THE CROATIAN ACADEMY OF SCIENCES AND ARTS
The Department of Biomedical Sciences in Rijeka
THE CLINICAL HOSPITAL CENTER RIJEKA
UNIVERSITY OF RIJEKA - FACULTY OF MEDICINE
THE CROATIAN NEUROLOGICAL SOCIETY
THE CROATIAN MEDICAL ASSOCIATION – Branch office Rijeka

9th RIJEKA FORUM ON NEURODEGENERATIVE DISEASES

"Mechanical treatments, viruses, genetics, neuroaging and neuroimmunology"

Endorsed by Associations

Rijeka, September 15-16, 2025
08:30 am
University Campus Rijeka, Faculty of Civil Engineering
Lecture halls G-003 and G-004, Radmile Matejčić 3, Rijeka

Organizers

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Scientific Committee

Stipan Jonjić, Vladimira Vuletić, Nenad Bogdanović, John Hardy, Alen Ružić, Zdravka Poljaković

Organizing Committee

Vladimira Vuletić, president
Zoran Tomić, Eliša Papić, Srđan Novak

Registration: online via registration form

Free admission for registrations

Information

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PROGRAM
OPENING
(8:30-9:00)

Introduction

Stipan Jonjić, M.D., PhD, F. C. A, Professor, Head of the Department for Biomedical Sciences in Rijeka, Croatian Academy of Sciences and Arts, Rijeka, Croatia

Vladimira Vuletić, M.D., PhD, Professor, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Welcome address

Zdravka Poljaković, M.D., PhD, Professor, President of the Croatian Neurological Society, Medical Faculty, University of Zagreb, Zagreb, Croatia

Alen Ružić, M.D., PhD, Professor, Director, Clinical Hospital Center, Rijeka, Croatia

Goran Hauser, M.D., PhD, Professor, Dean, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Senka Maćešić, PhD, Professor, Interim Vice-Rector for Science, Art and Digitalization, University of Rijeka, Rijeka, Croatia

1st day – September 15th, 2025

PROGRAM

9,00 – 12,00 h

I. ALZHEIMER'S DISEASE UPDATES

Chairs: Nenad Bogdanović and Elka Stefanova

John Hardy, M.D., PhD, Professor, Institute of Neurology, University College London, London, UK
We have amyloid therapies: what next?

Claudio Lino Alberto Bassetti, MD, PhD, Professor, Dean, Medical Faculty, University of Bern, Director of Teaching and Research, Insel Gruppe, Neurology Department, Bern, Switzerland
Sleep, cognition and dementia: a bidirectional link

Catherine Mummery, M.D., PhD, Professor, National Hospital for Neurology and Neurosurgery, London, UK
Lost in translation: the long road from genetics to practice

Dean Nižetić, M.D., Ph.D., Professor, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, UK
Mechanistic insights into neuronal ageing in Down syndrome, the most common genetic form of early onset Alzheimer's dementia

Nenad Bogdanović, M.D., PhD, Professor, Karolinska Institute, Stockholm, Sweden
Facts and challenges of antiamyloid therapy: from first-generation antibodies to brainshuttle technology

Elka Stefanova, M.D., PhD, Professor, School of Medicine, University of Belgrade, Belgrade, Serbia
APOE Genotype and CSF Biomarkers in Alzheimer's Disease

Discussion: 12:00 – 12:15

Break for refreshment: 12:15 – 12:30

12,30 – 14,30 h

II. ALPE ADRIA SECTION AND MOVEMENT DISORDERS (1st PART)

Chairs: Vladimira Vuletić and Per Odin

Kailash Bhatia, M.D., PhD, Professor, Institute of Neurology and University College London, London, UK
Immune mediated hypokinetic disorders- an update

Angelo Antonini, M.D.,PhD, Professor, Neurology Clinic Padua and University of Padua, Padua, Italy
Disease modifying strategies

Cristian Falup-Pecurariu, MD, PhD, Professor, Transylvania University of Bra□ov, Brasov, Romania
Visual dysfunction in synucleinopathies

Per Odin, MD, PhD, Professor, Head, Division of Neurology Department of Clinical Sciences Lund, Lund University Skane University Hospital, Sweden
Late-stage Parkinsonism: characteristics and the role of specialized care and palliative care

Discussion: 14:30 – 14:45

Lunch break and Flesh presentation of young researchers: 14:45– 15:45

15,45 – 17,15 h

III. MULTIPLE SCLEROSIS AND NEUROIMMUNOLOGY

Chairs: Mario Habek and David Bonifačić

Mario Habek, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Autonomic dysfunction in multiple sclerosis

Uroš Rot, M.D., PhD, Professor, University Medical Centre Ljubljana, Ljubljana, Slovenia
Intrathecal immunoglobulin synthesis in multiple sclerosis: why to talk about it in 2025?

Arianna Sartori, M.D., PhD, Ass. Professor, University of Trieste, ASUITs, Cattinara Hospital, Trieste, Italy
Progressive multiple sclerosis: therapeutic perspectives with a focus on symptomatic treatments

David Bonifačić, M.D., PhD, Ass. Professor, Clinical Hospital Center Rijeka, Rijeka, *Croatia*
Remyelination therapies and neuroprotection: where do we stand?

Discussion: 17:05 – 17:15

17,15 – 17,45 h

III.a CHOOSING THE OPTIMAL TREATMENT PATHWAY IN MULTIPLE SCLEROSIS: NEW INSIGHTS AND CLINICAL APPLICATION

Roche

Mario Habek, M.D., Clinical Hospital Center Zagreb, Zagreb Croatia
David Bonifačić,M.D., Clinical Hospital Center Rijeka, Rijeka, Croatia

2nd day – September 16th, 2025

9,00 – 11,15 h

IV. ALPE ADRIA SECTION AND MOVEMENT DISORDERS (2nd PART) TREATMENTS

Chairs: Maja Trošt and Cristian Falup-Pecurariu

Maja Trošt, M.D., PhD, Professor, University Medical Centre Ljubljana, Ljubljana, Slovenia
Early experience with subcutaneous levodopa treatment in advanced Parkinson's disease

Iva Stanković, M.D., PhD, Assistant Professor, School of Medicine, University of Belgrade, Belgrade, Serbia
Differential diagnosis of multiple system atrophy: video atlas on mimicking conditions

Dejan Georgiev, M.D., PhD, Professor, University Medical Centre Ljubljana, Ljubljana, Slovenia
Immunomodulatory effects of deep brain stimulation

Vladimira Vuletić, M.D., PhD, Professor, Clinical Hospital Center Rijeka and Faculty of Medicine, University of Rijeka, Rijeka, Croatia
Technological advances in invasive treatment of Parkinson's disease

Nataša Dragašević Mišković, MD, PhD, Professor, University Clinical Centre of Serbia and School of Medicine, University of Belgrade, Belgrade, Serbia
Hereditary ataxias: an update

Paolo Manganotti, M.D., PhD, Professor,Cattinara University Hospital ASUGI and University of Trieste, Trieste, Italy
Transcranial pulse stimulation as a not invasive forma of brain stimulation in neurodegenerative disorders

Discussion: 11:15 – 11:30

Break for refreshment: 11:30 – 11:45

11,45 – 14,45 h

V. NEURODEGENERATIVE DISORDERS UPDATES – part I

Chairs: Patrick Küry and Zvezdan Pirtošek

Vida Demarin, M.D., PhD, F. C. A, Secretary of the Department of Medical Sciences of the Croatian Academy of Sciences and Arts, President of International Institute for Brain Health, Zagreb, Croatia
The role of art in neurodegenerative diseases

Amos D. Korczyn, M.D., PhD, Professor Emeritus, CONy President, Tel Aviv University, Tel Aviv, Israel
Apraxia

Anja Kovanda, PhD**,** Ass.Professor,University Medical Center Ljubljana, Ljubljana, Slovenia
Borut Peterlin, M.D.,PhD, Professor,University Medical Center Ljubljana, Ljubljana, Slovenia
From genetic diagnostics to mechanisms of neurodegenerative disorders?

