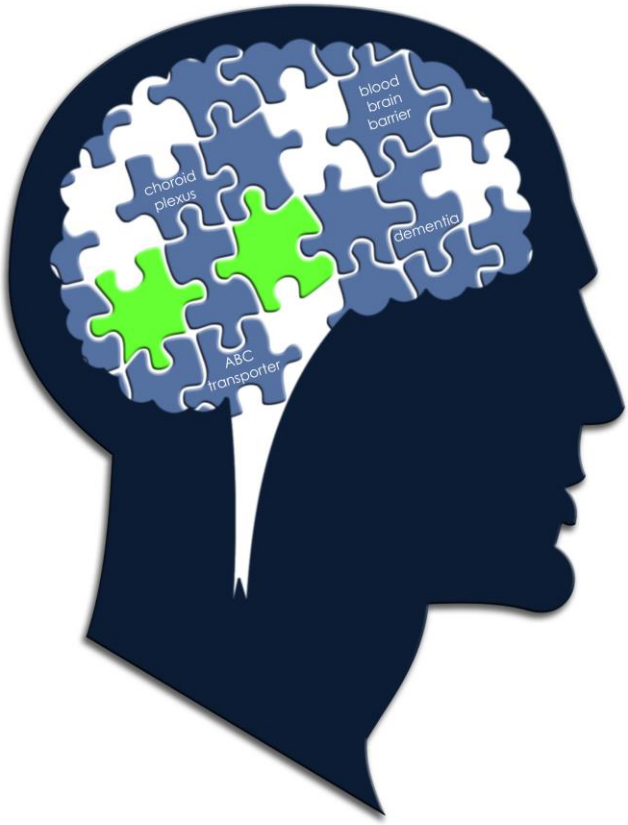
TransportDEMENTIA4

General Information

PROGRAM

MAY 20TH 2021



The meeting is supported by the following project fundings:

FLPP project No. Izp-2018/1-0275 ShortAbeta (2018-2021)
JPND and Norges forskingsråd international consortia PROP-AD (2016-2021) and PETABC (2021-2024)
Deutsche Forschungsgemeinschaft/ Germany (DFG 263024513)
EFRE and Ministerium für Wirtschaft, Wissenschaft und Digitalisierung Sachsen-Anhalt/ Germany (ZS/2016/05/78617)
EU #643417 (JPco-fuND)

TRANSPORTDEMENTIA4

Dear Ladies and Gentlemen,

The TransportDEMENTIA meeting series has already reached the fourth venue. The first meeting in Oslo in December 2015 set the start for this exceptional event series.

We are very pleased to invite you all to the fourth meeting about ABC transporters and dementia.

In light of the continuing uncertainty about the evolution of the COVID-19 pandemic and its impact on travel restrictions and physical distancing requirements throughout 2021, the organizers have decided to transform this conference from 3 days to a 5 hours online event using ZOOM Platform at the 20th May 2021.

We hope this meeting will give us the opportunity for discussions leading to new collaborations and projects.

The TD5 meeting is planned to be in person again !

Jens Pahnke & Baiba Jansone

The organizers

ZOOM MEETING LINK

ZOOM Link (Meeting ID: 666 4794 8234 and Passcode: 375157)

CONTACT

If you have any further questions regarding the conference, do not hesitate to contact **Jolanta Upīte**.

E-Mail: TransportDementia@gmail.com
jolanta.upite@lu.lv

THURSDAY, MAY 20TH

Session I

12:00 – 12:10 **Jens Pahnke**
(University of Oslo, Norway; University of Latvia, Latvia; University of Lübeck, Germany)

Introduction

12:10- 12:30 **Ludger A. Wessjohann and Katrin Franke**
(Leibniz Institute for Plant Biochemistry, Halle, Germany)

Identification and properties of FAE-20, the strong cognition enhancing principle from *Rhodiola rosea*

12:35 - 13:55 **Maria A. Deli**
(Institute of Biophysics, Biological Research Centre, Szeged, Hungary)

