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

7th RIJEKA FORUM ON NEURODEGENERATIVE DISEASES

NEURODEGENERATIVE DISEASES: MECHANISTIC THERAPIES - HYPE OR HOPE?

Endorsed by Associations
"Parkinson i mi" and "Neurodeg"

Rijeka, September 18-20, 2023
8.30 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, Robert Živadinov, Vanda Juranić Lisnić, Alen Ružić, Zdravka Poljaković

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Registration: online via registration form

Free admission for registrations

Information

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P R O G R A M
OPENING
(8:30-9:00)

Introduction

Stipan Jonjić, M.D., PhD, Professor, F.C.A., Head of the Department of 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, Associate Professor, Dean, Faculty of Medicine, University of Rijeka, Rijeka, Croatia

Snježana Prijić Samaržija, PhD, Professor, Rector, University of Rijeka, Rijeka, Croatia

1st day – September 18th, 2023

PROGRAM

9,00 – 11,00 h

I. AMYLOID DISEASE - PATHOLOGY AND TREATMENTS

Chairmen: Nenad Bogdanović and Vladimira Vuletić

John Hardy, M.D., PhD, Professor, Institute of Neurology, University College London, London, UK
Amyloid therapies work (somewhat). What next?

Dean Nižetić, M.D**,** PhD, Professor, Blizard Institute, Barts and the London School of Medicine and Dentistry, London, UK
Uncovering pathogenic and protective mechanisms for Alzheimer's disease using human cerebral organoids

Catherine Mummery, M.D., PhD, Professor, National Hospital for Neurology and Neurosurgery, London, UK
Genetic therapies in dementia: innovation in early phase trials

Elena Moro, M.D., PhD, Centre Grenoble University Hospital Center, and Grenoble Alpes University, Grenoble, France
Towards personalized medicine in neurodegenerative disorders: The importance of sex and gender

Break for refreshment: 11:00 – 11:30

11,30 – 14,00 h

II. PROTEINOPATHIES, TAUPATHIES, ALPHA-SYNUCLEOPATHIES - TOWARDS PERSONALIZED MEDICINE

Chairmen: Zvezdan Pirtošek and Nenad Bogdanović

Kailash Bhatia, M.D., PhD, Professor, Institute of Neurology, University College London, London, UK **"Atypical"- atypical parkinsonism**

Vladana Vukojević, Associate Professor, Karolinska Institute, Stockholm, Sweden
Amyloid nano-plaque detection with single-molecule sensitivity as a potential for early diagnosis of Alzheimer's disease

Nenad Bogdanović, M.D., PhD, Professor, Karolinska Institute, Stockholm, Sweden
Synuclein Family and three unpredictable children

Nir Giladi, M.D., Tel Aviv Medical Center, Center for Prevention and Treatment of Parkinson's Disease; Faculty of Medicine and Sagol School of Neuroscience, Tel Aviv University, Israel
What can be learned from the Biogen anti synuclein monoclonal Ab study and the Venglustat study in GBA PD, two negative clinical trials targeted the basic mechanisms of Parkinson's disease

Tamas Revesz, M.D, PhD, FRC Path, Professor Emeritus, Institute of Neurology, University College London, London, UK
An up-to-date classification of tauopathies

**** NOTE - Workshop - Neuroimaging in Multiple Sclerosis - current practice and national standardization of MRI reports." (limited number of participants- room 030 Biotechnology) from 12:00 – 13:00h.**

Lunch break: 14:00 – 15:00

15,00 – 18,30 h

III. NEURODEGENERATIVE DISEASES - BIOMARKERS AND TREATMENTS

Chairmen: Bettina Balint and Fran Borovečki

Bettina Balint, M.D., PhD, University Hospital Zurich, University of Zurich, Zurich, Switzerland
Autoimmune mechanisms of neurodegeneration

Mario Habek, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
The importance of autonomic nervous system testing in early neurodegenerative diseases

Niels Bergsland, PhD, Assistant Professor, University at Buffalo, Buffalo, USA
New imaging biomarkers in Parkinson's disease

Borut Peterlin, M.D., PhD, Professor, University Medical Center Ljubljana, Ljubljana, Slovenia
Integratomics of Parkinson's disease: towards the mechanisms of disease

Zvezdan Pirtošek, M.D., PhD, Professor, University Medical Center Ljubljana, Ljubljana, Slovenia
Visuo-spatial impairment in Parkinson's disease - associated cognitive decline

Fran Borovečki, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
Biomarkers in early Alzheimer's disease

Elka Stefanova, M.D., PhD, Professor, School of Medicine, University of Belgrade, Belgrade, Serbia
Monogenetic Forms of Early Dementias -One Gene Different Phenotypes.

2nd day – September 19th, 2023

9,00 – 11,00 h

IV. MULTIPLE SCLEROSIS

Chairmen: Robert Živadinov and David Bonifačić

Robert Živadinov, M.D., PhD, Center for Biomedical Imaging at Clinical Translational Science Institute and Department of Neurology, University at Buffalo, Buffalo, USA
Role of iron in multiple sclerosis: Should we target neurodegeneration and repair?

Menno Schoonheim, PhD, Associate Professor, VU University Medical Center, Amsterdam, Netherlands
Cognitive reserve and network efficiency in multiple sclerosis

Michael G. Dwyer, PhD, Associate Professor, University at Buffalo, Buffalo, USA
Artificial intelligence in multiple sclerosis and other neurodegenerative disorders

David Bonifačić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka, Croatia
Disease Modifying Therapies (DMT) in multiple sclerosis - now and in the future

Break for refreshment: 11:00 – 11:30

11,30 – 14,00 h

V. NEUROPLASTICITY AND NEURODEGENERATIVE DISEASES

Chairmen: Paolo Manganotti and Gabriela Novotni

Vida Demarin, M.D., PhD, Professor, 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
Harnessing neuroplasticity in neurodegenerative disorders

Amos D. Korczyn, M.D., PhD, Professor Emeritus, CONy President, Tel Aviv University, Tel Aviv, Israel
What is cognitive reserve?

Nataša Klepac, M.D., PhD, Professor, University Hospital Centre Zagreb, Zagreb, Croatia
The holy grail of cognitive training in the treatment of cognitively impaired patients

Gabriela Novotni, M.D., PhD, Professor, University Clinic of Neurology, Medical Faculty, University "Ss Cyril and Methodius", Skopje, North Macedonia
Deciphering neurodegenerative diseases - from a clinician's perspective to future implications

Paolo Manganotti, M.D., PhD, Professor, Cattinara University Hospital ASUGI and University of Trieste, Trieste, Italy
Brain stimulation in neurodegenerative diseases

Lunch break: 14:00 – 15:00

15,00 – 16,30 h

VI PARKINSON'S DISEASE

Chairmen: Maja Trošt and Norbert Kovacs

Vladimira Vuletić, M.D., PhD, Professor, Clinical Hospital Center Rijeka and Faculty of Medicine, University of Rijeka, Rijeka, Croatia
Nonmotor symptoms (NMS) in Parkinson's disease - Is this the way towards personalized medicine

Norbert Kovacs, M.D., PhD, Professor, Department of Neurology, University of Pecs, Pecs, Hungary
Functional symptoms in Parkinson's disease patients treated with device-aided therapies

Dejan Georgiev, M.D., PhD, Professor, University Medical Centre Ljubljana, Ljubljana, Slovenia
Mechanisms of action of deep brain stimulation: do we really know how does it work?

Maja Trošt, M.D., PhD, Professor, University Medical Centre Ljubljana, Ljubljana, Slovenia
Is parenteral levodopa treatment a mechanistic one?

Break for refreshment: 16:30 – 17:00

17,00 – 19,00 h

VII. OTHER NEURODEGENERATIVE DISORDERS AND NEUROLOGICAL CONDIOTION

Chairmen: Dejan Georgiev and Darko Chudy

Marina Svetel, M.D., PhD, Professor, School of Medicine, University of Belgrade, Belgrade, Serbia
What we have learned of our more than 150 Wilson's disease cases

Patrick Küry, M.D., PhD, Professor, Medical Faculty, Heinrich-Hein University of Düsseldorf, Düsseldorf, Germany
A mechanistic approach to the development of myelin repair therapies for multiple sclerosis

Darko Chudy, MD, PhD, Professor, University Hospital Dubrava, Zagreb, Croatia
Deep brain stimulation (DBS) in patients with disorder of consciousness - updates

Ivana Munitić, M.D., PhD, Professor, Department of Biotechnology, University of Rijeka, Croatia
Neuroimmunity in amyotrophic lateral sclerosis (ALS) – mechanistic potential

Silva Katušić Hećimović, PhD, Professor, Ass. Professor, Institut Ruđer Bošković, Zagreb, Croatia
The role of neuroinflammation in a "childhood Alzheimer's disease" Niemann-Pick type C

Martin Rakuša, M.D., PhD, Professor, University Hospital Center Maribor, Maribor, Slovenia
Biomarkers of frontotemporal dementia (FTD)