Vladana Vukojević, MD, PhD, Professor, Karolinska Institute, Department of Clinical Neuroscience, Center for Molecular Medicine, Stockholm, Sweden
Time-Resolved Methods with Single-Molecule Sensitivity: From Fundamental Insights to Early Disease Diagnostics

Jasna Križ, MD, PhD, Professor, Department of Psychiatry and Neurosciences, Faculty of Medicine, University of Laval, Québec, Canada
The regulation of innate immune gene expression in neurodegenerative disorders

Patrick Küry, M.D., PhD, Professor, Medical Faculty, Heinrich-Hein University of Düsseldorf, Düsseldorf, Germany, Bern University Hospital and University, Bern, Switzerland
Of glial cells and endogenous retroviruses in MS related de- and regeneration

Zvezdan Pirtošek, M.D., PhD, Professor, University Medical Center Ljubljana, Ljubljana, Slovenia
Neuroaging unmasked: why time is the brain's greatest enemy?

Ivana Munitić, M.D., PhD, Professor, Faculty of Biotechnology and Drug Development, University of Rijeka, Rijeka, Croatia
Context-specific roles of OPTN variants in ALS, FTD and Glaucoma: insights from experimental models and computational analyses

Discussion: 14:45 – 15:00

Lunch and flesh presentation of posters of young researchers: 15.00-15.45

15,45 – 16,45 h

VI. NEURODEGENERATIVE DISORDERS UPDATES- part II

Chairs: Gabriela Novotni and Vladimira Vuletić

Gabriela Novotni, M.D., PhD, Professor, University Clinic of Neurology, Medical Faculty, University "Ss Cyril and Methodius", Skopje, North Macedonia
How old is your brain? On brain health and neurodegeneration through the exposome lens

Nataša Klepac, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Impact of cognitive reserve on dementia progression

Jan Kobal, MD, PhD, Professor, University of Ljubljana, Medical faculty of Ljubljana, Ljubljana, Slovenia
Ksenija Cankar, MD, PhD**,** University of Ljubljana, Medical faculty of Ljubljana, Ljubljana, Slovenia
Živa Melik, MD, PhD, University of Ljubljana, Medical faculty of Ljubljana, Ljubljana, Slovenia
Autonomic nervous system in Huntington disease, what are promises for the future?

16,45 h

VII. CLOSING REMARKS

Chair: Vladimira Vuletić

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ABSTRACTS

We have amyloid therapies: what next?

John Hardy[1,2]
[1]UCL Institute of Neurology, London, UK
[2]Dementia Research Institute of Neurology, London, UK

With lecanemab and donanemab we now have very imperfect therapies for Alzheimer's disease: imperfect because they slow but do not halt the disease and because they have serious side effects which require expensive and invasive monitoring. This has led to differing regulatory outcomes when presented to different regulatory agencies. My purpose in my talk will not be to rehearse the arguments about the approvals of these drugs, but to look forward as to how we might go from here towards better mechanistic therapies.
There are several ways including:

1) Earlier diagnosis: preliminary data suggests that earlier diagnosis results both in better outcome in terms of clinical effect and ARIA complications.
2) Antibodies which are transported across the blood brain barrier should theoretically reduce the blood vessel complications: of these trontinemab is an example for which there is public data
3) We need examine the residual pathology after anti-amyloid therapy to understand what is driving the continuing cognitive decline so that we can target these pathologies for intervention.

However, even though we now know what anti-amyloid therapies need to do to achieve clinical efficacy, new therapies will have to go through long and extensive trials based on clinical outcomes. My purpose will be to suggest we should look to the approval processes for statins for heart disease where high cholesterol was used as a surrogate biomarker, and consider when we might switch to approving anti-amyloid drugs based on their effects on plasma biomarkers.

Lost in translation: the long road from genetics to practice

Catherine Mummery
UK Dementia Trials Network, London, UK
Dementia Research Centre, University College London, London, UK

In this talk I will discuss the complexities of translation from understanding the pathophysiology of a disease to finding an effective treatment that can be used in practice. Following genetic advances in our understanding of familial Alzheimer's disease (AD), we have in recent years made significant advances in our knowledge of the pathophys-

iology and have successfully developed the first disease modifying therapies (DMTs) in AD. But how well does that translate into benefit? What can we do to improve on the current efficacy and safety? I will discuss a novel method of delivery using active transport that may enhance our ability to penetrate the Blood brain barrier with large molecules and improve delivery of drug to the central nervous system, and I will present data on the early trials results using a new drug, trontinemab.

Studies in genetic AD have provided a wealth of data on the AD disease course and how pathology exists decades before symptom onset. Trialling therapies in this population is providing groundbreaking insights into the potential for prevention, both secondary and primary. This raises the possibility of a 'statin for the brain', but how close to translating this work into prevention for the general population are we? I will discuss the current trials such as DIAN-TU and also advances in sporadic AD in the preclinical space and touch upon the challenges for prevention in the wider population.

In addition to the known gene mutations that cause familial AD, other risk factors for AD exist such as apoe4, TREM2 amongst others. I will briefly update on work ongoing to target these different pathways using different methodologies including on how they inform us as to the known side effects of anti-amyloid therapies and may challenge the current hypotheses. In addition, we can intervene in the translation of a gene into a protein in order to reduce that protein and potentially alter the course of disease - I will give examples of gene silencing therapies, and how we might be able to use the innovative platforms being developed in delivery to enhance patient experience as well as drug efficacy.

Finally, the advent of DMTs has had consequences in terms of equity. Some patients are able to access these, many are not. Even within high income countries, there is inequity; this is amplified for low and middle-income countries. How do we ensure that development of novel therapies in AD provides treatments for all, rather than the privileged few?

Mechanistic insights into neuronal ageing in Down syndrome, the most common genetic form of early onset Alzheimer's dementia

Aoife Murray[1‡], Ana Cindrić[2], Frano Vučković[2], Gillian Gough[3], Ingeborg Barišić[4], Ana Muniz-Garcia[1], Amal Kasri[5], Marie-Claude Potier[5], Susana de la Luna[6], Gordan Lauc[2,7‡], Jasminka Krištić[2‡], Ivan Alić[1,8‡], & Dean Nižetić[1,3‡]

[1]The Blizard Institute, Barts & The London School of Medicine, Queen Mary University of London, UK.

[2]Glycoscience Research Laboratory, Genos Ltd., Zagreb, Croatia.

[3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore.

[4]Department of Medical Genetics, Children's Hospital, School of Medicine, University of Zagreb, Croatia.

[5]Sorbonne Université, Institut du Cerveau - ICM, CNRS, APHP, Hôpital de La Pitié Salpêtrière, InsermParis, France

[6]ICREA, Genome Biology Programme (CRG), Universitat Pompeu Fabra (UPF), CIBER of Rare Diseases, Barcelona, Spain.

[7]Faculty of Pharmacy and Biochemistry, University of Zagreb, Croatia.

[8]Department of Anatomy, Histology and Embryology, Faculty of Veterinary Medicine, University of Zagreb, Croatia.

