in motor neuron diseases: a nationwide comparative analysis across France and Sweden (2003-2023)

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Background:
Understanding temporal trends in motor neuron diseases (MND) incidence and survival is essential for guiding clinical planning and public health policy. Using harmonized methodologies applied to large-scale national datasets in France and Sweden, we evaluated changes over time in MND epidemiology, with comparative insights drawn from other neurodegenerative diseases—Parkinson's disease (PD) and multiple sclerosis (MS).

Methods:
We identified incident MND cases in France (2010–2023) and Sweden (2003–2016) using validated algorithms based on hospital records and disease-specific treatments. Crude and age-standardized incidence rates were calculated per 100,000 person-years. Time trends were assessed using Poisson and mixed-effects regression models. Survival analyses were performed via Kaplan–Meier and Cox proportional hazards models.

Results:
A total of 32,821 incident and 37,405 prevalent MND cases were identified across both countries, with a median age at diagnosis of 69 years. In contrast to declining standardized incidence rates observed for PD (combined France-Sweden: IRR=0.998) and MS (IRR=0.992), MND incidence rose significantly (IRR=1.018, p<0.001). This increase persisted even after adjusting for population aging (standardized IRR=1.018, p<0.001). From 2020 to 2023, MND incidence fell below expected levels, particularly in 2022, likely reflecting disruptions from the COVID-19 pandemic. Median survival for MND patients remained stable over time (from 18.1 months in 2010 to 17.8 months in 2015, log-rank p-value=0.4), unlike PD and MS, where survival improved.

Conclusion:
MND shows a distinct epidemiological trajectory compared to PD and MS, with rising incidence and stagnating survival, suggesting a growing healthcare burden. While aging populations partially explain the trends, other etiological or systemic factors may be contributing. Continued disease-specific surveillance, particularly in MND, is crucial to understanding emerging patterns and informing timely healthcare interventions.

Keywords: MND, epidemiology, incidence trends
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P13: Deep cerebellar nuclei circuitry in Amyotrophic Lateral Sclerosis (ALS)

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Amyotrophic Lateral Sclerosis (ALS) is a fatal neurodegenerative disease characterized by progressive motoneuron degeneration and paralysis. Increasing evidence suggests that circuit dysfunction beyond the motor cortex and spinal cord contributes to disease progression. Notably, early degeneration of inhibitory V1 interneurons, which directly innervate motoneurons, occurs before motoneurons death, implicating their loss in non-cell-autonomous mechanisms of neurodegeneration. Recent studies have identified direct projections from the deep cerebellar nuclei (DCN) to spinal V1 interneurons [1], positioning the cerebellum as a potential direct modulator of spinal motor circuits. However, the role of DCN connectivity and function in ALS remains unknown. Using the ALS $SOD1^{G93A}$ mouse model, our preliminary data reveal early inhibitory synaptic dysregulation in DCN neurons before ALS symptom onset, as early as P21. Furthermore, these synaptic alterations coincide with a significant decline in fine motor skills, as assessed by the single-pellet reaching task at P40. We hypothesize that early cerebellar circuit dysfunction contributes to ALS pathophysiology. Our aim is to define the cellular and molecular mechanisms that disrupt DCN inhibitory synapse formation and organization. In addition, we will investigate how these alterations impact DCN to V1 interneuron connectivity, potentially driving V1 interneuron loss and early motor deficits. Elucidating these mechanisms may uncover novel insights into cerebellar involvement in ALS and reveal new therapeutic targets for mitigating disease progression.

Keywords : deep cerebellar nuclei, circuitry, ALS

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P14: Neurodevelopmental epigenetic alterations prime cortical neurons to dysfunction and degeneration in ALS mouse models

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ALS mostly manifests during adulthood, implicitly suggesting that it hits the fully mature central nervous system. However, the evidence of a long prodromal phase, the existence of juvenile forms, and the developmental roles of genes implicated in familial cases suggest that ALS may take its root during development [1]. Of note, neurodevelopmental and neurodegenerative diseases share several mechanisms, including alterations in one-carbon metabolism (1Cmet). 1Cmet intertwines the folate and methionine cycles, is controlled by four key enzymes (DHFR, MTHFR, MAT2A and AHCY), and is central to purine synthesis and cellular proliferation, and to methylation