Slavica Kovačić, M.D., PhD, Assistant Professor, Clinical Hospital Center Rijeka, Rijeka, Croatia
Role of magnetic resonance imaging (MRI) in the modern treatment of neurodegenerative diseases

3rd day – September 20th, 2023

9,00 – 12,30 h

Satellite symposium: CNS disorders associated with COVID-19 and other viral infections

Chairman: Stipan Jonjić

Gregor Hutter, M.D., PhD, Professor, Department of Biomedicine, University of Basel, Basel, Switzerland
Actionable biomarkers for NeuroCOVID and LongCOVID

Glenn Bantug, M.D., PhD, Department of Biomedicine, University of Basel, Basel, Switzerland
Metabolic drivers of T and B cell function in CNS pathologies

Ilija Brizić, PhD, Assistant Professor, Faculty of Medicine, University of Rijeka, Croatia
Glial cell adaptation to latent cytomegalovirus Infection in the central nervous system

Break for refreshment: 10:30 – 10:45

Ulrich Kalinke, PhD, Institute for Experimental Infection Research, TWINCORE, Hannover, Germany
A call for help from the infected brain

Shirin Hosseini, PhD, Technical University of Braunschweig, Braunschweig, Germany
Effects of influenza A virus infection on hippocampal neuron structure and function in aged wild-type mice

Marina Babić Čač, PhD, Assistant Professor, Faculty of Medicine, University of Rijeka, Croatia
Immune cell crosstalk during neuroinflammation - role for cellular stress sensors

Lunch break: 12:30 – 13:00

13,00 – 14,00 h

**** NOTE - New technology of continuous application of levodopa (Maja Trošt)**

14,00 – 15,00 h

YOUNG RESEARCHER FORUM
Lectures

Valentino Rački, M.D., Clinical Hospital Centre Rijeka, Rijeka, Croatia
Whole-exome sequencing study of Parkinson's disease in the Croatian population

Laura Reiche, Heinrich Heine University, Düsseldorf, Germany
Translating promising myelin repair drug candidates to Down syndrome (DS): new opportunities for white matter restoration in DS?"

Lea Vidatić, Ruđer Bošković Institute, Zagreb, Croatia
BACE1 as a molecular target against neurodegeneration

Josip Peradinović, University of Rijeka, Rijeka, Croatia
Immunity in optineurin insufficiency mouse model during aging: From the central nervous system to the periphery

15,00 – 16,00 h

POSTER SECTION

16,00 – 16,30 h

CLOSING REMARKS

Chairman: Vladimira Vuletić

Supported by Croatian Science Foundation grant no. 7276
"The Epidemiology of Parkinson's Disease in Croatia and the Influence of Genetic Factors and Microbiota on the Progression and Treatment Outcomes of the Disease"

Supported by Sponsors:

Golden:

Other:

ABSTRACTS

Amyloid therapies work (somewhat). What next?

John Hardy
Institute of Neurology and Dementia Research Institute, UCL, London, UK

The recent successful clinical trials of lecanemab and dononemab finally offer hope for successful mechanistic treatments for Alzheimer's disease. However, these treatments did not halt the disease but rather slowed progression by ~30%. In my talk I will discuss these therapies, and the background to their success. I will also discuss the effectiveness of genetic analysis and fluid biomarkers to aid with earlier and accurate diagnosis and whether such earlier diagnosis may lead to better outcomes. Finally, I will also discuss other potential targets for AD therapy and whether combination therapies are a likely potential way to halt disease progression.

Uncovering pathogenic and protective mechanisms for Alzheimer's disease using human cerebral organoids

Aoife Murray[1], Emre Fertan[2], Dorothea Boeken[2], Pollyanna Goh[1], Gillian Gough[3], Ana Muniz-Garcia[1], Ivan Alic[1,4], David Klenerman[2] and Dean Nizetic[1]
[1]Centre for Genomics and Child Health, Blizard Institute,
Faculty of Medicine and Dentistry,
Queen Mary University of London, 4 Newark Street, London, E1 2AT, UK
[2]Yusuf Hamied Department of Chemistry, University of Cambridge,
Lensfield Road, Cambridge, UK
[3]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore
[4]Croatian Institute for Brain Research and Faculty of Veterinary Medicine,
University of Zagreb, Croatia.

We recently developed a model that establishes reproducible AD-like pathology in human cerebral organoids grown in vitro from non-invasively sampled strands of hair from 71% of Down syndrome donors (in a donor–specific manner), secretes Aβ peptides in the picomolar range, and faithfully reproduces proteolytic processing of Aβ detectable in patients' CSF1. From a trisomy 21 (T21) iPSC line that does not show overt organoid pathology, by CRISPR elimination of a single copy of the chr21 protective gene (BACE2), we developed a unique, isogenic T21 iPSC line (T21C5Δ7) that shows the accelerated (in 6 weeks) a triad of AD-like pathologies (amyloid plaque-like structures, pathologically conformed intra-neuronal Tau, and neuronal loss) which can be completely prevented by combined chemical β and γ-secretase inhibition1. Our main result was recently reproduced by others, who grew organoids from individuals with 2 copies of APP, but only one functional copy of BACE2, and these organoids too developed a similar triad of AD-related pathologies2.

We now have new data that establish the correlation of the visible AD pathology with the abundance of soluble toxic oligomeric aggregates of Aβ and Tau, secreted by the organoids, detectable and quantifiable using super-resolution imaging of single-molecule soluble aggregates that are smaller than 200 nm (the diffraction limit of light). We have also established two separate experimental paradigms for the transmission of AD pathology from the pathology positive, to the pathology negative recipient organoids.

These new data show the promise of this cerebral organoid system in mechanistically understanding the AD pathogenic process, as well as its potential to be developed into a drug screening system for compounds affecting pathological protein aggregation, and transmission of AD pathology in human brain.

References:
1 Alic I, Goh P, Murray A, Portelius E et al., Mol Psychiatry 2021 Oct;26(10):5766-5788.
2 Luo J, Zou H, Guo Y, Huang K, Ngan ES, Li P. Cell Death Discov. 2022 Feb 2;8(1):47.

Genetic therapies in dementia: innovation in early phase trials

Catherine Mummery
National Hospital for Neurology and Neurosurgery, London, UK

Recent focus in Alzheimer's disease (AD) trials has been on anti-amyloid immunotherapies, following the long-awaited breakthrough with approval of Leqembi and drugs showing increasing consistency in results with modest disease modification. There is wide-ranging discussion as to how these therapies might herald changes in treatments, services and research. We are in a new era with many lessons to learn on the implementation of these drugs; in parallel, it is critical we continue to diversify our drug portfolio, to explore other targets such as tau and inflammation, as it is highly likely we will need to use drugs in combination to comprehensively treat Alzheimer's disease. In this talk, I will discuss the use of novel cutting-edge therapeutic mechanisms such as gene silencing to treat not just genetic but also non-genetic forms of AD and other dementias.

There has been an explosion in the assessment of genetic therapies in recent years with dramatic success in some hereditary neurodegenerative diseases such as SMA, though there have also been disappointing results in Huntington's disease, for example. In AD there has been a rapidly growing interest in the use of genetic therapies such as anti-sense oligonucleotides and interference RNA to target production of tau and a-beta upstream, aiming to prevent accumulation.

I will explore the opportunities and challenges associated with these gene-silencing therapies. I will describe the pre-clinical and clinical work behind the phase 1 results of the first gene silencing treatment to be trialled in AD – an anti-tau antisense oligonucleotide – and the future plans for this therapy. I will update on the first interference RNA drug to be trialled in the brain - in young onset AD – and potential for other areas. I will touch on the new dynamic methods being explored to refine our understanding of real time production and clearance in the brain of these proteins by drugs, work which will directly impact our modelling of dosing regimes in these drugs and improve our understanding of drug effect.

For this work to be successful, close collaboration is essential between industry and academia, but also between clinical services and translational research. As new therapies come through, we must ensure we have the infrastructure required to complete these trials alongside new treatments, that we learn continuously from all trials, both negative and positive, and that patients are able to access therapies and trials equitably.

Amyloid nano-plaque detection with single-molecule sensitivity as a potential for early diagnosis of Alzheimer's disease

Ann Tiiman[1], Vesna Jelić[2], Jüri Jarvet[3], Sebastian Wärmländer[3], Lars Terenius[1], Astrid Gräslund[3], Nenad Bogdanović[1,2], Vladana Vukojević[1]

[1]Center for Molecular Medicine, Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden

[2]Division of Clinical Geriatrics, Department of Neurobiology, Care Sciences and Society (NVS), Karolinska Institute, Stockholm, Sweden

[3]Arrhenius Laboratories, Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden

Recent results of several clinical trials of therapeutic antibodies targeting amyloid beta (Aβ) peptides[1], which have shown positive results in both, decreasing amyloid plaque burden and slowing cognitive decline, highlight the importance of detecting amyloids – peptide/protein aggregates that are characterized by their unique cross-beta sheet secondary structure of beta strands align perpendicularly to the fibril axis, while they are still small and suspended in the biological fluids and not yet deposited as insoluble fibrils in plaques. We have recently developed a novel, time-resolved fluorescence correlation spectroscopy (FCS)-based method that can measure the concentration and size of Thioflavin T (ThT)-binding amyloids in serum and cerebrospinal fluid (CSF)[2-6]. In this method, the amyloid-specific fluorescent dye ThT, from which several amyloid-specific probes for positron emission tomography (amyloid-PET) were derived, is used to render amyloids fluorescent and thus amenable for detection using our method. We present this method and results obtained by serum and CSF analysis in healthy individuals and patients in naturalistic and well characterized memory clinic cohorts. We also discuss the potential of our method for early AD diagnosis, for monitoring its progression, and for assessing the therapeutic efficacy of treatments aiming to reduce the amyloidogenic load.