‡Shared senior authors

While ageing and β-amyloid are two important contributors to AD pathogenesis, the molecular mechanisms linking these cellular processes and how they ultimately result in cognitive decline are not well understood. Down syndrome (DS) is the most common genetic form of early-onset-AD. However, not just neurons, but multiple cell types from people with DS show faster accumulation of DNA damage and epigenetic senescence marks. Causative mechanisms remain un-proven ranging from amplified chromosomal instability to actions of chromosome 21 genes. Plasma immunoglobulin G (IgG) glycosylation profiles are established as a reliable predictor of biological and chronological ageing. We performed IgG glycan profiling of n=246 individuals with DS (208 adults and 38 children) clinically characterised for co-morbidities, from three European countries, and compared these to age-, sex- and demography-matched general populations. We uncovered that average levels of IgG glycan markers of ageing, as a function of age in persons with DS, corresponded to levels detected in 19-years older euploid individuals. Importantly, no difference in slope of the curve relating IgG-glycan-age to chronological age was observed for any of the 3 analysed populations, discouraging the amplified-chromosomal-instability explanation. Changes are detectable from early childhood, and do not require a supernumerary chromosome, but are seen in segmental duplication of only 31 genes, along with increased DNA damage and decreased levels of LaminB1 in nucleated blood cells. We show that these effects of T21 can be modelled in undifferentiated isogenic iPSCs, and assign these abnormalities to overdose of DYRK1A. We further demonstrate that hypo-expression of LaminB1 seen in iPSCs is also observed in some foetal and infant DS tissues, including liver, skin fibroblasts and brain. Using cerebral organoids, we demonstrate that reduced cortical folding (a shared phenotype of DS and LMNB1+/– patients) can be restored by CRISPR-Cas9 reduction of DYRK1A copy number, and that neuronal DNA damage, senescence and LaminB1 depletion in early DS organoids can be corrected by pharmacological inhibition of DYRK1A. This shifts the paradigm from an (essentially untreate-

able) "amplified instability" mechanism, to a specific gene-overdose-driven cause of a progeria-like syndrome, opening possibilities for therapeutic amelioration strategies, and provides a biological rationale for very early intervention in people with DS using both senolytic and anti-amyloid therapies.
[*Murray, Gough, Cindrić, Vučković et al. EBioMedicine (Lancet)doi: 10.1016/j.ebiom.2023.104692*]

Facts and challenges of antiamyloid therapy: from first-generation antibodies to brainshuttle technology

Nenad Bogdanovic[1,2]
[1]Karolinska University Hospital, Stockholm, Sweden
[2]Karolinska Institute, Stockholm Sweden

The amyloid hypothesis has guided Alzheimer's disease (AD) drug development for >30 years. Early programs established biological plausibility yet exposed key developmental and clinical hurdles that shape today's practice.

Historical precursors (active and passive immunotherapy). The first active Aβ vaccination (**AN1792**, Aβ42 + QS-21) was halted when meningoencephalitis occurred in ~6% of immunized participants; most subjects received only two or three injections before discontinuation. Despite interruption, phase IIa analyses showed small signals on composite neuropsychology in antibody responders and CSF tau reductions in subsets. A ~4–5-year follow-up led by **Bruno Vellas** reported that **antibody responders declined less functionally than placebo** (e.g., Disability Assessment for Dementia/ Dependence Scale), with no further encephalitis and brain volume loss comparable to placebo—suggesting durable biological impact from limited dosing in those who mounted a response.

Among passive antibodies, **bapineuzumab** (N-terminal Aβ) produced biomarker effects (PiB-PET, CSF p-tau) but **failed** on primary clinical endpoints in Phase 3 and revealed **dose- and APOE ε4–related ARIA-E**, leading to termination. **Solanezumab** (soluble monomer Aβ) showed **low ARIA** but **negative** primary outcomes in EXPEDITION 1/2 and EXPEDITION-3, underscoring the importance of target species and brain exposure for efficacy.

First-generation approved antibodies. *Aducanumab* reached approval despite inconsistent Phase 3 outcomes and high ARIA burden; use waned as efficacy, cost, and safety concerns mounted. *Lecanemab* (CLARITY-AD) and *donanemab* (TRAILBLAZER-ALZ2) consistently **cleared plaques and modestly slowed decline** (e.g., CDR-SB ≈ −0.45 at 18 months for lecanemab; ≈ −0.70 at 76 weeks for donanemab, larger in low/medium-tau strata), but both require MRI monitoring for ARIA.

Antibodies vs AChE inhibitors: quantitative comparison and context. A recent Bayesian network meta-analysis of double-blind RCTs in MCI due to AD and mild AD found that, versus placebo, **mAbs improved ADAS-Cog by ≈ −1.35 and CDR-SB by ≈ −0.41**, while **AChE inhibitors'** credible intervals often crossed zero on cognition. Directly

comparing classes, **mAbs outperformed AChEIs on CDR-SB by ≈ −0.30**—yet **none** of these effects **exceeded minimally important difference thresholds** (ADAS-Cog −2; CDR-SB −1). Safety (acceptability, tolerability, SAEs, mortality) was broadly similar; within mAbs, **ARIA risk** varied (higher with aducanumab/donanemab; **lecanemab** relatively lower ARIA-H), and **APOE ε4 homozygosity** markedly increased **ARIA-E** risk. **Most mAb RCTs permitted stable background symptomatic therapy**; roughly, **50–60%** of participants received **AChEIs and/or memantine**. Prespecified subgroup analyses **found no effect modification** by concomitant AD meds. Still, cross-class inferences remain **indirect**: no head-to-head trials; **era/enrollment differences** (symptom-based AChEI trials circa 2000–2010 vs **biomarker-confirmed** mAb trials post-2020); and **varying treatment durations**.

Next-generation approach: BrainShuttle antibodies (Trontinemab). A central limitation of conventional mAbs is low brain exposure across the BBB. **Trontinemab (RG6102)** is a **bispecific "BrainShuttle"** (gantenerumab backbone + TfR1 module) designed for receptor-mediated transcytosis—**monovalent TfR1 engagement for transport with preserved bivalent Aβ binding and Fc effector function**. In Phase Ib/IIa, trontinemab induced **rapid, deep plaque clearance** with **~90% becoming amyloid-PET negative by ~28 weeks** and **early ARIA-E <5%** (including APOE ε4 homozygotes); **Phase III programs** are now initiating in early symptomatic and preclinical AD. If replicated, this profile could **reduce MRI burden, ease infusion/imaging bottlenecks**, and **improve cost-effectiveness** by delivering higher CNS target engagement with lower safety overhead.

Conclusions. From **AN1792** (efficacy–safety trade-offs, limited dosing but sustained functional benefit in antibody responders) to **bapineuzumab/solanezumab** (target/species and exposure constraints) to **lecanemab/donanemab** (biologically meaningful yet modest clinical benefits with ARIA management), the field has progressed but remains operationally demanding and socioeconomically challenging. **Most mAb evidence sits atop symptomatic therapy**, and cross-class comparisons with AChEIs are **indirect**. **Trontinemab** exemplifies a BBB-penetrant evolution—**very rapid plaque clearance** with **favorable early safety**—now poised to test whether **efficient brain delivery** can translate into **sustained, clinically meaningful preservation** at a **sustainable health-system cost**.