and epigenetic regulation [2]. This project aims at investigating whether ALS might arise from neurodevelopmental 1Cmet impairments, focusing on the motor cortex and the upper motor neurons using various omics approaches in the genetically and phenotypically complementary *Sod1*^{G86R} and *Fus*$^{+/\Delta NLS}$ mouse models of ALS. Using RNAscope, we reveal that *Dhfr* expression is significantly increased in cortical progenitors of both ALS mouse models at the time when they generate upper motor neurons. Cellular proliferation was unaltered, as assessed by BrdU labelling, DNA content analysis and immunofluorescence, suggesting that increased *Dhfr* expression might affect other cellular mechanisms, such as epigenetic regulation of gene expression. Metabolomic analyses revealed increased methylation index in developing cortex of *Sod1*^{G86R} mice. Epigenetic Cut&Tag analyses of cortical progenitors from *Sod1*^{G86R} and *Fus*$^{+/\Delta NLS}$ embryos using H3K4me3 and H3K27me3 epigenetic marks are ongoing. Preliminary data reveal altered synaptogenesis, DNA damage and neurodegeneration pathways, suggesting that, prior to their birth cortical neurons may already be primed to dysfunction and degeneration.

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Key words: neurodevelopment, 1C metabolism, epigenetics

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P15: Functional analysis of new molecular markers of motoneurons vulnerable to Amyotrophic Lateral Sclerosis

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Abstract:

Modification of the electrical properties of motoneurons is a key contributor to the progression of amyotrophic lateral sclerosis (ALS) disease. Experimental studies have revealed a differential vulnerability of motoneurons in ALS, with the low -excitability fast fatigable (FF) motoneurons being the most vulnerable and the first to degenerate, while high- excitable slow (S) motoneurons exhibit the greatest resistance. These findings support the hypothesis that the high functional demand on FF motoneurons underlies their increased vulnerability.

To broaden our understanding of the role of neuronal excitability in selective degeneration and to improve the functional characterization of motoneuron subtypes, we performed single-cell transcriptomic analysis using the patch-seq method on FF and S motoneurons, identified through patch-clamp electrophysiology [1] [2].

We analyzed the expression of voltage-gated ion channels in RNA samples from FF and S motoneurons. We found that *Cacna2d3*, a gene coding for the $Ca_V\alpha2\delta3$ regulatory subunit of high voltage-gated calcium channels, was significantly upregulated in FF motoneurons. Due to its elevated expression in ALS vulnerable motoneurons, we are currently investigating its role in both motoneuron physiology and under ALS pathological condition.

In *Cacna2d3*$^{-/-}$ deficient motoneurons, we observed a drastic change in the subcellular localization of the P/Q type calcium channel $Ca_V2.1$, the main calcium channel involved in motoneuron neurotransmission, suggesting a regulatory role of $Ca_V\alpha2\delta3$. Consistently, motor behavioral studies show that Cacna2d3$^{-/-}$ mice display enhanced endurance, yet show increased sensitivity to physical exhaustion.

This project aims to define the molecular basis of electrophysiological features underlying motoneuron vulnerability in ALS. We will evaluate the impact of $Ca_V\alpha2\delta3$ loss on neurotransmission and firing properties through spinal cord electrophysiological recordings in wildtype and *Cacna2d3*$^{-/-}$ mice. We will also evaluate its impact on ALS onset and progression by analyzing behavioral and histopathological changes in *SOD1*^{G93A} mice with a Cacna2d3-deletion.

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Keywords: Motoneuron vulnerability, Calcium channel, Electrical activity

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P16: Connecting Calcium Signaling Alterations to Mitochondrial Dysfunction in Spinal Muscular Atrophy

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Spinal muscular atrophy (SMA), or specifically 5-q linked SMA, is a rare monogenic neuromuscular disorder caused by the autosomal recessive inheritance of *SMN1* gene mutations. Located on chromosome 5q13, *SMN1* gene encodes the ubiquitously expressed SMN protein, which has been reported to participate in various intracellular processes, especially RNA metabolism. Motor neurons are the most susceptible to SMN deficiency, and observed in SMA patients are the selective degeneration of lower motor neurons and progressive proximal muscle atrophy due to SMN deficits. SMN-restoring gene therapies have been approved for clinical use since 2016; however, despite the restoration of SMN level, treated patients continue to exhibit residual symptoms or even disabilities. To this date, it is yet unclear which pathway involving SMN is the major cause of neurodegeneration. Using CRISPR/Cas9 mediated gene knockout, we generated a novel SMA zebrafish model for omics study and drug screening. DNA sequencing confirmed the removal of a targeted sequence in *smn1* exon 7 and splicing analysis later revealed exon 7 skipping events. The *smn1* E7 KO zebrafish crispants exhibited consistent and robust phenotype characterized by locomotor deficits, motor neuron defects and premature mortality. Transcriptomics validated the SMA zebrafish model by a number of previously reported *SMN1* related genes and common differentially expressed genes with SMA human motor neurons. Furthermore, major pathways of interest were significantly altered at the transcriptional level: neurotransmission pathways, calcium signaling, mitochondrial dysfunction, and energy metabolism pathways. Based on cross comparison of these pathways and previous reports on SMA, we hypothesized that transcriptomic alterations in calcium signaling were intercorrelated with mitochondrial dysfunction in our SMA zebrafish model. We further investigated the status of