References

1. Söderberg L, Johannesson M, Nygren P, Laudon H, Eriksson F, Osswald G, Möller C, Lannfelt L. Lecanemab, Aducanumab, and Gantenerumab - Binding Profiles to Different Forms of Amyloid-Beta Might Explain Efficacy and Side Effects in Clinical Trials for Alzheimer's Disease. Neurotherapeutics. 2023 **20(1):**195-206.
2. Tiiman A, Jelić V, Jarvet J, Järemo P, Bogdanović N, Rigler R, Terenius L, Gräslund A, Vukojević V. Amyloidogenic Nanoplaques in Blood Serum of Patients with Alzheimer's Disease Revealed by Time-Resolved Thioflavin T Fluorescence Intensity Fluctuation Analysis. J Alzheimers Dis. 2019 **68(2):** 571-582.

3. Aksnes M, Müller EG, Tiiman A, Edwin TH, Terenius L, Revheim ME, Vukojević V, Bogdanović N, Knapskog AB. Amyloidogenic Nanoplaques in Cerebrospinal Fluid: Relationship to Amyloid Brain Uptake and Clinical Alzheimer's Disease in a Memory Clinic Cohort. J Alzheimers Dis. 2020 **77(2):** 831-842.
4. Aksnes M, Tiiman A, Edwin TH, Terenius L, Bogdanović N, Vukojević V, Knapskog AB. Comparison of Cerebrospinal Fluid Amyloidogenic Nanoplaques With Core Biomarkers of Alzheimer's Disease. Front Aging Neurosci. 2020 **12:** 608628.
5. Aksnes M, Aass HCD, Tiiman A, Edwin TH, Terenius L, Bogdanović N, Vukojević V, Knapskog AB. Associations of cerebrospinal fluid amyloidogenic nanoplaques with cytokines in Alzheimer's disease. Transl Neurodegener. 2021 **10(1):** 18.
6. Aksnes M, Aass HCD, Tiiman A, Terenius L, Bogdanović N, Vukojević V, Knapskog AB. Serum Amyloidogenic Nanoplaques and Cytokines in Alzheimer's Disease: Pilot Study in a Small Naturalistic Memory Clinic Cohort. J Alzheimers Dis. 2022 **86(3):** 1459 – 1470.

Synuclein Family and three unpredictable children

Nenad Bogdanović
Karolinska Institute, Stockholm, Sweden

Synucleins are a family of natively unfolded (or intrinsically unstructured) proteins consisting of α-, β-, and γ-synuclein involved in neurodegenerative diseases and cancer. They are very much in focus since they are associated with several human diseases and lack of understanding their physiological function. The first synuclein was identified in cholinergic synaptic vesicles from the electric organ of Torpedo californica in 1988. Two others are identified by Goedert group in 1994.They are vertebrate-specific proteins since there is no equivalents identified in invertebrates. In mammals and birds three genes encoding α-, β-, and γ-synuclein are present, while in some fishes like fugu four genes are encoding α, β, and two g (g1 and g2) isoforms. Most of the research is focused on **α-synuclein** due to its involvement in Parkinson's disease and other synucleinopathies. Two other proteins **β**- and γ- synucleins assembled in neuronal terminals and implicated in the long-term regulation and maintenance of nerve terminal function and dopamine homeostasis. While α-synuclein is present in Lewy bodies, β-synuclein and γ-synuclein are not, but they are present in the central nervous system and enriched in neuronal synaptic terminals.

A role of **γ-synuclein** and its post-translationally modified forms in neurodegeneration is not investigated in such details as of **α**-synuclein. However, aberrant γ-synuclein that accumulate in neurons indicates the important role in neurodegeneration Furthermore, its presence in cerebrospinal fluid and elevation in aged subjects with neurodegenerative and vascular changes suggest that γ-synuclein can be used as a biomarker of neurodegeneration, gliosis in dementia with Lewy bodies and other neurodegeneration as suggested by Mukaetova 2008. The γ-synuclein is increased in CSF in AD, DLB and vascular dementia and specifically from Braak stage III and onwards. Since γ-synuclein shows the greater elevation in LBD it is intriguing to understand if γ-synuclein can discriminate LBD from other types of neurodegenerative and vascular dementias.

Of exceptional interest is **β-synuclein** which might be an important biomarker for the early stages of Alzheimer's disease. The concentration of **β**-synuclein gradually in-

creases in the CSF beginning from the preclinical AD phase. It may be considered a promising biomarker of synaptic damage in this disease. β-Synuclein may be used as a CSF biomarker for synaptic damage in AD; its level is elevated in both dementia and predementia stages of AD. Importantly, higher CSF α-synuclein levels are reported in pre-AD subjects but not in MCI-AD and dementia AD, pointing to its specificity as a biomarker.

While α-synuclein has been reported in AD as a CSF biomarker of synaptic derangement, decreased α-synuclein levels may indicate the presence of α-synucleinopathy. Elevated CSF levels of both β-synuclein and α-synuclein may, hence, reflect the earliest synaptic dysfunction occurring in AD. Given that β-synuclein concentrations are not influenced by the presence of synucleinopathy thus CSF β-synuclein might be an even more robust synaptic biomarker than α-syn. Moreover, the stronger correlation of β-synuclein with t-tau than with Neurofilament Light may reflect distinct pathways of neurodegeneration, especially in the earliest disease phases.

What can be learned from the Biogen anti synuclein monoclonal Ab study and the Venglustat study in GBA PD, two negative clinical trials targeted the basic mechanisms of Parkinson's disease

Nir Giladi[1,2]
[1]Brain Institute – Ichilov, Tel – Aviv, Israel
[2]Faculty of Medicine, Tel-Aviv University, Tel – Aviv, Israel

There is an urgent need to tackle the basic mechanisms of Parkinson's disease (PD) in order to modify the disease course. Over the past year 3 large scale randomized, prospective controlled, phase 2, multi-center, clinical trials have tested ground breaking technologies aiming synuclein aggregates and lysosomal dysfunction. Unfortunately, all 3 trials had negative results but much can be learned from those pivotal trials.

Based on the hypothesis that synuclein aggregates are contributing to the neurodegenerative process responsible for the progression of PD a recently developed technology using human-derived anti-synuclein monoclonal antibodies, Cinpanemab (SPARK-Biogen) and Prasinezumab (PASADENA- Hoffmann-La Roche) have been tested. Both trials recruited naïve PD subjects, patients on MAO-B inhibitor could stay on it in PASADENA. Monoclonal anti-synuclein Abs were infused intra-venous once a month. After 52 weeks, both studies did not show any beneficial effect on rate of PD progression compared to placebo neither any sign of effecting DaT binding or any secondary outcomes.

Previous studies have proposed that inhibiting the activity of glucosylceramide synthase in PD patients with mutation in the GBA1 gene will decreased the accumulation of glucosylceramide at the brain level and PD progression will be slowed down. Based on those early reports, Sanofi Inc. have developed a brain penetrating molecule called Venglustate which is inhibiting the Glucosylceramide and decided to test its effect on disease progression in GBA1-PD patients. A randomized control trial (MOVES-PD) for 52 weeks with 221 GBA1-PD patients H&Y ≤2, who were enrolled to get 15mg\day Venglustate tablet (110 patients) or placebo (111 patients), did not show any benefit. Interestingly, the Venglustate treated arm deteriorated faster on the MDS-UPDRS right from the first visit at 3-month post randomization, to suggest negative effect on PD symptoms and signs. Venglustte showed excellent target engagement, decreasing plasma and CSF glucosylceramide level by 80% after 2-4 weeks of treatment.

During the talk, I will discuss the challenges of recruiting naïve PD patients to long-term interventional clinical trials with technologies targeting synuclein aggregates as well as the need for better characterization of PD patients for anti-synuclein clinical trials. In addition, I will discuss the lessons from the first ever-clinical trial targeted genetic cohort of PD patients, its challenges and future need for better characterization. In addition, I will discuss the lesson learned from the MOVES-PD trial in regards to the fact that target engagement is not the only goal and possible explanations for the possible negative effect of Venglustate on PD symptoms.