Table: Comparative effectiveness and adverse events (key trial signals)

Therapy	Key Phase/ Study	Clinical effectiveness (primary clinical endpoint)	Notable biomarker effect	ARIA-E (edema/ effusion)	Symptomatic ARIA-E	ARIA-H (microhemorrhage/ siderosis)	Other common AEs / notes
Aducanumab	Phase 3 **EMERGE/ ENGAGE**	**Mixed:** EMERGE met primary endpoint (CDR-SB ≈ −0.39 at 78 wk; ~22% slowing); ENGAGE negative	Dose-dependent amyloid-PET reduction	**~35%** (high-dose)	**~9%** of all high-dose pts (≈26% of ARIA-E cases)	Microhemorrhage ~19%, superficial siderosis ~15% (high-dose)	Infusion reactions; intensive MRI monitoring needed

Therapy	Key Phase/ Study	Clinical effectiveness (primary clinical endpoint)	Notable biomarker effect	ARIA-E (edema/ effusion)	Symptomatic ARIA-E	ARIA-H (microhemorrhage/ siderosis)	Other common AEs / notes
Lecanemab	Phase 3 **CLARITY-AD**	**CDR-SB –0.45 at 18 mo** (~27% slowing)	~59-centiloid PET reduction; broad biomarker improvement	**12.6%**	**2.8%**	**~17%**	Infusion reactions ~26% (vs 7% placebo)
Donanemab	Phase 3 **TRAILBLAZER-ALZ 2**	**CDR-SB –0.70 at 76 wk** (~29% slowing; larger effect in low/ medium tau)	Rapid plaque clearance; high PET-negativity by 76 wk	**24%**	**~6%**	**~31%** (vs ~14% placebo)	Infusion reactions ~9%; a few treatment-related deaths reported
Trontinemab	**Phase Ib/IIa** (ongoing); **Phase III** starting	**No Phase 3 clinical outcomes yet** (early-phase not powered for CDR-SB)	**~90% amyloid-PET negative by ~28 wk**; strong CSF/ plasma biomarker shifts	**<5%** (early-phase)	Very rare symptomatic cases reported to date	Not clearly elevated so far (early-phase)	BrainShuttle aims for higher CNS exposure at lower doses ▫ potential for reduced monitoring burden if Phase 3 confirms safety/ efficacy

APOE Genotype and CSF Biomarkers in Alzheimer's Disease

Elka Stefanova
Faculty of Medicine, University of Belgrade, Belgrade, Serbia

Certain genes can increase the risk of developing dementia, including Alzheimer's disease. One of the most significant genetic risk factors is a form of the apolipoprotein E (APOE) gene called **APOE4**. Approximately 25% of people carry one copy of APOE4, while 2–3% carry two copies. APOE4 is the strongest known genetic risk factor for Alzheimer's disease, though inheriting it does not guarantee that an individual will develop the condition.The **APOE gene** exists in several forms (alleles), with **APOE3** being the most common and not associated with increased Alzheimer's risk. **APOE2** is relatively rare and may offer some protective effects. The reason APOE4 increases the risk of Alzheimer's is not fully understood. The APOE protein plays a role in transporting cholesterol and other fats through the bloodstream. Recent research suggests that disruptions in how brain cells process fats (lipids) may contribute to Alzheimer's and related neurodegenerative diseases.The **APOE ε4 (epsilon4)** allele appears to influence levels of **beta-amyloid 42 (Aβ42)** in cerebrospinal fluid (CSF). It remains unclear whether this effect is due to the allele's association with amyloid deposits in the brain or whether APOE ε4 directly alters CSF Aβ42 levels, independently of amyloid pathology. To determine whether the APOE genotype affects the diagnostic accuracy of CSF biomarkers for Alzheimer's disease (AD), particularly Aβ42 levels.

We analyzed data from 1,000 individuals aged 45 to 78 with baseline CSF samples. The cohort included participants with AD, prodromal AD, mild cognitive impairment (MCI), other dementias, and cognitively normal controls. We measured CSF levels of Aβ42, total tau, and phosphorylated tau in relation to the APOE ε2/ε3/ε4 genotype across diagnostic categories. CSF Aβ42 levels—but not total or phosphorylated tau—were significantly lower in APOE ε4 carriers compared to non-carriers, regardless of diagnostic group. Despite this, CSF Aβ42 levels were able to distinguish individuals with AD from both controls and those with stable MCI, even after accounting for APOE genotype. Both CSF Aβ42 levels and APOE ε4 carrier status were **independent predictors** of AD diagnosis. However, in non-AD groups, APOE ε4 status did **not** significantly affect Aβ42 levels. CSF Aβ42 levels are strongly associated with Alzheimer's disease and provide diagnostic value independently of APOE genotype. APOE ε4 affects Aβ42 levels in AD, but does not influence these levels in individuals without the disease.

Visual dysfunction in synucleinopathies

Cristian Falup-Pecurariu[1,2]
[1]County Clinic Hospital, Brasov, Romania
[2]Transylvania University of Brasov, Romania

Visual dysfunction is increasingly recognized as a prevalent and clinically relevant non-motor manifestation in synucleinopathies, mainly of Parkinson's disease (PD), reflecting both peripheral ocular abnormalities and central neurodegenerative processes. These disturbances significantly impair daily functioning, compromise quality of life, and may provide valuable insights into disease progression.

Peripheral visual alterations are common, with dry eye disease representing the most frequent manifestation, affecting over half of patients. This condition arises from reduced blink frequency, autonomic dysfunction, and adverse effects of antiparkinsonian medications, resulting in ocular discomfort, blurred vision, and fluctuating visual clarity. While management with lubricating agents and adjunctive therapies is available, therapeutic adherence is often hindered by motor limitations, and no PD-specific interventions have been validated.

Central visual deficits contribute substantially to disease burden. Impaired contrast sensitivity, reduced color perception, and abnormalities of ocular motility are frequently observed, with diplopia affecting a significant proportion of patients. Diplopia, often linked to convergence insufficiency and cognitive decline, may coexist with visual hallucinations, one of the most disabling manifestations of PD. Visual hallucinations are strongly associated with disease progression, cognitive deterioration, and an increased risk of dementia, underscoring their potential as clinical markers of neurodegeneration. Comprehensive evaluation of visual dysfunction in PD requires a multimodal approach, integrating structured clinical assessment, non-motor symptom questionnaires, vision-specific scales, and advanced ophthalmological techniques. Optical coherence tomography has demonstrated retinal layer thinning in PD, suggesting potential utility as a biomarker for neurodegenerative progression.

Despite its prevalence and impact, visual dysfunction in PD remains underdiagnosed and undertreated. Current management strategies are primarily symptomatic and fragmented, highlighting the urgent need for systematic screening protocols, targeted therapies, and longitudinal studies to clarify the role of visual biomarkers in disease monitoring.

Visual dysfunction in PD represents a critical interface between peripheral pathology and central neurodegeneration. Its recognition and integration into routine clinical practice have the potential to enhance patient care and reduce morbidity.

Late-stage Parkinsonism: characteristics and the role of specialized care and palliative care

Per Odin[1,2]
[1]Lund University, Lund, Sweden
[2]Skane University Hospital, Lund Sweden

The number of studies focusing on the last stages of Parkinson´s disease (PD) is still relatively limited. Patients often develop a severe symptomatology with increasing immobility, decreasing effect of the medication and an increasing load of non-motor symptoms. They often have difficulties to come to specialist care and many are mainly treated by general practioners with limited experience of PD. Many have insufficient dopaminergic medication and it is not uncommon with contraindicated medication. In the European Care of Late Stage Parkinsonism, "CLASP" project we could confirm that the health-related quality of life (hr-QoL) of the patients is very low, but also that contact with specialist neurological care (Neurologists with good experience with PD and PD nurses) correlated with better QoL. An intervention including receiving advice from a PD specialist resulted in higher doses of dopaminergic medication, improved motor symptomatology and better hr-QoL. This was the starting point of the European PD_pal project, where patients got specialist care in form of a PD nurse who repeatedly visited the patient at home and developed an advanced care plan together with patient and caregiver. Palliative care and end-of-life care principles were included in the plan when relevant. This plan was then communicated to all personel involved in the patients medical and social care. The results of the study on the European level are still analyzed. Preliminary results from the Swedish population show improved hrQoL for the patient, without an increase in costs for the society. The results demonstrate the importance of providing specialist care also in the late stages of PD. Recognising Parkinson's disease as a neurodegenerative condition that benefits from specialist care and palliative care approach throughout its entire trajectory and not least in the late stages of the disease is of paramount importance, along with the imperative need to implement person-centred care approach.