Brain endothelial surface charge and its role in the transfer of molecules and nanoparticles across the blood-brain barrier

14:00 - 14:20 **Tuula Anneli Nyman**
(Department of Immunology, University of Oslo and Oslo University Hospital, Norway)

Proteomics in personalized medicine
www.napi.uio.no

Short break for getting coffee or tea (10 min)

THURSDAY, MAY 20TH

Session II ***New Methods***

14:30 – 14:45 **Luisa Möhle**
(University of Oslo/Oslo University Hospital, Oslo, Norway)

Using machine learning for automated histological analyses of brain sections

14:50- 15:05 **Jolanta Upīte**
(Department of Pharmacology, Faculty of Medicine, University of Latvia, Latvia)

New quantification method for amyloid-β plaques in relation to intracerebral injection channels

15:10 - 15:25 **Mariia Borovkova**
(Optoelectronics and Measurement Techniques Research Unit, University of Oulu, Finland)

Perspectives of Stokes polarimetry for screening and quantitative evaluation of Aβ deposits in Alzheimer's disease

15:30 - 15:45 **Sven Marcel Stefan**
(University of Oslo/Oslo University Hospital, Oslo, Norway)

Computational Approaches for the Discovery of Multitarget ABC Transporter Modulators – the Key for the Development of Novel Alzheimer's Disease Therapeutics?

THURSDAY, MAY 20TH

15:50 - 16:05 **Maciej Lalowski**
(Meilahti Clinical Proteomics Core Facility, University of Helsinki, Finland; Department of Biomedical Proteomics, Poznań, Poland)

Development of quantitative mass spectrometry methods to measure the Aβ content in the brain

Short break for organizing a coffee (10 min)

Session III

16:10 - 16:30 **Martin Fuhrmann**
(Neuroimmunology & Imaging, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany)

Microglia and neuronal networks – new ways to tackle memory loss

16:35 - 16:55 **Anika Hartz**
(Sanders-Brown Center on Aging, Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY, USA)

Blood-Brain Barrier Dysfunction in Alzheimer's disease: An Environmental Health Perspective

17:00 -17:05 **Closing remarks**

Jens Pahnke

Translational Neurodegeneration and Neuropathology Lab

University of Oslo and University of Oslo, Norway

University of Lübeck, Germany

University of Latvia, Riga, Latvia

Jens Pahnke, MD, PhD, is Professor of Neuropathology at the University of Oslo (UiO) and head of the Section of Neuropathology at the Oslo University Hospital (OUS) since 2014.

He is also affiliated to the University of Lübeck (UzL), the Leibniz Institute for Plant Biochemistry (IPB) in Halle/Germany and the University of Latvia in Riga.

The lab focusses on the function of the blood-brain barrier for the clearance of the brain with special emphasis on ABC transporters.

Recent projects investigate the infectious nature of neurodegenerative diseases: i) the **JPND PROP-AD** project (2016-2021) disproved the hypothesis that amyloid-related disease are prion-like diseases, ii) the **JPND PETABC** project (2021-2024) investigates ABCC1 and ABCA7 as new PET targets for early diagnostics and treatment stratification, iii) the **TARIMAD EEA Norway grants** project (2021-2024) develops ABC transporter activators, iv) the **LZPP ShortAbeta** (2018-2021) project aims to assess sequence and aggregation propensity of fragments of Aβ peptides for the treatment of AD, v) use of herbal extracts from *Hypericum perforatum* and *Sideritis scardica* for the treatment of AD.

More projects are described on the webpage of the lab:

www.pahnkelab.eu/funding

Baiba Jansone

Head of the Department of Pharmacology

Vice -President of the Latvian Society of Pharmacology

University of Latvia, Department of Pharmacology, Riga, Latvia

Baiba Jansone, PhD, is Professor of Neuropharmacology and Head of the Department of Pharmacology at the University of Latvia.

Our research focuses on studies using rodent models followed by the pharmacological intervention and behavioural studies, an examination of changes in biomarker levels in the various brain regions and analysis of mitochondrial function using high-resolution respirometry.