An up-to-date classification of tauopathies

Tamas Revesz
Institute of Neurology, University College London, London, UK

Tauopathy is a term used for a group of neurodegenerative disorders characterized by pathological intracellular deposition of the microtubule-associated protein tau. Classical neuropathological classifications consider whether abnormal tau deposition takes place in neurons or in both neurons and glial cells together with the distribution of the cellular inclusions in the central nervous system. With the availability of Western blot analysis of insoluble tau extracted from brains with different tauopathies and study of the tau inclusions using a differential tau immunohistochemical approach, the isoform composition of the tau inclusions can be established. On the basis of this information, a group of tauopathies is characterised with abnormal tau that is composed of 4-repeat tau (4R-tau) isoforms and this group includes progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), argyrophilic grain disease (AGD) and globular glial tauopathy (GGT) while in others the inclusions possess 3-repeat tau isoforms (an example is Pick's disease) or both 4R-tau and 3R-tau isoforms. This latter group includes Alzheimer's disease, other cerebral amyloid diseases and also some other rarer diseases such as chronic traumatic encephalopathy (CTE) due to repetitive head injury, the enigmatic Guam parkinsonism–dementia complex, subacute sclerosing panencephalitis (SSPE) due to chronic measles infection or the IgLON5-related tauopathy of suspected autoimmune mechanism. It is of note that the type of the tau (*MAPT*) gene mutation will determine the isoform composition of the tau inclusions in variants of frontotemporal dementia with parkinsonism linked to chromosome 17.

With the recent advent of the cryo-electron microscopy (cryoEM) technique, important knowledge has become available about the atomic models of the tau filaments in the different tauopathies, which also led to the introduction of a molecular classification. The results of the cryoEM studies include that the tau filaments are identical in Alzheimer's disease and other rare cerebral amyloid diseases. It has also been discovered that in CTE, in which the disease-associated tau is also composed of both 3R-tau and 4R-tau isoforms, the structure of the tau filaments is somewhat different from that seen in Alzheimer's disease. CryoEM studies also demonstrated that a unique structure of the filaments is responsible for the selective incorporation of 3R-tau isoforms into the tau filaments in Pick's disease and showed that the tau filaments are disease-specific in each of four sporadic 4R-tauopathies: CBD, PSP, AGD and GGT. A common unique feature of the different structures of the tau filaments in these 4R-tauopathies is that they prohibit the incorporation of 3R-tau isoforms into the 4R-tau assembles. These

novel discoveries strongly support the notion that distinct disease-specific tau conformers, 'strains', behaving in a 'prion-like' manner, define the different tauopathies.

Autoimmune mechanisms of neurodegeneration

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Autoimmune movement disorders are rare, but treatable, and may mimic primarily neurodegenerative disease. Over the last few years, we have been recognising an expanding clinical spectrum of autoimmune movement disorders, and gained a better understanding of the pathophysiological underpinnings. This lecture summarises the current knowledge of the borderland between neuroimmunology and neurodegeneration.

New imaging biomarkers in Parkinson disease

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Background: While the lack of disease-modifying therapies for Parkinson's disease (PD) remains an ongoing challenge, the last several years have resulted in a number of novel imaging biomarkers for monitoring the progression of the disease. Recent developments have allowed for a better characterization of the underlying pathology that manifests itself in the brains of patients with PD.

Objectives: To review the progress that has been made with the advent of new imaging biomarkers in the field of PD and how such developments have led to a better understanding of the disease.

Methods: A literature review was performed regarding the development and application of new biomarkers in the field of PD.

Results: Most of the recently proposed imaging biomarkers in PD have been developed using various magnetic resonance imaging (MRI) techniques. A considerable amount of research has focused on the subcortical gray matter structures, particularly with respect to the substantia nigra and other regions that make up the basal ganglia. Increased iron deposition within the substantia nigra, as described post-mortem, has been consistently shown in-vivo using various iron-sensitive imaging techniques (e.g., quantitative susceptibility mapping, R2*). However, the associations between iron accumulation in the substantia nigra and clinical outcomes have not been consistently reported between studies. Free-water imaging, obtained from diffusion-weighted sequences, has been identified as a promising biomarker of disease progression. In addition, other techniques such as resting state functional MRI and arterial spin labeling have been useful in demonstrating altered functional connectivity and perfusion characteristics, respectively, in PD patients with respect to healthy controls. Other imaging modalities, such as positron emission tomography (PET) of the brain and optical coherence tomography (OCT) of the eye, seem to hold promise in monitoring disease progression in PD.

Conclusion: Recent advances in the neuroimaging field, particularly with respect to MRI, have helped characterize neural pathology that is associated with the progression of PD. Future clinical trials of disease-modifying therapies aimed at slowing PD disease course are likely to benefit from the application of imaging-derived biomarkers.

Visuo-spatial impairment in Parkinson's disease - associated cognitive decline

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Parkinson's disease (PD) is a neurodegenerative disorder primarily characterized by motor symptoms. However, mounting evidence suggests that cognitive impairments are also a significant aspect of PD, impacting various domains including attention, memory, executive functions, and visuo-spatial abilities (VSI). VSI, in particular, has gained attention as a distinctive cognitive deficit within the spectrum of PD-associated cognitive decline. Recent research has highlighted the clinical significance of VSI as a predictor of PD progression. Studies have shown that its presence in the early stages of PD is associated with a higher likelihood of developing more severe cognitive decline and dementia over time. Furthermore, VSI in PD might have distinct underlying mechanisms compared to other cognitive impairments, suggesting its potential as a unique target for interventions. VSI refers to difficulties in perceiving, processing, and interpreting visual and spatial information. This can manifest as challenges in tasks involving spatial orientation, navigation, object recognition, and mental rotation. In the context of PD, VSI can lead to a range of functional limitations, affecting daily activities such as driving, reading maps, and even recognizing familiar places or faces. Understanding the mechanisms and implications of this impairment is crucial for both patients and healthcare providers. The underlying neurobiological mechanisms contributing to VSI in PD multifaceted. The degeneration of dopaminergic neurons in the substantia nigra is central to its motor symptoms. However, other brain regions, including the parietal cortex, hippocampus, and visual association areas, also play a vital role in processing VSI. VSI in Parkinson's disease (PD) might be particularly associated with cholinergic dysfunction. It remains unclear however, whether degeneration of the cholinergic basal forebrain is directly related to cognitive decline, or whether relationships between this region and cognitive function are mediated by closely related brain structures such as those in the medial temporal lobe. To evaluate relationships between structure of the cholinergic basal forebrain, medial temporal lobe and cognition, 27 PD patients without dementia and 20 controls underwent neuropsychological assessment and MRI. Volumes of the cholinergic basal forebrain nuclei, the entorhinal cortex, the hippocampus and its subfields were measured. In PD, visuospatial memory was correlated with hippocampal volume, particularly CA2-3, and basal forebrain subregion Ch1-2, but not Ch4. In addition, hippocampal volume was correlated with Ch1-2 in PD. The relationship between Ch1-2 and visuospatial memory was mediated by CA2-3 integrity. There were no correlations between cognitive and volumetric measures in controls. Our data imply that the integrity of the cholinergic basal forebrain is associated with subregional hippocampal volume.These findings are consistent with the recent hypothesis that forebrain cholinergic degeneration results in cognitive deficits via cholinergic denervation, and subsequent structural degeneration, of its target regions.

In conclusion, VSI is a noteworthy aspect of cognitive decline in PD, impacting patients' QoL and functional independence, and an early indicator of dementia. Understanding the intricate interplay of neurobiological will enable new interventions that address its specific challenges, e.g. the role of the cholinergic system..

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Role of iron in MS: Should we target neurodegeneration and repair?

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While iron has an important role in the normal functioning of the brain owing to its involvement in several physiological processes, dyshomeostasis has been found in many neurodegenerative disorders, as evidenced by both histopathological and imaging studies. Although the exact causes have remained elusive, the fact that altered iron levels have been found in disparate diseases suggests that iron may contribute to their development and/or progression. As such, the processes involved in iron dyshomeostasis may represent novel therapeutic targets. There are, however, many questions about the exact interplay between neurodegeneration and altered iron homeostasis. Some insight can be gained by considering the parallels with respect to what occurs in healthy aging, which is also characterized by increased iron throughout many regions in the brain along with progressive neurodegeneration. Nevertheless, the exact mechanisms of iron-mediated damage are likely disease specific to a certain degree, given that iron plays a crucial role in many disparate biological processes, which are not always affected in the same way across different neurodegenerative disorders. Moreover, it is not even entirely clear yet whether iron actually has a causative role in all of the diseases where altered iron levels have been noted. For example, there is strong evidence of iron dyshomeostasis leading to neurodegeneration in some neurologic diseases, but there is still some question as to whether changes in iron levels are merely an epiphenomenon in multiple sclerosis (MS). Recent advances in neuroimaging now offer the possibility to detect and monitor tissue iron levels in vivo (susceptibility weighted-imaging, quantitative susceptibility mapping), identify chronic active lesions in MS patients (PRLs, paramagnetic rim lesions), which allows for an improved understanding of both the temporal and spatial dynamics of iron changes and associated neurodegeneration compared to post-mortem studies. In this regard, iron-based imaging will likely play an important role in the development of therapeutic approaches aimed at addressing altered iron dynamics in neurodegenerative diseases.