Intrathecal immunogloblin synthesis in multiple sclerosis: why to talk about it in 2025

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Cerebrospinal (CSF) oligoclonal band (OB) testing reflects intrathecal IgG synthesis. It is a very sensitive method in the diagnosis of multiple sclerosis (MS) which has been used for many decades. CSF free kappa light chain (FKLC) determination is a modern test of intrathecal immunoglobulin synthesis that was recently included in the revised McDonald criteria for MS in addition to the OB.

OB determination is a demanding semiquantitative method which takes 2 or 3 days and the intepretation of results is subjective. On the other hand, FKLC determination is very simple and even more sensitive than OB testing that is easy to perform, cheap and gives a quantitative result. FKLC were also sometimes found to be present in OB-negative clinically isolated syndrome or MS patients and in patients with a single CSF band. Disadvantages of FKLC are lower specificity and lack of consensus on standardized interpretation method. There are also only few data about prognostic value of FKLC testing in early MS.

Taken together, CSF FKLC testing is complementary method to OB determination. Experts from German Society of Cerebrospinal Fluid Diagnostics and Neurochemistry recommend both tests to be done in suspected MS. Our data, however, indicate that the added value of parallel testing is minor in patients with highly positive or extremly low FKLC values (together observed in nearly 50% of testing samples). Two cut-off approach testing could therefore significantly reduce the workload of a specialized laboratory.

Progressive multiple sclerosis: therapeutic perspectives with a focus on symptomatic treatments

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Progressive multiple sclerosis (PMS), encompassing primary progressive (PPMS) and secondary progressive (SPMS) forms, presents significant therapeutic challenges due to its neurodegenerative nature and limited responsiveness to current disease-modifying therapies (DMTs). Agents like ocrelizumab and siponimod offer partial benefits in slowing disease progression in PPMS and SPMS, respectively. Promising developments include Bruton's tyrosine kinase inhibitors, particularly tolebrutinib. Nevertheless, these medications do not substantially alleviate the broad range of symptoms that severely impact patients' quality of life.

Spasticity is one of the most prevalent and debilitating symptoms in PMS, affecting up to 80–90% of individuals with MS. It is associated with reduced mobility, pain, fatigue, bladder dysfunction, and overall impairment of quality of life. Effective management requires a multidisciplinary approach, with physiotherapy and oral agents playing a central role. Second- and third-line treatments, such as cannabinoid-based therapies and botulinum toxin injections—especially for focal spasticity—are increasingly important and can be combined to optimize outcomes.

Other symptoms affecting quality of life in PMS patients include fatigue, pain, cognitive decline, and autonomic dysfunction, all of which require appropriate evaluation and treatment. A multidisciplinary, patient-centered approach is essential for improving daily function and overall quality of life, particularly in patients with a progressive disease course.

Early experience with subcutaneous levodopa treatment in advanced Parkinson's disease

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Continuous subcutaneous infusion of foslevodopa and foscarbidopa significantly improves motor fluctuations in patients with advanced Parkinson's disease whose symptoms are not adequately controlled by optimized oral levodopa regimens. In a pivotal phase 3 randomized, double-blind, active-controlled trial, this therapy led to a greater increase in "on" time without troublesome dyskinesia (mean difference vs. oral levodopa-carbidopa: 1.75 hours, 95% CI 0.46–3.05; p=0.0083) and a greater reduction in "off" time (mean difference: –1.79 hours, 95% CI –3.03 to –0.54; p=0.0054) over 12 weeks compared to oral therapy alone. These benefits were clinically meaningful and sustained in longer-term open-label extensions up to 124 weeks. [1-3]

The therapy is generally well tolerated, with the most common adverse events being infusion site reactions (erythema, pain, cellulitis, edema), which are usually mild to moderate but can lead to discontinuation in a minority of patients (22% in the phase 3 trial).[1-3] Serious adverse events are infrequent and similar in incidence to oral therapy. Systematic reviews and expert opinion confirm that foslevodopa/foscarbidopa infusion offers a non-surgical, reversible alternative to device-aided therapies for patients with refractory motor fluctuations, with efficacy comparable to other infusion therapies and a favorable benefit-risk profile. Long-term patient experience data also highlight high satisfaction, improved symptom control, and successful integration into daily life. Further research is ongoing to clarify long-term safety and comparative effectiveness.[2][4][5]

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Immunomodulatory effects of deep brain stimulation

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Deep brain stimulation (DBS), a neurosurgical therapy primarily used for movement and neuropsychiatric disorders, has been increasingly recognized for its immunomodulatory effects. Emerging evidence indicates that DBS can modulate both central and peripheral immune responses through various mechanisms. In the central nervous system, DBS has been shown to reduce neuroinflammation by decreasing microglial activation and altering cytokine expression, favoring an anti-inflammatory profile. Peripherally, DBS influences immune function by modulating circulating cytokines and immune cell activity, potentially through interactions with the autonomic nervous system and hypothalamic-pituitary-adrenal axis. These effects appear to be target- and condiion-specific, with implications for the treatment of disorders with neuroinflammatory components such as Parkinson's disease, depression, and obsessive-compulsive disorder. While the precise mechanisms remain under investigation, the immunomodulatory properties of DBS may contribute to its therapeutic efficacy and broaden its potential clinical applications. However, this is still a developing area, and more research is needed to clarify the mechanisms of these immune changes, their clinical relevance (e.g., whether they contribute to therapeutic effects or side effects), and the long-term impact of chronic DBS on immune function.

Technological advances in invasive treatment of Parkinson's disease

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Technological advances in invasive Parkinson's disease (PD) treatments include improved Deep Brain Stimulation (DBS) with sensing and closed-loop capabilities, novel drug delivery systems like subcutaneous apomorphine infusion, and evolving ablative therapies such as MR-guided focused ultrasound (MRgFUS). Also, this includes pumps for continuous subcutaneous (under the skin) or intrajejunal (into the small intestine) delivery of dopaminergic drugs to avoid problems in the functioning of the GE tract in advanced Parkinson's disease. With such continuous dopamine stimulation, we can achieve better management of the severe motor fluctuations and reduce "off" time by providing a steady drug supply. These innovations are enhancing precision, efficacy, and personalization in treating motor symptoms, particularly when medication becomes insufficient, integrating advanced imaging, electrode technology, and artificial intelligence (AI)-driven decision-making for better patient outcomes. We have enhanced electrodes with segmented leads that allow us using directional steering and "closed-loop" stimulation, which adapts to brain activity. Sensing Capabilities are also a huge improvement with brain leads developed to not only deliver stimulation but also to sense neural activity, enabling more dynamic and precise modulation. AI-driven planning and machine learning are used with neuroimaging to better identify optimal targets and stratify patients for DBS, leading to more personalized treatment.

Advances in drug delivery innovations and new formulations in continuous Infusion Pumps help us with providing 24-hour symptom control. The new evolving ablative therapy MR-Guided Focused Ultrasound (MRgFUS) uses focused ultrasound waves to create small, precise lesions in specific brain areas (like the thalamus or globus pallidus) to target tremor, rigidity, and bradykinesia. Advances in imaging and stereotactic techniques allow for more accurate targeting and less invasive procedures for ablative treatments compared to older methods. Technologies like MRI and CT scans provide detailed visualizations of the brain, which is crucial for planning and guiding these complex surgical procedures. The development and refinement of stereotactic frames allow neurosurgeons to precisely target deep brain structures for therapeutic interventions. Software, including AI and machine learning, is integral for analyzing neuroimaging data, monitoring patient symptoms in real-time with wearable biosensors, and enabling dynamic, closed-loop treatment systems.
All these technological advances that help us better manage and control the symptoms of Parkinson's disease patients will be presented in the lecture.