Current projects - JPND PETABC project (2021-2024) and LZPP **ShortAbeta** (2018-2021) - for research in neurodegenerative disorders involve a close scientific collaboration with Translational Neurodegeneration and Neuropathology Lab at the University of Oslo that is under the supervision of Prof. Jens Pahnke.

Explore more on the webpage of the Department of Pharmacology: https://www.mf.lu.lv/petnieciba/farmakologijas-katedras-petnieciba/

Ludger Wessjohann & Katrin Franke

Leibniz Institute of Plant Biochemistry
Halle, Germany

Title: Identification and properties of FAE-20, the strong cognition enhancing principle from *Rhodiola rosea*

Ludger A. Wessjohann, PhD, is director of the Department of Bioorganic Chemistry at the Leibniz Institute of Plant Biochemistry (IPB) in Halle (Germany), and in parallel holds the Professorship of natural product chemistry of the Martin Luther-University Halle-Wittenberg. His research focuses on the discovery, synthesis, understanding, production and application of nature inspired small molecules, which is reflected in over 400 publications and 36 patent applications. The development of a metabolite profiling based Activity-Correlation-Analysis tool facilitates the identification of bioactive components in complex mixtures like plant extracts and avoids dereplication procedures. This could be successfully applied to identify the new memory-enhancing compound from rose root. The work was published in "Science Advances" and received a Hugo Junkers innovation prize of the state Saxony-Anhalt.

Since more than 20 years, the research of Dr. Katrin Franke focus on isolation and structure elucidation of bioactive plant secondary metabolites. Presently, K. Franke is heading the project group Neuroactives within the Department of Bioorganic Chemistry at the Leibniz Institute of Plant Biochemistry. The group is interested in the investigation of neuroactive natural products derived from plants and fungi with special emphasis on substances with potential effects against dementia and other age related cognitive disorders. Plants and fungi which influence the central nervous system are used by mankind for ages. Within the frame of the research network "Autonomy in old age" we contribute with several projects funded by EFRE and the state Saxony-Anhalt (PhytoAD, ProCognito, HyperSpEED) to the characterization of CNS active compounds, especially from traditional medicinal plants like antidepressive Hypericum species and the adaptogenic Rhodiola. The assessment of the biological activity of extracts and isolated natural products is performed in cooperation with partners with neurobiological expertise from OvGU, LIN, and DZNE in Magdeburg and the Pahnke group from the University of Oslo.

Rhodiola rosea roots (rose root, Arctic root) are known as neuroactive traditional medicine applied for stress relief and the focusing of attention. By correlation of Rhodiola metabolite profiles with data from associative learning experiments on Drosophila melanogaster larvae we could identify ferulic acid eicosylester (FAE-20) as rewarding and memory enhancing compound. This compound was previously not detected in Rhodiola preparations. The effects were verified with synthetic FAE-20, which also improves memory in aged flies and mice. First pharmacological investigations indicated non-toxic properties of FAE-20 in different organism.

References:

https://pubmed.ncbi.nlm.nih.gov/30417089/

https://pubmed.ncbi.nlm.nih.gov/32848044/

Maria A. Deli

Institute of Biophysics, Biological Research Centre, Szeged, Hungary

Title: Brain endothelial surface charge and its role in the transfer of molecules and nanoparticles across the blood-brain barrier

Maria Deli, MD, PhD is the head of the Biological Barrier Research Group at the Biological Research Centre and honorary professor at the University of Szeged. The major research interests of the laboratory include integrated lab-on-a-chip models of different epithelial barriers, the blood-brain barrier and organoids, glycocalyx and surface charge of barrier forming cells, targeted delivery of nanoparticles and protein complexes across biological barriers, protection of biological barriers in diseases.