Cognitive reserve and network efficiency in multiple sclerosis

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Multiple sclerosis (MS) commonly features clinical impairments such as physical disability and cognitive dysfunction. These symptoms can become highly disabling, but remain very difficult to predict in clinical practice. How such clinical features relate to patterns of damage remains difficult to grasp, given the clinico-radiological paradox. In fact, some people with MS show extensive damage on clinical MRI sequences with seemingly few clinical consequences, and vice versa. This has led to the investigation of buffer capacities in the form of cognitive reserve, as well as advanced ways of visualizing damage and how it responds to this damage by changing brain function.

This lecture will provide an overview of recent breakthroughs in the MS field using structural and functional MRI, providing new insights into mechanisms underlying clinical impairments and especially cognition.

Insights from MRI techniques will be outlined, with a focus on what we have learned from conventional (clinical) MRI, as well as advanced ways of visualizing damage, such as lesions, network disconnection and atrophy patterns. In addition, how the brain seems to compensate for these types of damage (neuroplasticity) and how such damage can lead to possible maladaptive brain network changes will be discussed.

The last few years have provided important new insights into the different ways multiple sclerosis damages brain and spinal cord tissue, and the different ways the central nervous system responds to this damage. Patterns of damage and neuroplastic changes seems heterogeneous between individuals, which might explain why predicting progression has been so difficult. The variable cognitive reserve capacity can become exhausted, leading to the appearance of seemingly maladaptive network changes in the form of an overload of hub regions. This can result in a network collapse, leading to clinical progression.

As such, structural and functional MRI provide highly valuable ways to monitor disease activity and to investigate mechanisms underlying clinical progression in MS.

Artificial intelligence in multiple sclerosis and other neurodegenerative disorders

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Background: Artificial intelligence (AI) is playing a transformative role in many fields, including radiology. In neurodegenerative disorders in particular, it has provided new approaches for acquisition, processing, diagnosis, prognosis, and monitoring. These in turn may meaningfully impact quality and availability of neurological care through a variety of mechanisms.

Objectives: To review current progress and trends in the use of AI in neurodegenerative disorders and to evaluate how they impact quality and accessibility of patient care.

Methods: Literature review was conducted of recent advances in neuroradiology artificial intelligence methods, including both deep learning and more traditional machine learning.

Results: Deep learning and the recent availability of large datasets have had a tremendous impact on the growth of AI in MS and other neurodegenerative disorders. Progress has been made on myriad fronts, but a few general categories are particularly noteworthy. First, AI-based MRI acquisition improvements can simultaneously reduce MRI costs and improve resulting images' value for clinical care. These improvements include deep learning reconstructions capable of dramatically reducing scan time or allowing acquisition at lower field strengths, methods for synthetic generation of additional contrasts from a subset of acquired images, and automated protocoling and quality control. Second, AI tools can assist in differential diagnosis and earlier disease identification. Specific approaches for this include automated lesion detection and classification (i.e. central vein sign), anomaly detection, and rapid integration of multimodal data. Finally, prognosis and monitoring can be more quantitative, multifaceted, and standardized. Approaches include automated image biomarker assessment, semi/un-supervised disease subtyping, and automated integration of "omics" style data. On the other hand, while all of this progress is highly encouraging, there are also important caveats to consider, including interpretability, ethical implications, mixed quality of validation, and generalizability, which should govern how AI is adopted.

Conclusion: AI is already playing an important role in improving neurological care on multiple fronts, and improvements are very likely to continue rapidly in the near future, although care should be taken in how they are applied.

Disease Modifying Therapies (DMT) in multiple sclerosis - now and in the future

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Multiple sclerosis (MS) is a complex, chronic neurological disease that affects the central nervous system, causing a wide range of symptoms and varying degrees of disability. Scientists strive to understand the intricate mechanisms that cause MS, the role of immune cells, and explore innovative treatment options with the goal of improving the lives of patients.

Traditional treatment methods focus on managing the symptoms associated with MS, reducing relapses, and slowing the progression of the disease using disease-modifying therapies, medications, and lifestyle modifications.

We categorize MS according to different clinical descriptors as relapsing-remitting, secondary progressive and primary progressive. Clinical trials have played a significant role in the development of treatments aimed at specific stages of MS, such as those aimed at treating relapsing forms of the disease or resolving clinically isolated syndrome.

There are more than 18 different disease modifying therapy (DMT) options covering 10 mechanisms of action for the treatment of relapsing-remitting multiple sclerosis (RRMS). Given the recent international consensus guidelines and the multitude of available treatment options offering different recommendations, there is wide heterogeneity in how DMTs are used in clinical practice. Selecting DMTs for newly diagnosed MS patients, historically an escalation approach to DMT has been used for newly diagnosed patients with RRMS. However, evidence is emerging for the clinical benefits of early treatment with highly effective therapies (HETs) in this population. By reducing the accumulation of neurologic damage early in the course of the disease, early treatment with HETs may improve long-term clinical outcomes throughout the patient's lifetime.

Accumulating research evidence suggests that the clinical course of MS is best viewed as a continuum, with the contributions of concurrent pathophysiological processes varying between individuals and over time. The apparent evolution to a progressive course reflects a partial shift from predominantly localized acute injury to widespread inflammation and neurodegeneration, together with failure of compensatory mechanisms, such as neuroplasticity and remyelination.

These observations encourage a new consideration of the course of MS as a spectrum defined by the relative contributions of overlapping pathological and reparative or compensatory processes. New understanding of the key mechanisms underlying progression and measures to quantify progressive pathology will potentially have important and useful implications for clinical care, treatment goals, and regulatory decision making.

Harnessing neuroplasticity in neurodegenerative disorders

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Neuroplasticity can be viewed as a general umbrella term that refers to the brain's ability to modify, change, and adapt both structure and function throughout life and in response to experience and disease. Just as individual differences contribute to variability observed in brain structure and function, mechanisms of neuroplasticity also show significant variability across individuals.

The brain's propensity for neuroplasticity is influenced by lifestyle factors including exercise, diet and sleep, being mostly researched. An emerging body of evidence suggests exercise triggers several plasticity related events in the human brain in Parkinson's disease (PD) as well as in Alzheimer disease (AD) including corticomotor excitation, increases and decreases in gray matter volume and changes in BDNF levels. There are data showing that exercise interventions in individuals with PD incorporate goal-based motor skill training in order to engage cognitive circuitry important in motor learning. An individual's dietary choices clearly effect neuroplastic processes in the brain. Adherence to certain dietary interventions such as the Mediterranean diet, ketogenic diet, caloric restriction, intermittent fasting and diet supplementation appear to increase measures of neuroplasticity. Sleep is a complex biological process which has a multitude of effects on neuroplastic processes in the brain, both during sleep and while awake. Findings suggest that getting the adequate amount of sleep based on recommended guidelines may increase the propensity for neuroplasticity in the brain.

Several brain stimulation techniques are currently available to assess or modulate human neuroplasticity, which could offer clinically useful interventions as well as quantitative diagnostic and prognostic biomarkers. Studies using several brain stimulation techniques, with a special emphasis on transcranial magnetic stimulation and deep brain stimulation (DBS) techniques are carried on in order to examine or modulate impaired neuroplasticity at the local and network levels in patients with AD or PD. The impaired neuroplasticity can be detected in patients at the earlier and later stages of both neurodegenerative diseases. Enhancing neuroplasticity holds as a promising therapeutic approach to improve cognition in AD. In recent years, studies showed

treatments with multiple sessions of rTMS can influence cognition in people with neurodegenerative diseases. Targeting the impaired neuroplasticity with improved brain stimulation techniques could offer a powerful novel approach for the treatment of AD and PD.

In keeping with the increasing shift in focus from illness to what maximizes better health, psychologists are uniquely trained to use evidence based behavioral techniques as effective methods for driving neuroplasticity in a positive direction.

What is cognitive reserve?

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Cognitive reserve (CR) is defined as a relative resistance to develop dementia at an advanced age, reflected as normal cognition in spite of neuropathological brain changes characteristic of Alzheimer's disease (AD), or delayed onset of dementia.

Actually, the first definition is based on the acceptance of amyloid and tau as causative, which may be wrong.

The second definition needs to take into account the factors which are known to be responsible for cognitive decline. Cognitive reserve (CR) is actually surrogate to brain reserve, reflected by its structure. Cognitive reserve (CR) cannot be measured directly and instead uses years of education as a surrogate. However, higher education is associated with better health in general, reflected in brain resistance to degenerative changes.

The term CR is misleading because it implies that the brain has functions which are constant, whereas in reality the resistance to decline is fluid and can be increased.