Key words: Technological advances; invasive treatment; Parkinson's disease

Hereditary ataxias: an update

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The hereditary ataxias are a clinically and genetically heterogeneous group of disorders characterized by slowly progressive incoordination of gait and often associated with poor coordination of hands, speech, and eye movements.Autosomal recessive ataxias (ARCA) are a complex group of diseases that present as primary ataxias or rare, complex metabolic disorders, with ataxia being one of the clinical manifestations. To date, over 40 genes that can give an autosomal recessive form of ataxia have been described, and if we add metabolic diseases and complex diseases manifesting with ataxia together with other neurological and systemic signs, that number is even higher. Genetic panels that would diagnose most of these diseases involve a very large number of genes. Therefore, in the literature have been various attempts to classify these diseases as well as attempts to create algorithms based on which patients could be referred to targeted testing.The majority of ARCA cases typically present in childhood, though some may manifest later with atypical symptoms. A small number of ARCA cases present exclusively in adulthood. We propose an algorithm that could be used when encountering patients with adult-onset sporadic or recessive ataxia for whom acquired causes have been excluded. The differential diagnosis of adult-onset ataxias does not always consider ARCA to be a potential cause. Raising awareness of their clinical significance is important not only because some of these disorders may be treatable but also for prognostic implications and for including patients in future clinical trials with disease-modifying agents.

Transcranial pulse stimulation as a not invasive forma of brain stimulation in neurodegenerative disorders

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Tremor is a common sign in movement disorders, and is especially evident at rest in neurodegenerative conditions such as Parkinson's Disease (PD). It has been evident that, in PD, resting tremor relief may be sensitive to brain stimulation protocols, ranging from (invasive) Deep Brain Stimulation to (non-invasive) Transcranial Magnetic Stimulation. In this context, Transcranial Pulse Stimulation (TPS) is a painless and non-invasive recent technique, which allows to obtain magnetic fields by means of low frequency ultrasounds. We investigate the possibility to observe changes in resting tremor's parameters (and, thus, in neural activity) induced by single-session TPS delivered on the motor cortex of PD patients. TPS was delivered in 6 patients: resting tremor was measured at baseline (T0), after the TPS intervention (T1; single-session stimulation administered at 4Hz, 0.20 mJ/mm2; 1500 pulses delivered covering the contralateral motor cortex -with respect to the most affected side-), and after 24 hours from treatment (T2). At baseline, resting tremor was present in all patients, with an average frequency of 9-10 Hz/sec. After intervention, a tremor reduction was noted at T1 and T2 (compared to baseline), ranging from (X) to 57% in amplitude. Importantly, in all the patients we noted a decrease in amplitude (and/or duration) of tremor at rest, but not in its frequency. No effect was noted after placebo stimulation. TPS is a new non-invasive brain stimulation solution that may induce a reduction of resting tremor in PD patients, lasting for at least 24 hours after a single-session intervention. Importantly, no side effects were noted. Evidence is discussed suggesting a signif icant physiological change in neural circuits that are normally affected in this type of patients.
TPS is new form of transcranial brain stimulation for degenerative disorders actually used for treatment of Alzheimer disease and psychiatric disorders. The novelty is the efficacy on motor disorders usually sensitive to brain stimulation.

The role of art in neurodegenerative diseases

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The art plays a vital role in promoting and maintaining brain health by stimulating cognitive functions, enhancing emotional well-being, and encouraging neural plasticity, what is especially important in neurodegenerative diseases.
Activities such as painting, music, dance, writing, and drama are not only forms of self-expression but also engage various brain regions involved in memory, attention, sensory processing, and problem-solving. Regular participation in creative activities has been linked to improved mental sharpness and the preservation of cognitive functions, particularly as we age. For example, playing a musical instrument or engaging in visual arts involves intricate motor skills, auditory processing, and memory, which together contribute to stronger neural connections and improved brain function.

Beyond cognitive enhancement, the art has therapeutic benefits, particularly for emotional and psychological health. Engaging in artistic practices can help reduce stress, anxiety, and depression, all of which are known to negatively impact brain health. Activities like drawing, writing, or even listening to music provide an emotional outlet, fostering a sense of well-being and reducing the physiological effects of stress on the body and brain. This can be particularly beneficial for those facing mental health challenges or for patients with neurodegenerative diseases, offering a safe space for self-reflection and emotional release.

Furthermore, the art has demonstrated its effectiveness in rehabilitation, particularly for individuals recovering from brain injuries or managing neurodegenerative diseases such as Alzheimer's and Parkinson's. Art therapies have been shown to help stimulate memory recall, improve motor skills, and enhance the quality of life for patients by fostering a sense of purpose and connection. In people with dementia, for instance, art therapy can evoke positive memories and emotions, improving communication and social interaction, and slowing down cognitive decline.

From genetic diagnostics to mechanisms of neurodegenerative disorders

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Is it possible for routine genetic diagnostics to give rise to important insights into the mechanism of neurodegenerative disorders? Despite advances in methodology and interpretation and many discoveries recently made in the field of neurodegenerative disorders, their routine genetic diagnostics appear rather complicated at first glance. While there are many commercial tests available for diseases with a single molecular cause, such as Friedreich's ataxia or Huntington's disease, other neurodegenerative disorders, such as Parkinson's disease or ataxias, are more complex and require a different approach. Good practices in genetic diagnostics of such neurodegenerative disorders include an optimization of the routine genetic testing (e.g. c9orf72 and SOD1 testing for amyotrophic lateral sclerosis (ALS)), evaluation of the clinical utility of testing (e.g. Parkinson's disease), the rapid implementation of testing for novel diseases (e.g. Cerebellar ataxia neuropathy, and vestibular areflexia syndrome (CANVAS) and FGF-14 related ataxia), and continuous implementation of improvements in testing and interpretation pipelines, automated reinterpretation of variants of uncertain significance. The establishment of the National centre for undiagnosed rare disease in Slovenia enables our undiagnosed patients access to state-of-the-art testing using new technologies, such as whole genome sequencing (WGS), optical genome mapping (OGM), and long read sequencing (LRS) through collaboration with Solve-Rare Disease (Solve-RD) and European Rare Diseases Research Alliance (ERDERA), and to various supporting resources such as a dietitian, psychologist, and various rare-disease specialists as part of the European Reference Network (ERN) and JARDIN (Joint Action to integrate ERN into National Healthcare Systems). Through the implementation of these measures, including responsible data sharing and patient matching e.g.(Matchmaker Exchange

and GeneMatcher), routine genetic diagnostics lead to solving clinical cases and the discovery of new genes and mechanisms in neurodegenerative disorders.

Time-resolved methods with single-molecule sensitivity: from fundamental insights to early disease diagnosis

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Time-resolved methods with single-molecule sensitivity are transforming our understanding of complex biomolecular processes *in vitro* and in live cells. Unlike ensemble approaches, these techniques can resolve lowly populated, transient dynamical states that often drive pathogenic pathways, providing insights that can directly inform early disease detection. We have recently developed a novel, time-resolved fluorescence correlation spectroscopy (FCS) method that can measure the concentration and size of Thioflavin T (ThT)-binding amyloid aggregates in serum and cerebrospinal fluid (CSF) [1-4], enabling detection of disease-relevant amyloids before plaque deposition. In this method, the amyloid-specific fluorescent dye ThT, from which several amyloid-specific probes for amyloid positron emission tomography (amyloid-PET) were derived, is used to render amyloids fluorescent and thus amenable for detection using our approach. We have also used this methodology to investigate novel small-molecule decoys that interfere with early Aβ aggregation stages, providing mechanistic insight into protofibril formation and offering promising leads for therapeutic modulation [5]. Furthermore, we have applied super-resolution stimulated emission depletion (STED) microscopy to reveal heterogeneous amyloid fibril morphology *in situ* with nanoscale precision [6]. In my presentation, I will describe these methods and results obtained by serum and CSF analysis in healthy individuals and patients from naturalistic and well-characterized memory clinic cohorts. I will also discuss the potential of our method for early Alzheimer's disease diagnosis, for monitoring disease progression, and for assessing the therapeutic efficacy of treatments aiming to reduce the amyloidogenic load.