mitochondrial respiration through functional assays and identified two calcium inhibitors that rescued the locomotor deficits of *smn1* E7 KO zebrafish crispants, potentially through regulating calcium homeostasis and improving mitochondrial function.

Keywords: spinal muscular atrophy, zebrafish, transcriptomics

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P17: FUS$^{p\text{-}Y526}$ localization during neurogenesis and neuromuscular junction formation

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Protein aggregation in neurons, which leads to the degeneration of axons and neuromuscular junctions (NMJ), is an early feature of neurodegenerative diseases. FUS (Fused in sarcoma) is a predominantly nuclear RNA-binding protein that mislocalizes to the cytoplasm in these diseases, where it aggregates. Under normal conditions, only a small amount of FUS is present in the cytoplasm, where it functions as an mRNA transporter to the distal neuronal sites where local protein translation is required. Since phosphorylation of the C-terminal tyrosine of FUS inhibits its binding to the nuclear importer transportin 1, allowing FUS to remain in the cytoplasm [1-2], we hypothesized that phosphorylated FUS$^{p\text{-}Y526}$ may be observed during neuronal cell differentiation and NMJ formation when distal translation is most active. The activity of Src family kinases is increased during embryonic development, is later downregulated and abnormally increased again during neurodegeneration. We have shown that c-Src, c-Abl and c-Fyn all phosphorylate FUS at Y526. Our aim was therefore to investigate the localization pattern of FUS$^{p\text{-}Y526}$ during neurogenesis using mouse and human neurospheroids and co-cultures of human myotubes innervated by neurons from embryonic rat spinal cord explants. By immunocytochemical staining, we showed that FUS$^{p\text{-}Y526}$ is present in the differentiating neurons and astrocytes of the neurospheroids. In the co-culture model, FUS$^{p\text{-}Y526}$ was preferentially observed in maturing axons and at the motor plates of the NMJ. Overall, this suggests an active role of FUS$^{p\text{-}Y526}$ during neuronal differentiation and NMJ formation, which could be perturbed by aberrant kinase activity and the consequent transition from FUS to FUS$^{p\text{-}Y526}$ during neurodegeneration. Deciphering the mechanisms underlying the normal and aberrant transition of FUS to FUS$^{p\text{-}Y526}$ could lead to new strategies for the treatment of neuromuscular disorders.

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Keywords:
FUS phosphorylation, nucleocytoplasmic shuttling, neuronal development
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P18: Break the oxidative stress and neuroinflammation loop with hybrid compounds to cure ALS

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Amyotrophic lateral sclerosis (ALS) is characterized by a degeneration of motor neurons, leading to muscle weakness and progressive paralysis. Currently, no cure is available to halt or reverse the progression of the disease. The “one target, one weapon” strategy has proven to be difficult in reaching therapeutic agent for ALS. Among key mechanisms in ALS, oxidative stress triggers neuroinflammation and vice versa. A potent therapeutic strategy would be to break this vicious circle leading to neuronal dysfunction and death. We wish to evaluate the protection offers by hybrid compounds that combine both antioxidant and anti-inflammatory properties. For that purpose, hybrid compounds had been developed to activate the NRF2 (nuclear factor erythroid-2 related factor 2) signaling and block the Toll-like receptor 4 (TLR4) cascade. NRF2 cascade controls both antioxidant defenses and inflammation while TLR4 represents one of the most crucial receptors triggering inflammation in the nervous system.