The holy grail of cognitive training in the treatment of cognitively impaired patients

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Cognitive training has shown promise in helping cognitive impaired patients, but it is essential to set realistic expectations and not consider it a "holy grail" solution. Cognitive training refers to various interventions and exercises designed to improve cognitive functions such as memory, attention, problem-solving, and processing speed. These programs often involve repeated practice of specific cognitive tasks to stimulate and strengthen neural connections in the brain.

While cognitive training can be beneficial for some individuals with cognitive impairments, it is not a one-size-fits-all solution, and its effectiveness can vary from person to person. Here are some key points to consider:

Efficacy: Research has shown mixed results regarding the effectiveness of cognitive training. Some studies have reported positive outcomes, while others have found limited or no significant improvements. The response to cognitive training may depend on various factors, including the type and severity of cognitive impairment, the specific training program used, the individual's motivation, and the frequency and intensity of training.

Multimodal Approach: Cognitive training should be viewed as part of a broader multimodal approach to managing cognitive impairments. Combining cognitive training with other strategies, such as physical exercise, social engagement, and medication when necessary, may yield better overall results.

Individualized Approach: Each person's cognitive impairment is unique, and a personalized approach to cognitive training is crucial. Tailoring the training program to an individual's specific needs and capabilities is more likely to be effective.

Long-term Maintenance: The benefits of cognitive training may not always be sustained over the long term, especially if training is discontinued. Continuous engagement in cognitively stimulating activities may be necessary to maintain improvements.

Early Intervention: Starting cognitive training early in the progression of cognitive impairment may yield better results. In some cases, cognitive training may slow down the decline of cognitive functions rather than fully restoring them.

Ethical Considerations: It is essential to manage expectations and avoid making unrealistic promises to patients and their families. Miracle cures or instant improvements are not guaranteed through cognitive training.

In conclusion, while cognitive training holds promise as an adjunctive tool in managing cognitive impairment, it is not a "holy grail" solution. It should be seen as part of a comprehensive and personalized approach that considers the individual's specific condition, needs, and overall health. Research in this field is continually evolving, and future advancements may further enhance our understanding of cognitive training's role in supporting cognitive health.

Deciphering neurodegenerative diseases - from a clinician's perspective to future implications

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We have and enjoy the opportunity of being the living witnesses of the blooming field of neurodegenerative disorders (NDD). The truth is, it has never been static, but for the last decade or two, major milestones in the early and precise diagnosis by using biomarkers and in exploring new treatment avenues have been achieved. This gives the clinician new perspectives and a role change. The clinician is gradually transformed, from a passive observer of the latest stages of the disease process, roughly lumping clinical syndromes into few, broad diagnostic categories, to a refined "splitter", dissecting diverse clinical phenotypes, decoding the underlying neuropathology and disease mechanisms in vivo. The phenotype- proteinopathy relation is complex itself. One distinct proteinopathy can be associated with multiple phenotypes and on the other hand a distinct phenotype can be produced by the coexistence of several proteinopathies, which from a therapeutic point of view, adds complexity in the clinical setting and makes the single treatment paradigm unlikely to work. This leaves the clinician puzzled, gazing at the broad, overlapping, multifaceted and complex spectrum of neurodegenerative diseases.

Should we lump or split in the diagnostic process of NDD, that is the question now? To answer this, I will start in a "lumper" manner, by defining what makes a disease a neurodegenerative one, by depicting the common denominators and connecting the

dots (from proteostasis, though microglia and neuroinflammation, mitochondrial dysfunction, oxidative stress etc.). I will discuss the diversity and complexity of the NDD spectrum, phenotype heterogeneity, raising the question of selective vulnerability, to come to a point where I illustrate, from a clinician's perspective, the challenges in relating the clinical phenotype to the underlying brain pathology, in a very peculiar case of a patient with an early onset dementia with parkinsonism, later discovered to be burdened by two pathogenic mutations in CSF1R gene and ABCD1 gene. The discussion develops in the direction of what might have been missed by "lumping" clinical phenotypes into broad diagnostic groups, and what might be revealed by fine splitting and applying genomic medicine in selected cases. Even though traditionally researchers are the "splitters", and the clinicians "lumpers", I believe that the clinician's role is to be transformed. Traditionally we translate research into clinical practice, but as we are not even close to understanding the pathobiology of all of the dementias, parkinsonisms and motor neuron diseases, the time has come to translate clinic into science and research. By deep diving and fine splitting of the diverse clinical phenotypes and applying genomic medicine, new mechanistic insights emerge, opening different treatment avenues. Exiting times are coming in the field of NDD. To simplify, the clinician of the future will be both a lumper and a splitter, a clinician with the mind of a researcher. By applying fine splitting in the diagnostic pathway, using algorithms, biomarkers and possibly AI (artificial intelligence) while predicting the underlying neuropathology and core mechanistic pathways early in the disease course, the clinician would eventually create a meaningful, precision medicine guided, "lumped" treatment plan.

Nonmotor symptoms (NMS) in Parkinson's disease - Is this the way towards personalized medicine

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Objective: In this study we want to see effects of deep brain stimulation (DBS) and continuous infusion of levodopa-carbidopa intestinal gel (LCIG) on nonmotor symptoms in advanced Parkinson's disease (APD).

Background: The modern management of PD is patient oriented. Nonmotor symptoms influence the most quality of life in APD.

Methods: We tested 50 patients before and 3 months after DBS and 15 patients before and 3 months after LCIG that came to our Center last year. The investigation was conducted with anamnesis and treatments data, Non-motor Symptom Scale (NMSS), Non Motor Symptoms Questionnaire (NMSQ), Visual Analogue Scale (VAS), McGill questionnaire and Hospital Anxiety and Depression Scale (HADS), Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE), Parkinson's;s disease sleep scale (PDSS), Unified Parkinson's Disease Rating Scale- part II (activities of daily living- ADL), part III (motor examination -ME), Hospital Anxiety and Depression scale (HAD), Parkinson's Disease Questionnaire- 39 (PDQ-39) and levodopa dosage. Statistical analysis was done.

Results: Mean age was 70.09±0.9 (man 57%; women 43%). Mean disease duration was 14.3±0.6. We found statistically significant improvement in nonmotor symp-

toms (NMSS total score and NMSQ), motor symptoms and PDQ-39 in both methods. Considering subdomains, we found significant beneficial effect on sleep, gastrointestinal, cardiovascular and urological symptoms in both methods, but better improvement in pain and sexual function in DBS and mood and apathy section in LCIG patients.

Conclusions: We found beneficial effects after 3 months of both invasive methods (DBS and LCIG) on nonmotor symptoms with good influence on quality of life and activities of daily living. Our study has shown that we must pay more attention to assess and control non-motor symptoms and psycho-social factors after them because they may impact patients' ability to access and continue successful therapy. This information might be valuable when deciding on advanced therapy for individual patients.

Is parenteral levodopa treatment a mechanistic one?

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Oral levodopa is a gold standard treatment for Parkinson's disease (PD). However, long term treatment with levodopa causes motor complications in majority of PD patients. Motor complications, i.e., fluctuations and dyskinesia, are hard to treat and deteriorate patients' functional abilities and quality of life. Although the pathophysiological mechanism that cause levodopa induced motor complications is not fully understood, it is believed that non-physiologic, discontinuous, and pulsatile dopaminergic stimulation cases it, via various pre- and post-synaptic mechanisms.

It has been shown that more constant dopaminergic stimulation significantly improves motor fluctuations and dyskinesia and prevents its development. There are various approaches towards continuous dopaminergic stimulation, oral and non-oral ones. Infusion and surgical therapies offer an alternative to oral medication. Levodopa infusion can nowadays be applied in combination with carbidopa or with carbidopa and entacapone, as an enteral suspension, via percutaneous gastrostomy (PEG). This treatment is indicated for advanced PD (aPD) stage, with already developed motor complications but preferably before major complications develop.

There is plenty of scientific literature available that proves a beneficial effect of continuous levodopa PEG infusions on motor complications, non-motor symptoms as well as on patients' functionality and quality of life. However, a timely and proper selection of eligible patients is crucial for good treatment outcome. Surveys have shown that majority of aPD patients who are eligible for non-oral continuous dopaminergic therapies, are not receiving one. An experienced extrapyramidal team of health care practitioners is required for timley recognition and long-term management of aPD patients treated with parenteral levodopa infusion.

New options for continuous levodopa delivery (oral, inhalable, and subcutaneous) are underway.

Mechanisms of action of deep brain stimulation: do we really know how does it work?

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Deep brain stimulation (DBS) is a well-established treatment option for movement disorders including Parkinson's disease, essential tremor, and dystonia. It can also be used to treat Gilles de la Tourette syndrome other treatment-resistant neuropsychiatric disorders including obsessive-compulsive disorder. Despite the wide use of DBS, the mechanism of action is still unknown. Rather than a single unifying mechanism, DBS mechanisms of action probably include several, nonexclusive mechanisms including local and network-wide electrical and neurochemical effects of stimulation, modulation of oscillatory activity, and synaptic plasticity. We will discuss these mechanisms of action through the use of DBS in different disorders by stimulating different targets.