The highly negative surface charge of brain microvessel endothelial cells is an important element of the defense systems of the blood-brain barrier (BBB). This negative charge is derived from the composition of plasma membrane lipids and the endothelial surface glycocalyx. Physiological factors, co-culture of endothelial cells with brain pericytes and/or astrocytes and fluid flow increased the surface glycocalyx thickness and made the zeta potential of the cells more negative measured by laser-Doppler velocimetry (LDv). Zeta potential can only be measured on cells in suspension by LDv, so we developed a new lab-on-a-chip (LOC) device equipped with two Ag/AgCl electrodes to monitor streaming potential parallel to the surface of confluent cell layers. We successfully recorded signals describing the surface charge properties of human brain endothelial cell monolayers. The negative surface charge of the BBB can be modulated by cleaving the glycocalyx with enzymes like neuraminidase or by altering the lipid membrane charge using cationic lipids (TMA-DPH) or lipophilic molecules like lidocaine. Lidocaine, an anesthetic and antiarrhythmic drug, turned the negative zeta potential of brain endothelial cells more positive. Short-term lidocaine treatment at a therapeutic concentration (10 μM) decreased the flux of another cationic lipophilic molecule across the BBB model without causing major change in BBB barrier function or morphology.

Neuraminidase, which cleaves the negatively charged sialic acid residues from the glycocalyx elevated the surface charge and significantly increased the uptake of targeted vesicular nanoparticles (100 nm size, -9 mV zeta potential) in brain endothelial cells. The cationic lipid TMA-DPH also raised the cellular uptake of targeted nanoparticles. In conclusion, co-culture and fluid flow turn the surface charge of brain endothelial cells more negative. The surface potential of brain endothelial cells is important in the transfer of charged molecules and the uptake mechanism of charged nanoparticles and can be modulated by modification of plasma membrane lipid composition or the glycocalyx.

Tuula Anneli Nyman

Department of Immunology,
University of Oslo and Oslo
University Hospital, Norway

Title: Proteomics in personalized medicine

Proteomics is the 'large scale study of proteins'. Proteins represent the actual functional molecules of the cell, and the fundamental importance of proteome level information in biomedical research is widely accepted. Accordingly, proteomic approaches play a central role in a broad range of research fields; from basic biology to biotechnology, to clinical studies such as those investigating disease biomarkers and novel therapeutic strategies. Proteomics can play an important role in future precision medicine, but for that to happen the seamless integration and close collaboration of proteomics researchers with clinical researchers and practicing clinicians is needed.

Proteomics is still technically more challenging than genomics and transcriptomics. However, recent developments in sample preparation, new high-resolution MS instruments, imaging MS, and advances in data analysis tools have enabled deeper and faster proteome characterization than previously possible, such that modern techniques are comparable in depth and accuracy to RNA sequencing. With these new developments, we can create essential data for personalized medicine and bring advanced proteomics closer to clinical decision makers.

Tuula Nyman, PhD, is Professor at the University of Oslo and project manager of NAPI - a Research Council of Norway-funded national infrastructure for advanced proteomics (https://www.napi.uio.no/).

She will introduce NAPI and the novel possibilities it provides to clinical applications.

The Proteomics Core Unit at the Department of Immunology (University of Oslo and Oslo University Hospital) is centrally located at the hospital. Tuula will also present selected examples on recent proteome studies we have done with different sample types.

Luisa Möhle

University of Oslo/Oslo University Hospital, Oslo, Norway

Title: Using machine learning for automated histological analyses of brain sections

Luisa Möhle, PhD, is Postdoc in the Translational Neurodegeneration and Neuropathology in Oslo.

In recent years, artificial intelligence and machine learning have been introduced to a growing number applications in different everyday life and scientific contexts. One field of application is the analysis of histological sections, where machine-learning models can greatly improve quantification of different histological features including Aβ plaques, microglia cells, astrocytes or deposits in haematoxylin-eosin stains.

To this end, DeePathology STUDIO™ offers a simple interface for developing custom machine-learning models without having to deal with the underlying computer science. The software includes tools to monitor and validate model performance, including training advance, precision (specificity), and recall (sensitivity). Once a model has been developed, it can be applied to experimental data and shared with other scientists for fast and reproducible analysis.