First, we determined whether mutant TDP43, a key ALS gene that regulates mRNA metabolism, affects the NRF2 and TLR4 pathways. Next, we evaluated how much efficient was a selected hybrid compound, PM111, on a zebrafish ALS model. PM111 rescued the locomotor defects of larvae expressing mutant TDP43. Rt-qPCR analysis confirmed that PM111 treatment increased several anti-oxidative defense genes. Moreover, to better characterize how the compound confers neuroprotection in the TDP43 context, a transcriptomic analysis is in progress on mutant TDP43-expressing zebrafish treated or not with PM111. Finally, the impact of each PM111 component will be assessed in order to better appreciate the advantage of developing a hybrid molecule.

Keywords: Tar DNA-binding protein 43 kDa (TDP43), NRF2, TLR4

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P19: Characterizing the presymptomatic phase of motor neuron diseases through drug prescription patterns in France and Sweden

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The prodromal phase of ALS has been primarily studied in individuals with familial genetic mutations [1][2], but little is known about early clinical manifestations in sporadic cases.

Using two large nationwide databases—the French SNDS and the Swedish National Registers—we explored the presymptomatic phase of motor neuron diseases (MND)— primarily ALS — through healthcare utilization and drug prescription patterns up to 10 years before diagnosis.

We identified 27,533 incident MND cases (mean age 64.4-69.6 years) and examined diagnostic and coding delays. In France, we observed a median interval of approximately 14.0 months (95% CI, 13.8 – 14.3) between the first neurologist consultation and formal diagnosis, marked by riluzole initiation. Many patients had prior consultations with other specialists, particularly rheumatologists and orthopedic surgeons, suggesting initial misattribution of early motor symptoms.

In a nested case-control analysis, we assessed drug use 5–10 years before diagnosis. Strikingly, despite the use of rich pharmaco-epidemiological data, only a few drug classes showed significant differences. Future MND patients were more likely to receive antidepressants (e.g., SSRIs, tricyclics ; ATC code N06, Sweden OR : 1.15 (0.91-1.45), France 1.1 (1.0-1.21)) and less likely to be prescribed antidiabetic drugs (e.g., metformin, insulin; ATC code A10, Sweden OR : 0.70 (0.49-1.01), France 0.78 (0.68-0.90)). No difference was observed for statins. These associations were consistent across both countries and robust to adjustment for age and sex.

Compared to other neurodegenerative diseases, the relative scarcity of detectable prescription signals highlights the clinical subtlety of MND during its presymptomatic phase. Nonetheless, real-world data offer a valuable window into early disease manifestations and care trajectories and may help better delineate the prodrome of MND.

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Keywords: MND, prodrome, pharmaco-epidemiology

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P20: Thyroid hormones and catabolism in ALS: a retrospective analysis

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Background. Amyotrophic lateral sclerosis (ALS) involves progressive motor neuron degeneration and profound metabolic disturbances, including hypermetabolism and weight loss, which negatively influence prognosis. Thyroid hormones (THs), as central regulators of metabolism, may contribute to these metabolic alterations. This study assessed whether variations in thyroid function within euthyroid ranges are associated with metabolic and neurodegenerative markers in ALS.

Methods. A retrospective cross-sectional analysis was performed on 1,754 ALS patients from the Ulm University ALS registry (2010–2024) with available data on thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and body mass index (BMI). Additional metabolic parameters included serum glucose, lipid levels, and cerebrospinal fluid (CSF) phosphorylated neurofilament heavy chain (pNfH). Spearman's correlations and Mann–Whitney U tests were used for statistical analysis.

Results. Thyroid values were within euthyroid reference ranges (TSH: 1.17 ± 0.80 mU/L; fT3: 2.77 ± 0.41 pg/mL; fT4: 1.22 ± 0.23 ng/dL). TSH showed a significant inverse correlation with age ($r = –0.1364$, $p < 0.05$), particularly in males, contrary to normal aging trends, suggesting hypothalamic-pituitary axis dysregulation. No associations were found between TSH and BMI or CSF pNfH. A weak negative correlation was observed between TSH and glucose ($r = –0.1185$, $p < 0.05$), stronger in males; glucose positively correlated with BMI and age, especially in females.

Conclusion. Although thyroid hormones remain within normal limits in ALS, altered TSH-age dynamics and glucose associations may reflect secondary hypothalamic dysfunction. THs do not appear to be

primary mediators of ALS-related catabolism or neurodegeneration. Further investigation of sex-specific metabolic regulation in ALS is warranted.