What we have learned of our more than 150 Wilson's disease

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Although Wilson s disease (WD) is an orphan disease and research are lacking in this field, it should be stated that much of the knowledge has accumulated in the decades following the first description of the disease.

Wilson s disease (WD) is an autosomal recessive disorder of copper metabolism, characterized by reduced copper incorporation into apoceruloplasmin and decreased biliary excretion of copper. WD leads to copper accumulation in liver and extrahepatic organs, resulting in clinical consequences varying from an asymptomatic state to fulminant hepatic failure, neurological, and psychiatric manifestations.

If Wilson's disease were diagnosed at an early stage of the illness and patients were subsequently put on an appropriate lifelong treatment, the patients would improve and be often largely asymptomatic for the rest of their lives. The diseases progressing is typically characterized by complex combinations of neurological symptoms and signs coexisting in a single patient, with a minor subset of predominating features. The responsible gene lies on chromosome 13q14.3 and encodes for a copper-transporting P-type ATPase (ATP7B). The spectrum of mutations in WD consists of small number of relatively frequent mutations and large number of rare mutations.

In addition to clinical and laboratory tests NMR changes play an important role in diagnostic procedures, as well as basal ganglia echogenicity. Recent studies have detected morphological changes of the retina in patients with WD using optical coherence tomography (OCT).

Treatment in WD patients is always a superior option. Untreated, the condition progresses to death within a few years. Discontinuation of treatment may be catastrophic, with a high toll on mortality.

Awareness of the whole spectrum of the possible neuropsychiatric manifestations of WD and their early recognition may help in a more comprehensive therapeutic management of WD. Despite an early diagnosis and appropriate therapy, a few pa-

tients have relentlessly progressive courses and disability, daily difficulties due to motor impairment, chronic liver disease, a wide range of social limitations and psychiatric comorbidity.

It is important to recognize, diagnose and to treat patients adequately and cautiously! If treated properly, Wilson disease is curable disorder!

A mechanistic approach to the development of myelin repair therapies for multiple sclerosis

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The adult central nervous system is vulnerable to disease and injury and shows a limited regeneration capacity only. Repair is mainly restricted to the replacement of oligodendrocytes and the reconstitution of white matter by means of precursor- and stem cell activation but remains overall inefficient. We investigated critical molecular and cellular processes responsible for the lack of efficient oligodendrogenesis and identified the p57kip2 gene encoding a negative regulator of oligodendroglial precursor- and adult neural stem cell differentiation. Subsequent work then revealed underlying regulatory mechanisms and the control of intracellular protein shuttling to be involved. Using a non-biased drug screening approach, we then searched for pharmacological substances able to modulate this inhibitor's activity by controlling its subcellular localization. To this end small molecules could be identified that successfully act on the p57kip2 protein, foster the differentiation of oligodendroglial precursor cells and are able to improve myelin repair in a currently used animal model for demyelination in multiple sclerosis (MS). As white matter is not only affected in such classical demyelination pathologies, but also contribute to long-term deficits in other neurological diseases/conditions, current investigations aim at exploring these active substances in other disease models such as related to ischemia/stroke or white matter maldevelopment as observed in Down Syndrome (DS).

Neuroimmunity in amyotrophic lateral sclerosis (ALS) – mechanistic potential

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Neuroinflammation is one of the most consistent signs of amyotrophic lateral sclerosis (ALS), a fatal motor neuron disease with the fastest progression among adult neurodegenerative diseases. It leads to damage and death of neurons by stimulating the formation of reactive oxygen species, protein aggregation, and increasing the toxicity of glutamate. Despite this, numerous anti-inflammatory and immunosuppressive therapies have failed in clinical studies for various neurodegenerative diseases, forcing us to reevaluate the role of the immune system in neurodegeneration, and focus on its protective capacity as well. Due to such dual role of the immune system in ALS, deeper understanding of its role in pathophysiology will be necessary to finally translate its potential into improved diagnosing, monitoring, and most importantly treating ALS.

The role of neuroinflammation in a "childhood Alzheimer's disease" Niemann-Pick type C

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It is intriguing that the two etiologically distinct neurodegenerative disorders, a single gene, rare disorder Niemann-Pick type C disease (NPC) caused by mutations in cholesterol transport genes *NPC1* or *NPC2* and a complex, the most common Alzheimer's disease (AD), share several similarities, including neurodegeneration, neuroinflammation, enhanced levels of amyloid-beta peptides and hyperphosphorylation of tau protein. NPC disease, has, thus, been called a "childhood Alzheimer's disease". Our prior work in NPC1-null cells and in mouse primary NPC1-null neurons showed that defects within endosomal pathway may cause AD-like features in NPC disease. It has been generally assumed that in neurodegenerative diseases neuroinflammation is a bystander of neuronal loss. However, our recent findings in NPC1 mice and in NPC patients' blood-derived macrophages together with other studies on the role of microglia dysfunction in neurodegeneration, suggest a possible causative rather than consequential role of neuroinflammation in neuropathology. We have recently demonstrated for the first time that NPC microglia proteome changes precede neuronal loss and act in cell autonomous manner, thus contributing to neuropathology. Importantly, we showed that lipid accumulation in NPC1-mouse microglia is a consequence of impaired lipid trafficking with a striking accumulation of multivesicular bodies, while lysosomal degradation function seems preserved. The late endosomal/exosomal marker CD63 was the most significantly changed protein at presymptomatic stage (P7), suggesting that defects within endosomal/lysosomal trafficking and sorting may be among the earliest pathological alterations in NPC microglia. Identifying the earliest changes in neurodegenerative diseases may lead to development of effective and, possibly, shared therapies against neurodegeneration and/or neuroinflammation.

Biomarkers for the frontotemporal dementia

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Frontotemporal dementia (FTD) is a group of neurodegenerative disorders. Most patients present with behavioural variants or primary progressive aphasia. A minority of patients initially have motor symptoms (FTD with amyotrophic lateral sclerosis). FTD is the third most common neurodegenerative dementia, after Alzheimer's disease and Dementia with Lewy bodies.

Diagnosis of the FTD may be challenging. Biomarkers can help establish correct diagnosis and distinguish FTD from other neurodegenerative disorders. They can be divided into five groups: genetics, neuropsychological, fluid, neuroimaging, and neurophysiological biomarkers.

Approximately one-third of the FTD is hereditary. With neuropsychological testing, MAPT mutation has been connected with patients with a behavioural variant of FTD, while GRN mutation was more common in patients with primary progressive aphasia.

Fluid biomarkers can be obtained from serum or cerebrospinal fluid (CSF). TDP-43, neurofilament light chain (NfL), and progranulin (PRGN) are possible serum biomarkers. In addition, tau, microRNA (miRNA) and proteomic investigation can be done in CSF.

The neuroimaging biomarkers may be structural or functional. The most convenient is MRI, which can demonstrate the insular and temporal cortex atrophy. In addition, we can also evaluate white matter anatomical changes. However, MRI findings are not specific enough for individuals, and additional biomarkers may be used. A more expensive neuroimaging tool is PET-CT. The most commonly used tracer is 18 F-fluorodeoxyglucose, with which we can identify glucose metabolism in the brain. Other tracers target tau misfolded proteins.

Neurophysiological biomarkers include EEG and EMG. Later, it has an important role in diagnosing amyotrophic lateral sclerosis. Both methods do not cost much and are widely available.

Some of the biomarkers are expensive and may not be available for all potential patients. At the moment, we do not have an optimal biomarker. Therefore, we must combine several of them to confirm the diagnosis.

The role of magnetic resonance imaging (MRI) in the modern treatment of neurodegenerative diseases

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In spite of morphological changes in neurodegenerative diseases appearing discreetly in magnetic resonance imaging (MRI) scans MRI imaging is part of diagnostic guidelines, and it forms part of most consensus criteria. Morphological MRI excludes brain lesions, provides insight on the atrophy pattern, assesses the vascular burden. Radiological findings may support the diagnosis of specific neurodegenerative disorders and sometimes radiological findings are necessary to confirm the diagnosis. Early diagnosis of neurodegenerative diseases are still chalenging There are several grading systems widely used in clinical practice that are well established. Advances in MRI techniques can determine brain pathological changes. The frequency of misdiagnosis of neurodegenerative diseases only based on clinical symptoms increases the need for objective biomarkers. Structural MRI is used to assess disease progression and is adopted in current trials investigating mild cognitive imapirment and Alzheimer's disease.

In daily practice we should score in a systematic way with visual grading system. Standardized assessment in a patient suspected of having a cognitive disorder includes: advanced GCA-scale for Global Cortical Atrophy, MTA-scale for Medial Temporal lobe Atrophy, Koedam score for parietal atrophy, Fazekas scale for white matter (WM) lesions. The findings in a normally aging brain can overlap with findings in dementia. The biggest challenge on a daily basis is not confusing neurodegenerative pattern with physiological brain aging.