Jolanta Upīte

Department of Pharmacology, Faculty of Medicine, University of Latvia, Riga, Latvia

Title: New quantification method for amyloid-β plaques in relation to intracerebral injection channels

Jolanta Upīte, is Researcher and PhD candidate of Pharmaceutical Sciences at the Department of Pharmacology, Faculty of Medicine, University of Latvia. Main Domain of Research: molecular mechanisms of neurodegenerative and inflammatory processes in Alzheimer's disease.

Background: To characterize amyloid-β (Aβ) pathology in mice, a wide range of techniques has been developed over the past decades. Until now, no method has been established to quantify spatial changes in Aβ plaque deposition due to targeted delivery of substances into specific locations using ALZET® pumps.

Objective: Development of a methodology to quantify the local distribution of Aβ plaques upon intracerebral infusion of compounds.

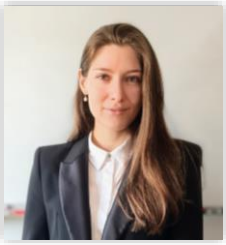
Methods: We have developed a toolbox to quantify Aβ plaques in relation to intracerebral injection channels by using AxioVision® and Excel® software. For the proof of concept, intracerebral stereotactic surgery was performed in 50-day-old APP-transgenic mice. At the age of 100 days, brains were collected for immunhistological analysis.

Results: The toolbox can be used to set reference points, e.g. the injection channel, to quantify Aβ plaques (number, size, and coverage), and to determine their precise distance from reference points. Furthermore, the tool also calculates the region of possible tissue loss after removal of the ALZET cannula.

Conclusion: This new analytic tool facilitates the analysis of long-term continuous intracerebral experimental compound infusions using ALZET pumps. This method helps to generate reliable data for Aβ deposition characterization in relation to the distribution of experimental compounds.

Mariia Borovkova

Optoelectronics and Measurement Techniques Research Unit, University of Oulu, Finland



Title: Perspectives of Stokes polarimetry for screening and quantitative evaluation of Aβ deposits in Alzheimer's disease

Mariia Borokova, PhD, works a physicist in the OMT lab in Oulu (Prof. Igor Meglinski) and works on optical analysis of amyloid in tissue.

The use of light in biomedical diagnosis is advantageous due to its high sensitivity to different structural alterations in the examined medium, including variations in size, shape, and/or density of light scattering inclusions, changes in fibrous structures organization, presence of chiral aggregates and other. We examine the fundamentals of circularly polarized light interaction with biological tissues with the ultimate aim to develop novel non-invasive optical imaging diagnostics of cells and biological tissues with the highest possible sensitivity. In this study, the approach, based on optical polarimetric imaging, is used to perform the functional characterization of mouse brain tissue affected by Alzheimer's disease. The described Stokes imaging system allows label-free non-contact screening of bulk brain tissue within formalin-fixed paraffin-embedded tissue blocks and provides several polarization metrics to distinguish different stages of Alzheimer's disease. The considered approach, furthermore, allows visualization of the individual amyloid-beta plaques, which are the key pathological hallmarks of Alzheimer's disease. The presented approach has a high potential for development of an automated stand-alone approach for segmentation of the abnormal regions in paraffin-embedded tissue block that are in good agreement with the ground truth provided by standard pathological analysis utilizing the microscopy slides. The proposed approach shows a high potential to revolutionize routine procedures in frame of current practice of histological clinical examination and grading the Alzheimer's stages within the tissue samples.

Sven Marcel Stefan

University of Oslo/Oslo University Hospital, Oslo, Norway

Title: Computational Approaches for the Discovery of Multitarget ABC Transporter Modulators – the Key for the Development of Novel Alzheimer's Disease Therapeutics?

Sven M. Stefan Luisa Möhle, PhD, is Postdoc in the Translational Neurodegeneration and Neuropathology in Oslo and has a background in Pharmacy. He has been working many years with ABC transporter inhibitors.