Keywords: ALS, thyroid hormones, catabolism

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P21: Identifying disease-predictive morphological biomarkers in motor neuron diseases using machine learning image analysis

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Morphological alterations in Motor Neurons (MNs) are a recurrent and understudied hallmark of Motor Neuron Diseases (MNDs) such as Amyotrophic Lateral Sclerosis (ALS) and Spinal Muscular Atrophy (SMA). Features like shortened neurites, altered extracellular matrix interactions [1], and impaired network formation have been reported both *in vivo* [2] and in patient-derived induced pluripotent stem cell (iPSC) models. Yet, reproducible and accurate quantification of these phenotypes remains a challenge, limiting mechanistic understanding of morphological defects in MNDs.

To address this, we have developed a Machine Learning (ML)-based image analysis pipeline that enables detailed and automated morphological profiling in iPSC-derived motor neuron cultures, in 96 well-plates. Built using *QuPath* image analysis software and *Cellpose's Cyto3* model [3], the pipeline performs segmentation and classification of soma, neurites, and debris from real-time phase-contrast images, which has not been achieved previously on neuronal networks. It extracts over 50 specific morphological measurements, including neurite length, soma area, texture, and spatial topology.

Applied to ALS and control patient lines, the pipeline generated a morphometric dataset that was used to train a *XGBoost*-based classifier. It successfully distinguished between patient and control images with over 90% accuracy. This demonstrates that subtle morphological patterns can robustly predict MND status. We are currently investigating the most predictive patterns, aiming at linking them to pathological mechanisms at play in MNDs.

This pipeline allows for the development of a high-throughput assay for disease and rescue phenotypes in MNs, which will accelerate the discovery of therapeutic molecules. Predictive morphological features will also be used to guide omics integration in the next stages of the project, in order to precisely investigate altered morphological pathways in MNDs.

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Keywords: Motor Neuron Disease, Cytoarchitectural defects, Machine Learning
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P22: The role of paraspeckles in the ALS muscle

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Amyotrophic lateral sclerosis (ALS) is an incurable neurodegenerative disease characterised by motoneuron degeneration and progressive paralysis. Skeletal muscle alterations, such as alterations of RNA and protein metabolism, mitochondrial homeostasis, neuromuscular junction (NMJ) and myogenesis[1], make this tissue a relevant research target for understanding the pathophysiology.

Some proteins mutated in ALS are also involved in the formation of paraspeckles, membraneless subnuclear bodies. These aggregates formed by the long non-coding RNA NEAT1_2 and RNA-binding proteins, sequester RNA and proteins, modulating gene expression.

They regulate pathways altered in ALS muscles and accumulate in ALS patients' motoneurons[2]. Considering the lack of information on paraspeckles in ALS muscle, our project aims to characterize their status, interactome and role in this tissue.

In ALS patients' primary myotube cultures, we observed less paraspeckles but they were bigger than in controls. Stress assays indicated an altered paraspeckle-dependent cellular stress response in ALS myotubes that could potentially participate in weakness and atrophy. Interestingly, in the $SOD1^{G93A}$ mice tibialis nuclei at the NMJ, we observed more paraspeckles which were significantly smaller. These alterations could be linked to denervation as paraspeckle number correlates with NMJ size which is reduced in ALS mice. Moreover, in controls, paraspeckle number correlates with nucleus size but not in ALS, further indicating altered regulation of paraspeckle formation at the NMJ in ALS mice.

I am exploring the causes and consequences of these alterations by studying the composition of paraspeckles. In addition, I am exploring the roles of paraspeckles in ALS muscle and their potential involvement in the pathophysiology of ALS.

With this research, we expect to shed light on the implication of paraspeckles in the development of ALS at the level of the muscle, which could in the long term open the way to a better understanding of the disease and new therapeutic targets.

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Keywords : ALS, muscle, paraspeckles
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P23: Common mechanisms between SCA36 and C9ORF72-ALS/FTD: insights from a novel zebrafish model

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Abstract :

Background:
Spinocerebellar ataxia type 36 (SCA36) is a rare late-onset neurodegenerative disorder caused by a GGCCTG hexanucleotide repeat expansion in the first intron of the *NOP56* gene. Clinically, it presents with cerebellar ataxia, sensorineural hearing loss, and lower motor neuron involvement [1]. Notably, the pathogenic expansion is structurally and mechanistically similar to the GGGGCC repeat expansion in *C9ORF72*, the most common genetic cause of ALS and FTD. Both expansions undergo repeat-associated non-ATG (RAN) translation, generating toxic dipeptide repeat proteins (DPRs). Among the DPRs produced, **poly-GP and poly-PR are common in both diseases,** suggesting common pathogenic mechanisms [2]. Although poly-GP has long been considered non-toxic, recent studies suggest it can trigger neurotoxicity in the context of partial gene haploinsufficiency [3].