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The regulation of innate immune gene expression in neurodegenerative disorders

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Inflammation is a key component of the innate immune response. Primarily designed to remove noxious agents and limit their detrimental effects, once prolonged and/or inappropriately scaled innate immune response may be detrimental to the host and lead to disease. Therefore, control checkpoint mechanisms implicated in the regulation of innate immune gene expression are instrumental in the maintenance of the host immune homeostasis. Microglia are the principal immune cells of the brain. Although major clinical symptoms in amyotrophic lateral sclerosis (ALS) and other neurological diseases arise from neurodegeneration and loss of neurons, it is now well established that non-neuronal cells such as microglia play an important role in disease pathogenesis. A current view is that over the course of disease, microglia change their phenotypes from initially beneficial into highly toxic and aberrant cells resistant to any conventional immune-modulatory therapeutic interventions. Indeed, our recent work suggest that in ALS, as disease progresses, microglial cell gradually lose their immune phenotype and function, robustly increase their mitotic index and develop unconventional proteomes. The molecular mechanisms involved in this apparent shift in cellular profile remain elusive. We recently described a novel ribosome-based check-point mechanism involved in translational control of innate immune genes and microglia activation involving RNA binding protein SRSF3. Using a model-system for analysis of the dynamic translational state of microglial ribosomes we show that SRSF3 binds to 3'UTR of highly regulated innate immune transcripts and acts as a suppressor of translation, resulting in a chronic dissociation of mRNA and protein networks. We found that expression levels of SRSF3 are increased in immune cells in neuroinflammatory conditions in the context of acute and chronic neurodegeneration as well as in human disease. Importantly targeted knockdown of SRSF3 using anti-sense morpholino approach, initiated at late symptomatic disease, in ALS mouse model alleviated translational arrest of selected immune genes, restored phagocytic properties of microglia, slowed down disease progression and exerted significant disease modifying effects. Together, our findings suggest that targeting SRSF3 and mRNA translation may open new avenues for therapeutic reprogramming of immune response in ALS and potentially other neurodegenerative disorders

Of glial cells and endogenous retroviruses in MS related de- and regeneration

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The adult central nervous system is vulnerable to disease and injury, with a limited regeneration capacity. Repair is mainly restricted to the replacement of oligodendrocytes and the reconstitution of white matter through the activation of precursor and stem cells, but remains inefficient overall. This is also true for Multiple Sclerosis (MS), where autoimmune activities coexist with neurodegeneration and neuroregeneration processes. In our research, we investigated critical molecular and cellular processes responsible for the lack of efficient myelin repair. We identified the p57kip2 gene, which encodes a negative regulator of oligodendroglial precursor- and adult neural stem cell differentiation. Studies addressing the underlying mode of action and potential biomedical applications of these observations will be presented. In the second part of my talk, I will discuss the relationship between human endogenous retroviruses (HERV) and MS. I will highlight the role of a specific entity called HERV-W in fostering microglial polarisation and neurodegeneration, while simultaneously interfering with myelin repair activities.

Neuroaging unmasked: why Time Is the Brain's Greatest Enemy

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Aging is the most powerful risk factor for neurodegenerative disorders, particularly Parkinson's disease (PD). As human longevity increases, the paradox emerges: extended lifespan accompanied by escalating vulnerability to cognitive decline, frailty, and neurodegeneration. This lecture explores why time itself is the brain's most relentless adversary, tracing the converging biological hallmarks that drive neuroaging and neurodegeneration.

At the cellular level, the aging brain undergoes mitochondrial dysfunction, impaired proteostasis, oxidative stress, and genomic instability. Telomere attrition, epigenetic drift, and chronic neuroinflammation progressively erode neural resilience. A crucial and emerging factor is the accumulation of senescent cells. These cells, characterized by growth arrest and the senescence-associated secretory phenotype (SASP), release pro-inflammatory cytokines (e.g., IL-6, TNF-α) that fuel "inflammaging" and compromise neuronal survival. Recent evidence shows elevated senescence markers (p16^INK4a, SASP factors) in substantia nigra tissue from PD patients, suggesting that senescence actively contributes to dopaminergic neurodegeneration.

Parkinson's disease exemplifies how age amplifies pathology. While α-synuclein aggregation, lysosomal dysfunction, and genetic variants (SNCA, LRRK2, GBA1) define PD neuropathogenesis, aging accelerates these processes by weakening compensatory plasticity and intensifying susceptibility to toxins and inflammation. Time is therefore not a passive backdrop but a pathogenic co-factor.

Yet neuroaging is not wholly irreversible. Lifestyle factors—exercise, cognitive stimulation, dietary modulation—enhance neurotrophic signaling and plasticity even in late life. Meanwhile, senolytic therapies such as Dasatinib, Quercetin, and Fisetin, as well as agents targeting mTOR, AMPK, and NAD+ metabolism, are being investigated as strategies to selectively eliminate senescent cells or blunt the SASP, offering a potential disease-modifying approach.

Ultimately, this lecture argues that unmasking neuroaging reveals time as both sculptor and saboteur: it shapes the developing brain and undermines it with age. Recognizing senescence and other hallmarks of aging as active drivers of neurodegeneration reframes PD and related disorders not only as diseases of protein or genes, but as diseases of time. The challenge before us is to transform aging from inevitability into opportunity—shifting from damage control toward preservation and resilience.

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Context-Specific Roles of *OPTN* Variants in ALS, FTD and Glaucoma: Insights from experimental models and computational analyses

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Mutations in the *OPTN* gene are associated with a range of neurological conditions, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and normal-tension glaucoma (NTG). The optineurin protein, encoded by *OPTN*, is a multifunctional polyubiquitin-binding adaptor involved in processes such as inflammatory signalling, autophagy, vesicle trafficking, and axonal transport. These roles point to a critical involvement of optineurin in neurodegenerative and neuroinflammatory pathways, but the precise mechanisms by which *OPTN* variants contribute to disease remain unclear. Here we analysed the role of *OPTN* variants in ALS, FTD, and NTG using a combination of experimental models and computational analyses. Our C-terminal truncation mouse model (Optn470T) was characterized at neurological, neuropathological, and immunological levels. Additionally, Optn470T mice were crossed with a previously established model carrying the human ALS/FTD-linked mutation TDP43-G348C, enabling us to explore how optineurin insufficiency influences pathology in the presence of another disease-relevant mutation. Experimental findings revealed that Optn470T mice did not exhibit ALS/FTD-like pathology compared to wild-type mice but displayed diminished activation of the TBK1 pathway and reduced secretion of IFN-beta and its downstream targets in myeloid cells upon lipopolysaccharide (LPS) stimulation. These impairments were also observed in myeloid cells derived from Optn470T x TDP43G-348C mice but not in cells from TDP-43G-348C mice alone. Interestingly, aged Optn470T x TDP43-G348C mice showed improved motor

and cognitive performance compared to TDP43-G348C mice, and increased resistance to LPS-induced sepsis. This suggests an unexpected protective effect of optineurin insufficiency in these contexts. Computational analyses provided further insight into >100 *OPTN* mutations reported in neurological patients, revealing an enrichment of loss-of-function mutations in ALS and FTD, with their near absence in NTG. Furthermore, missense variants with predicted pathogenicity in ALS were significantly enriched in the C-terminal zinc finger domain, whereas predicted pathogenic NTG variants were predominantly located in the N-terminal coiled-coil domain. These findings emphasize the heterogeneity of *OPTN* variants and highlight the importance of context-specific mechanisms in driving disease pathology.

How old is your brain?
-on brain health and neurodegeneration through the exposome lens

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Have you ever thought that your brain's age might differ from your actual chronological age? The gap between these values, the Brain Age Gap (BAG) offers important insights into the mysteries of brain aging, health, and disease. Taking a closer look at the factors behind BAG brings us to a shift in perspective that holds promise to fill in the gaps in our understanding of neurodegenerative disease causes and prevention, viewed through the exposome lens.