Molecular modelling approaches such as similarity search, pharmacophore modelling, or machine learning are considered to be useful tools to discover new, modern, highly potent, and effective modulators of ABC transport proteins. Based on existing data, these computational approaches – individually or combined – can be used to predict putative modulators by virtual screening of large compound libraries. These approaches were applied within the last approximately 20 years to validate structure-activity relationships of selective ABCB1, ABCC1, or ABCG2 inhibitors, as these transport proteins play a major role in multidrug-resistant cancer. Very recently, a computer-aided pattern analysis ("C@PA") has been developed to discover novel multitarget ABCB1, ABCC1, and ABCG2 inhibitors addressing specifically the question what structural features are required for broad-spectrum ABCB1, ABCC1, and ABCG2 inhibition. This model allows for targeting of understudied ABC transporters that currently cannot be addressed by small-molecules. It provides the unique opportunity to gain knowledge about these particular ABC transporters, their intracellular function, and pathological role in Alzheimer's disease and related neurodegenerative diseases.

Maciej Lalowski

Meilahti Clinical Proteomics Core Facility, University of Helsinki, Finland
&
Department of Biomedical Proteomics, Poznań, Poland

Title: Development of quantitative mass spectrometry methods to measure the Aβ content in the brain

Maciej Lalowski, PhD, is Ass. Professor at the University of Helsinki and head of the proteomics core facility at the Meilahti Center.

Alzheimer's disease is characterized by the deposition of aggregated amyloid-β (Aβ) peptides in the brain. We have established a pipeline for attomolar level detection of isotopic Aβ in brain structures and peripheral organs utilizing APPswe/PS1 transgenic (tg) AD mice (APPPS1) brain hemispheres spiked with known amounts ^{15}N labeled Aβ1-40/42 peptides. Spiked brain extracts were immunoprecipitated with anti-Aβ specific antibodies. Given the oligomerization/aggregation propensities of hydrophobic Aβ and its complex interactions with the column packing material, trypsin digestion strategies were employed. Aβ17-28 peptide was selected as a surrogate to measure the total Aβ level utilizing Single Reaction Monitoring (SRM) method. The developed methodology, capable to specifically measure the Aβ at very low level of detection, can be utilized to investigate other neurodegenerative diseases with misfolded protein/peptide aggregates and deposition in the brain.

Martin Fuhrmann

Neuroimmunology & Imaging,
German Center for
Neurodegenerative Diseases
(DZNE), Bonn, Germany

Title: Microglia and neuronal networks – new ways to tackle memory loss

Martin Fuhmann, PhD, is leader of the research group for Neuroimmunology and Imaging at the German Center for Neurodegenerative Disease and Professor at the University of Bonn.

The interplay between microglia and neurons has been in the focus of researchers for several years. The development and application of novel tools like awake imaging and optogenetics open up new avenues to causally link cellular activity of neurons and microglia with behaviour. I will give an overview of past and recent findings about how microglia might contribute to neuronal network dysfunction under neurodegenerative diseases. Furthermore, recent results from my lab point to a close relationship between microglia and synapse integrity under normal physiologic conditions. These findings are the starting point for future manipulations aimed at improving memory dysfunction via cell based methods.

Anika Hartz

Sanders-Brown Center on Aging,
Department of Pharmacology
and Nutritional Sciences,
University of Kentucky,
Lexington, KY, USA

Title: Blood-Brain Barrier Dysfunction in Alzheimer's disease: An Environmental Health Perspective

Anika Hartz, PhD, is pharmacologist and group leader at the Sanders-Brown Center on Aging.

Blood-brain barrier dysfunction contributes to cognitive decline in Alzheimer's disease. Two key elements of barrier dysfunction include loss of P-glycoprotein, a transporter that clears Aβ from the brain, and development of barrier leakage. We focus on environmental factors that trigger loss of P-glycoprotein and barrier leakage, and thus, pose a risk factor for cognitive impairment in Alzheimer's disease. We also develop therapeutic strategies to repair barrier dysfunction to lower amyloid-β brain burden with the ultimate goals of improving memory loss and delaying onset and slowing progression of Alzheimer's disease.