Objectives:
To investigate the molecular mechanisms underlying SCA36 and identify common pathological pathways with C9ORF72-ALS/FTD, using novel in vivo models.

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

Results:
SCA36 zebrafish exhibited neurodegenerative phenotypes and differential DPR aggregation depending on *nop56* dosage. Poly-GP aggregates were more prominent and insoluble under haploinsufficiency, correlating with greater neurotoxicity. Omics analyses revealed overlapped dysregulated pathways between SCA36 and *C9ORF72*-ALS/FTD, including alterations in RNA metabolism, proteolysis, and mitochondrial function.

Conclusion:
Our findings highlight shared pathological mechanisms between SCA36 and *C9ORF72*-ALS/FTD and establish zebrafish as a valuable model to study DPR toxicity. Understanding these overlaps may contribute to the identification of common therapeutic targets across repeat expansion disorders.

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Keywords: Repeat expansion disorders, neurodegeneration, zebrafish models

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P24: SOD1^{G93A} neurotoxicity initiated by subversion of cellular prion protein signaling in cell and mouse models of charcot disease

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Amyotrophic lateral sclerosis (ALS) is the most common motor neuron degenerative disease in adults. ALS is associated with the selective loss of motor neurons in the spinal cord, brainstem, and cortex, which causes progressive paralysis and death by respiratory failure. ALS is a proteinopathy, a disease caused by protein misfolding and dysfunction. Among other genes, the gene encoding Cu/Zn Superoxide Dismutase 1 (SOD1), an intracellular enzyme implicated in antioxidant processes, is frequently involved in ALS. The toxicity of SOD1 mutants relies on a toxic gain-of-function notably due to formation of intracellular aggregate inclusions of SOD1. However, the secretion and accumulation of ALS-linked SOD1 mutants in the surrounding milieu of motor neurons raises the unexplored possibility that abnormal SOD1 triggers neurotoxicity through binding to membrane receptors and alteration of their signaling activity. Exploiting neuronal cell lines exposed to misfolded human G93A SOD1 (hSOD1^{G93A}), primary cultures of mouse motor neurons isolated from Tg-hSOD1^{G93A} transgenic ALS mice (referred to as ALS neurons), and iPSC derived motor neurons of ALS patients with SOD1 mutations, we show that plasma membrane cellular prion protein (PrP^{C}) is a neuronal receptor for misfolded hSOD1^{G93A}. hSOD1^{G93A} interaction with PrP^{C} corrupts PrP^{C} signaling function, leading to 3-phosphoinositide-dependent kinase 1 (PDK1) overactivation and downstream under-shedding of TNFα receptors (TNFRs) by ADAM10/17 α-secretases. Cell surface accumulation of TNFRs renders ALS neurons hyper-vulnerable to TNFα inflammation. Intraperitoneal infusion of a PDK1 inhibitor in Tg-hSOD1^{G93A} ALS mice rescues the ADAM-mediated TNFR shedding, protects spinal cord motor neurons from neurodegeneration, improves motor performance, and extends survival. Our work highlights that excessive stimulation of PrP^{C} coupling to PDK1 by hSOD1^{G93A} contributes to ALS and posits PDK1 as a novel target for developing therapeutics to mitigate ALS.

Keywords: Amyotrophic Lateral Sclerosis, PDK1, therapeutic target

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P25: Short-term assessment of progression, muscle involvement asymmetry, and clinical correlates in ALS

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Abstract:

Background: To date, no curative treatment is available for ALS, which is characterized by a particularly rapid progression compared to other neurodegenerative diseases [1]. This accelerated course presents a challenge for the selection of relevant clinical outcomes that can accurately reflect the short-term natural history of the neuromuscular system in patients with ALS. This study aimed to characterize the functional motor progression of ALS over a six-week period by identifying the most sensitive clinical measures of change, evaluating muscle strength asymmetry, and analyzing the correlations between muscle strength, functional performance, and standardized clinical scales.

Methods: Ten patients with ALS were followed over six weeks during three assessment visits spaced three weeks apart. These visits included lower limb muscle strength measurement using dynamometry, functional tests of walking and balance, forced vital capacity (FVC) assessment via spirometry, and the administration of standardized clinical scales. Repeated-measures ANOVA, Wilcoxon signed-rank test, and Spearman rank correlation were used for statistical analysis (significance set at $p<0.05$).