I will challenge the common belief that old age is the leading risk for dementia and that the rising numbers approaching to a "pandemic to be", are simply the price of longer lifespans. On the other hand, early-onset Alzheimer's disease (EOAD, before the age of 65) is generally considered rare, with a genetic background, but this perception doesn't match reality at least not in North Macedonia (NM) which belongs to Europe geographically but is a LMIC. In 2024, EOAD (<65 years) accounted for 7.21% of all Alzheimer's cases in N.M., over twice the U.S. rate of 2.9%–3.6%. Dementia cases in North Macedonia are projected to rise by 166% by 2050, a much higher increase than in the neighboring countries. Raising questions and looking for answers, I will focus on brain "premature" ageing through the exposome lens (both physical and social) by providing data on BAG for two patients, showing accelerated brain ageing of 7.7 and 13.8 years, respectively, compared to their chronological age, based on gray matter volume. This could be partially explained by the diagnosis itself (atrophy is expected), but this acceleration also seems to be linked to macroscale exposomal factors (envi-

ronmental and societal exposures a person experience over lifetime). "Brain clocks" could be sensitive biomarkers of exposome effects, but it is important (and commonly overlooked) how combined physical, social, and political exposures impact brain aging. (results obtained in collaboration with the Latin American Brain Health Institute and the recent studies by Ibanez A. and Legaz A[1,2])

The discussion will examine how various exposomal factors may contribute to neurodegenerative disease pathogenesis (ex. air pollution- inflammation, DNA damage, epigenetic alterations), ending with a mathematical- philosophical perspective on how individual stress and (neuro)inflammation contribute to systemic dysfunction and affect global environment, thereby perpetuating inflammatory stress through a positive feedback loop.

This exposomal perspective on brain health, ageing and neurodegeneration is more comprehensive, multilayered, synergistic and closer to real world data, than looking at modifiable risk factors at an individual level only. It sheds light much further than amyloid clearing strategies only, or other single pathway DMTs, because we'll never come to a point to be able to "cure" more than the world we live in"produces"dementia cases and other neurodegenerative diseases including PD and ALS. While precision medicine has been and still is the "holy grail" in clinical medicine, there is also a need to broaden attention to *precision brain health* by incorporating exposomal science in preventive medicine.

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Impact of cognitive reserve on dementia progression

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Cognitive reserve denotes the brain's resilience to neuropathological damage, its ability to cope with and compensate for disease burden through more flexible or efficient cognitive strategies. This resilience largely stems from lifelong cognitive engagement, educational attainment, occupational complexity, and stimulating leisure activities. Understanding cognitive reserve is vital for clinicians and researchers aiming to interpret individual variability in dementia onset, progression, and outcomes.

The concept originated from epidemiological observations that individuals with higher educational or occupational achievements exhibited delayed onset of dementia despite comparable brain pathology. Cognitive reserve is often measured using proxy-

based indicators—such as education level, IQ, occupation, or leisure activity—and residual-based methods that quantify cognitive performance relative to brain pathology. Both approaches show protective effects, though residual-based measures can offer added precision.

A growing body of longitudinal research confirms that higher cognitive reserve significantly reduces the risk of progression to mild cognitive impairment (MCI) or dementia. Epidemiological studies support these findings: for example, individuals with fewer than 8 years of education had more than double the risk (2.2×) of developing dementia compared to those more educated. Similarly, low occupational attainment also increased dementia risk. Engaging in multiple leisure activities reduced dementia risk by 38%. Despite its protective role in delaying onset, cognitive reserve has been linked to more rapid cognitive decline once clinical symptoms appear. This paradox arises because higher- cognitive reserve in individuals may remain asymptomatic until neuropathology is advanced, resulting in a shorter clinical phase of dementia. More recently, a survey-based study using the Cognitive Reserve Index Questionnaire found that each unit increase in cognitive reserve score corresponded to an additional ~34 days before transition from mild to severe dementia, suggesting slower progression in higher cognitive reserve patients. Advances in neuroimaging and biomarker research help elucidate cognitive reserve mechanisms. PET imaging shows that in individuals with equivalent clinical severity of AD or MCI, higher cognitive reserve correlates with lower regional brain metabolism or blood flow, notably in posterior cingulate and precuneus areas—indicating that high- cognitive reserve brains cope despite advanced pathology. In cognitively normal individuals, higher cognitive reserve markers (education, IQ, occupation) were associated with slower decline of CSF $A\beta_{42}$ and more stable FDG-PET signals—suggesting not only compensation but also a possible neurobiological deceleration of pathology. This may seem contradictory to the paradox—implying potential heterogeneity depending on methodology, stage of disease, and type of measure used.

Cognitive reserve constitutes a dynamic, multifactorial construct central to variability in dementia onset and progression. It delays clinical manifestation but may coincide with accelerated decline once symptoms appear—reflecting an intricate interplay between compensatory mechanisms and pathology burden. Integrating cognitive reserve into clinical assessment, prognosis, and preventive strategies is essential for personalized, stage-sensitive dementia care.

Autonomic nervous system in Huntington disease: what are the promises for the future

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Background and objective: Autonomic dysfunction has been proven in Huntington disease (HD). Early research started in 1970-s. The progress was gradual with more studies ongoing in 21st century when our group joined the research. Increased sym-

pathetic reactivity in gene carriers and mildly to moderately affected patients were found as well as lower orthostatic ratio in advanced patients. After a reduced impact on decision-making processes in early HD was found we focused to the examination of central autonomic network (CAN) in early HD. Our aim was to find CAN reactivity in HD mutation carriers/patients and to find/follow relationship between autonomic activity and clinical decline.

Methods/results: Evaluation of motor functions, psychological tests and total functional capacity according to united Huntington disease rating scale (UHDRS) were performed in mutation carriers/patients. Heart rate (HR), blood pressure (BP) and cutaneous laser Doppler flux (LDF) were measured at rest, during mental stress, cold pressor and local cooling test. Autonomic tests were correlated to UHDRS motor and psychological tests and functional capacity. Analyses of heart rate variability (HRV) and RMSSD HR were performed. The tests were done in cross sectional and follow up studies. HD mutation carriers/subjects were assorted to groups: presymptomatic (PHD), early (EHD), mid stage (MHD) and late stage (LHD) patients. In cross sectional studies HR and/or BP values were higher in late (cortical) phase ($p<0.05$) in PHD/EHD group. A positive correlation was also found between better symbol digit modalities (SDMT) score and lower LDF. A longitudinal HRV study revealed a significant drop of sympathetic activity ($p<0.05$) and a drop of sympathetic modulatory activity during the observation time. An ongoing study revealed no differences in resting conditions and/or differences from the controls. Response to mental stress test in the stable HD group was better preserved than in the unstable group (BP systolic, $p=0.0036$, diastolic $p=0.0005$, HR $p=0.0492$). Correlations between Luria 3 step test and LDF at the beginning ($R=0.069$, $p=0.00273$) and HR at the end of observation time ($R=0.752$, $p<0.0001$) were also significant. Differences to controls were significant too. Rivastigmine treatment however did not show effect on cognitive functions, possibly due to absence of effect on executive functions.

Conclusions: After 10 years HRV revealed a drop of autonomic activity but not the same in all HD groups. In the stable group parasympathetic and sympathetic activity after 10 years were lower than at the beginning. In the unstable group parasympathetic activity was significantly lower with an unsignificant increase of sympathetic activity. In an ongoing study sympathetic response to mental stress was better preserved in the stable group. Components of sympathetic activity during mental stress (LDF and HR) correlated to Luria 3 step test (an executive functions test). The results are in line to previous cross-sectional studies.