As implicated earlier, there may be some degree of atrophy, though mainly of the white matter with increasing prominence of the perivascular (Virchow-Robin) spaces and non-specific fronto-parietal sulcal widening. The analysis is based on different

techniques from visual inspection to manual and automatic volume measurements, diffusion tensor MRI, and functional MRI. Functional imaging provides information about connections and disconnections between brain areas in normal and damaged brains, to provide early diagnosis and tracking of disease progression. Limitations of functional imaging such as Diffusion Tensor Imaging (DTI) and resting state functional MRI sequences can be reduced with advanced techniques such as neurite orientation dispersion and density imaging (NODDI), diffusional kurtosis imaging (DKI), and free water imaging (FWI). These techniques are used mainly for research purposes, as models for estimating the microstructures of brain tissue, without application in clinical practice where there is a persistent problem with a lack of more reliable imaging methods for morphological changes with visual grading system. A more accurate detection of these would positively impact the everyday clinical practice.

Actionable biomarkers for NeuroCOVID and LongCOVID

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We investigated the impact of SARS-CoV-2 on the central nervous system (CNS) and its neurological effects in COVID-19 patients. We conducted a cross-sectional study involving patients with varying levels of neurological symptoms, to understand the underlying mechanisms. The study used proteomics and antibody assays on matched cerebrospinal fluid (CSF) and plasma, along with brain imaging and clinical data.

Our findings reveal that severe Neuro-COVID is characterized by blood-brain barrier dysfunction, heightened microglia activity, and B cell responses targeting both self and non-self-antigens. COVID-19 patients also exhibited reduced olfactory region gray matter volumes associated with specific CSF parameters. Post-acute COVID-19 syndrome was linked to distinct CSF and plasma markers. These discoveries suggest potential targets for preventing or treating COVID-19-related neurological issues.

In summary, severe Neuro-COVID was marked by microglia reactivity, blood-brain barrier disruption, and CNS-invading B cells. A cytokine storm in the blood contrasted with a non-inflammatory CSF profile in severe cases. Certain CSF and plasma markers related to brain volume reduction and post-acute COVID-19 syndrome. These findings offer insights into mitigating COVID-19-related neurological damage.

Metabolic drivers of T and B cell (dys-)function in CNS pathologies

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The Central nervous system (CNS) is traditionally viewed as an immune-privileged site with limited resident T and B cells. However, following various neurologic disorders and diseases, the frequency of these lymphocyte populations in the brain are often increased. Unrestrained activity of these cells in the brain due to uncontrolled infection, autoimmunity, neurodegeneration or malignancy can contribute to protracted inflammation and tissue damage. Both T and B cells possess cell-type specific metabolic requirements for differentiation into effector populations. Likewise, the functionality,

differentiation trajectory, and persistence of either lymphocyte population in inflamed tissues are often influenced by immune and metabolic signals emanating from the local microenvironment. Indeed, the metabolic interplay between infiltrating lymphocytes and resident cells in inflamed tissues is vital for T and B cell adaptation in hostile microenvironments. The metabolic microenvironments of healthy and inflamed CNS are distinct from other tissues. Consequently, brain-infiltrating lymphocytes are impacted by distinct metabolic features observed in various CNS pathologies. This presentation will discuss the metabolic drivers of T and B cell activity in the diseased brain. In particular, the focus will be on altered metabolic states in the CNS and systemically during acute SARS-CoV-2 infection and following post-acute sequelae of SARS-CoV-2 infection (PASC), also known as "long COVID". The potential role of metabolic perturbations systemically and in the CNS on T cell (dys-)function will be discussed. Understanding the roles of T and B cells in SARS-CoV-2 associated pathology will increase our understanding on PASC and have implications on the development of novel biomarkers and therapeutic strategies.

Glial cell adaptation to latent virus infection in the central nervous system

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Congenital cytomegalovirus (CMV) infection is a leading infectious cause of neurodevelopmental deficits. Using a murine model of congenital cytomegalovirus infection, it was previously shown that infection with mouse cytomegalovirus (MCMV) is associated with a strong host inflammatory response in the brain, which leads to pathological damage. Following the resolution of productive infection, the virus establishes latency. Virus-specific T cells are retained in the brain and control reactivating virus. Whether these permanent changes in brain homeostasis affect resident glial cells is not known. To answer this question, we have performed single-cell transcriptomic analysis of microglia and astrocytes from latently infected mice. Our analysis revealed that latent MCMV infection drastically changes the composition of microglia at the single-cell level, while astrocyte homeostasis is minimally affected, indicating differential homeostatic features of these glial cells following infection. Infection induced novel clusters of microglia, characterized by the expression of different pro-inflammatory gene sets (encoding for MHC-I and II molecules, interferon type I and II inducible genes). Infection-associated microglial clusters remained activated and expressed MHC-II during latency. Observed changes were not due to virus latency in microglia, as viral genomes were not detected in these cells. Surprisingly, interferon-γ signaling was required during latency to maintain microglial MHC-II expression, indicating that inflammatory milieu caused by the presence of virus in brain perpetuates microglial adaptation. Antiviral treatment administered early during acute infection can reduce the impact of infection on microglia, however, such treatment during latency is not effective. Altogether, our results show that latent CMV infection in the brain leads to permanent perturbation of microglial homeostasis and drives persistent neuroinflammation.

A call for help from the infected brain

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Viral encephalitis initiates a series of immunological events in the brain that can cause brain damage. Astrocytes express IFN-β in response to neurotropic virus infection, whereas activated microglia produce proinflammatory cytokines and accumulate at sites of infection. Here, we observed that vesicular stomatitis virus (VSV) infection of the brain causes recruitment of leukocytes into the central nervous system (CNS), which requires MyD88, an adaptor of Toll-like receptor and interleukin-1 receptor signaling. Infiltrating leukocytes, and in particular CD8+ T cells, protected against lethal VSV infection of the CNS. Reconstitution of MyD88, specifically in neurons, restored chemokine production in the olfactory bulb as well as leukocyte recruitment into the infected CNS and enhanced survival. To study the translatome of brain-resident cells we exploited the ribosomal tagging (RiboTag) approach. Comparative analysis of the translatomes of neurons and astrocytes verified neurons as the critical source of chemokines, which regulated leukocyte infiltration of the infected brain and affected survival.

Effects of influenza A virus infection on hippocampal neuron structure and function in aged wild-type mice

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Influenza A viruses (IAVs) remain a leading cause of severe pandemics worldwide and pose a major threat to human and animal health. Although the primary target of IAVs is the lungs, infection may manifest with acute and even chronic neurological complications (e.g., status epilepticus, encephalopathies, and encephalitis) potentially increasing the long-term risk for neurodegenerative diseases. Evidence suggests that susceptibility to pulmonary infections caused by respiratory viruses increases with age. Indeed, a progressive decline in the integrity of the immune system, termed 'immunosenescence', is one of the most striking physiological changes during aging in mammals. Accordingly, we aimed to investigate whether age is a risk factor for the development of a more pronounced chronic immune response in the CNS of elderly individuals. Therefore, 15-month-old C57BL/6J mice were intranasally infected with non-neurotropic (H1N1 and H3N2) and neurotropic H7N7 IAV subtypes to determine potential long-term effects on hippocampal structure and function. Synapse loss detected at 30 dpi was associated with deficits in spatial learning and impaired synaptic plasticity. In addition, evidence of synaptic stripping by increased activated phagocytic microglia engulfing the postsynaptic compartment was detected in the hippocampus. While neuroinflammation induced by H7N7 IAV showed the strongest effect, systemic infection with H1N1 and H3N2 subtypes resulted in long-term impairment of hippocampal structure and function. Remarkably, the deficit in spatial learning at 120 dpi was still detectable in aged H7N7 IAV-infected mice, in contrast to fully recovered

young mice. These results suggest that IAV infection has longer-lasting and more severe effects on hippocampal function in older animals.

Immune cell crosstalk during neuroinflammation - role for cellular stress sensors

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Elucidating the basis of chronic disease courses and the development of appropriate treatment methods for inflammatory diseases still represent a big challenge for medical science, as the mechanisms driving aberrant immune reactions are mostly still unknown. Of particular interest is the identification of checkpoints that regulate the function and differentiation of proinflammatory cells during pathogenesis, along with methods for modulation of specific checkpoints as a treatment approach. The role of innate receptors in driving aberrant immune responses during multiple sclerosis and experimental autoimmune encephalomyelitis (EAE), a mouse model thereof, remains largely unclear.

Using the EAE model, we performed single-cell transcriptome analysis of CD4+ T cells at disease peak, revealing a transcriptional continuum within CNS CD4+ T cells with distribution skewed by the expression of key effector cytokines and activation markers. One prominent feature associated with CNS, was the expression of innate receptors, particularly *Klrk1*, coding for Natural Killer Group 2, Member D (NKG2D), a key innate sensor of cellular danger signals. Importantly, using genetically modified mice, we could demonstrate a functional impact of *Klrk1*-deficiency in the T cell compartment on the outcome of EAE. Altogether, our findings suggest the role for the stress-sensing innate receptor NKG2D in the modulation of Th cell-mediated neuroinflammation.