Results: All motor outcome measures showed a general trend towards deterioration. Muscle strength measures that showed significant changes over six weeks were left hip extension ($p=0.03$), right and left knee extension ($p=0.02$ and $p=0.01$, respectively) and left dorsiflexion ($p=0.04$). Additionally, significant declines were observed in the total score of the ALSFRS-R ($p=0.01$) and its gross motor subscore (ALSFRS-R-GM) ($p=0.02$). Muscle weakness was generally asymmetrical. Strength in hip extension, knee extension and flexion was significantly greater on the right side ($p=0.03$, $p<0.001$, and $p=0.003$, respectively). Hip, knee, and ankle muscle strength was significantly correlated with the 6-Minute Walk Test, the 10-Meter Walk Test, ALSFRS-R-GM and balance as assessed by the *Berg Balance Scale*. Although other significant correlations were observed depending on the muscle group, these four parameters were the clinical measures consistently associated with overall lower limb muscle strength evaluated.

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Keywords: Amyotrophic lateral sclerosis, natural history, clinical outcomes.

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P26: Leveraging multicohort ALS data for trial improvement

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Clinical heterogeneity of Amyotrophic Lateral Sclerosis (ALS) is a critical challenge for prognosis and patient management. Statistical models built on large observational datasets, such as Prediction Powered Inference for Clinical Trials (PPCT)[1], can capture this to support clinical trial design. The objective of the study was to investigate how models built on various ALS cohorts improve negative clinical trial[2].

Longitudinal data were collected from three ALS patients' cohorts: PULSE, ANSWERALS (bio data repositories) and PROACT (pooled clinical trials). We modeled the ALS disease progression using a disease course mapping model[3]. We then used baseline data from patients in TROPHOS, clinical trial, to predict the progression of the ALSFRS-R and survival rate if they had a similar evolution to that of the observational cohorts (personalization step). PPCT uses prognostic scores to enable an unbiased comparison of the observed and predicted outcome progression in treated patients. Based on the prognostic scores generated by the model, we applied PPCT to increase the statistical power of this trial.

An ALS course model was built, showing that muscle (MMT) scores closely mirrored the ALSFRS-R motor subitems progression, while respiratory scores (SVC and FVC) showed earlier decline. Onset timing and progression were different between cohorts, in line with the different cohorts' baseline characteristics. Combining the three cohorts improved the accuracy of prognostic score predictions for the TROPHOS trial (R^2=10.5%). Using PPCT reduced the variance of the treatment effect estimator from 0.48 to 0.43 compared to classical methods, thereby increasing statistical power. Notably, PPCT could reduce the required sample size by 10.5% while maintaining the same power in the treatment effect estimate.

We demonstrate the value of modeling ALS natural history to capture distinct progression patterns. Integrating these predictions into the analysis of a clinical trial through the PPCT framework leads to more efficient treatment effect estimation.

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P27: Exploring the impact of NUP50 loss on nuclear pore complex integrity and the structural consequences of ALS-linked variants

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In our laboratory, we identified a common NUP50 variant in ALS patients associated with reduced protein levels and increased ALS risk, as well as several rare variants of unknown significance [1]. NUP50 is a mobile nucleoporin located in the nuclear pore complex (NPC) basket, involved in both nucleocytoplasmic transport and chromatin organization.

We hypothesized that NUP50 is critical for preserving the structural integrity of the NPC, and that its loss may disrupt nucleocytoplasmic transport and chromatin organization, thereby contributing to motor neuron degeneration. My PhD project aims to elucidate the role of NUP50 in ALS through two complementary objectives.

First, I am investigating how NUP50 loss affects NPC architecture and heterochromatin organization in human induced pluripotent stem cells (iPSC) and iPSC-derived motor neurons using super-resolution microscopy. Preliminary results suggest that NUP50 deficiency alters the spatial distribution of heterochromatin, supporting its potential role in maintaining nuclear chromatin organization.

Second, we are using X-ray crystallography to analyze ALS-associated NUP50 variants in order to determine how these mutations affect protein structure and function. So far, I have successfully expressed NUP50 in a bacterial system and obtained the protein in a soluble form, enabling large-scale production and purification. The next steps involve crystallization trials and structural determination to compare wild-type and mutant proteins. Resolving the three-dimensional structure of NUP50 will provide key insights into how ALS-linked variants affect its conformation, stability, and functional domains. In parallel, recombinant wild-type and mutant NUP50 proteins will be used in liquid–liquid phase separation (LLPS) assays to determine whether NUP50 exhibits LLPS behavior, and whether this property is altered by disease-associated variants.

This combined cellular and structural approach will help elucidate the molecular mechanisms by which NUP50 contributes to motor neuron dysfunction and may open new avenues for understanding nucleocytoplasmic transport defects in ALS.

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Keywords: Nuclear pore complex, chromatin, structure.

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P28: Hypothalamic mechanisms of high-calorie intervention in ALS

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Amyotrophic lateral sclerosis (ALS), a severe neurodegenerative disease, with on average 2 to 5 years lifespan after the onset of the first motor symptoms, remains incurable. Apart from motor symptoms, significant weight loss is also observed in ALS patients and ALS mouse models, linked to altered energy expenditure in which the hypothalamus primarily involves. Previous studies showed abnormalities in the hypothalamic volume and metabolism-related neuropeptides in ALS [1]. Moreover, some studies claimed that high-calorie diet (HCD) could compensate weight loss and prolong survival in ALS mice [2], while clinical researches have not yet concluded clear benefits of HCD for ALS patients. Given these evidences, investigating the underlying mechanisms of hypothalamic alterations and HCD-associated beneficial effects in ALS is crucial for deciphering the pathology of ALS and exploring more therapeutic strategies.

Beyond energy metabolism, another aspect that hypothalamus contributes to is also dysregulated in ALS--sleep. Earlier results from our group declared apparent sleep deficiency in ALS like high level of wakefulness in ALS mice and patients, and even in gene-carriers and mice at the pre-symptomatic stage, which could be rescued in ALS mice by applying dual orexin receptor antagonist (DORA) – suvorexant [3]. Hence, this project is also trying to reveal the influence of HCD on sleep in ALS.

To achieve above objectives, three main parts of experiments are undergoing: 1. Transcriptomics of hypothalamus in ALS mice; 2. Metabolic measurement in ALS mice with HCD; 3. Sleep assessment in ALS mice with HCD.

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P29: Alliance on Clinical Trials for ALS-MND

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ACT4ALS-MND is a French clinical research network established in 2020 by the national rare diseases health network FilSLAN. Gathering 22 ALS/MND expert centers across France, the network leverages its members' clinical expertise and a large active patient cohort to initiate national multicenter clinical trials (CTs) and foster collaborations at both European and international levels. Based at the Paris Brain Institute, ACT4ALS-MND ensures centralized operational coordination. In 2022, it was labeled by the French Clinical Research Infrastructure Network (F-CRIN), a national platform supported by the Ministry of Health to strengthen the performance and global visibility of French clinical research, both academic and industrial.

The network's mission is to promote high-impact clinical and translational research programs built around four thematic pillars: patient stratification and precision medicine, innovative therapeutic strategies and drug repurposing, improved understanding of ALS pathophysiology, and the development of novel clinical trial designs and more efficient trial implementation in France.

In this context, ACT4ALS-MND is actively supporting the extension across Europe of MND-SMART, the largest-ever MND platform trial initially launched in the UK, with over 1,000 participants randomized since 2020. Co-produced alongside MND patients and co-designed with world-leading statisticians, the trial is structured to detect subtle neuroprotective effects of investigational drugs. Its platform design allows for the simultaneous evaluation of multiple treatment arms against a single, contemporaneously randomized control group, a model that offers significant efficiencies in terms of time, cost, and required sample size when compared to conventional trials.

The deployment of decentralised trial delivery methods further strengthens MND-SMART's innovative approach, helping to overcome traditional barriers to participation. Notably, France, Germany, and Belgium currently have no platform trials dedicated to ALS, despite a clear unmet need for studies with broader, more inclusive eligibility criteria and decentralised models. By contributing to the European expansion of MND-SMART, ACT4ALS-MND helps lay the foundation for a new, connected research infrastructure that aims to democratize access to clinical trials for people living with ALS.

Its overarching goal is to expand the number of ALS/MND clinical trials and patient enrollments in France by providing operational and methodological support at every stage of research: scientific expertise, study design, regulatory guidance, feasibility assessment, site selection, budget evaluation, and recruitment monitoring. The network also promotes dialogue between academia and industry to accelerate therapeutic innovation for ALS and MND patients.

Since its creation, ACT4ALS-MND has contributed to six academic research projects and thirteen industry-sponsored clinical trials.

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