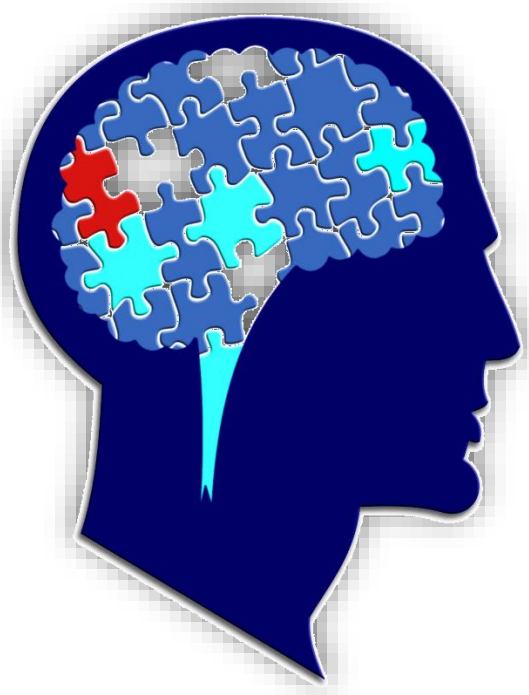
TransportDEMENTIA5 - 2023

General Information

PROGRAM

28TH AUGUST – 1ST SEPTEMBER, 2023

Thanks for a nice time !



The meeting is supported by the following project funding:

JPND and Norges forskingsråd international consortia PETABC (2021–2024)

www.pahnkelab.eu/TD5/

TRANSPORTDEMENTIA5

Dear Colleagues and Friends,

Since more than two decades, ABC transporters are investigated in the field of neurodegenerative diseases – an exotic topic from the start many dementia researchers were smiling about. Today, the hard facts state several ABC transporters as important risk factors for Alzheimer's disease – and investigations of these and other membrane-bound transporters in Alzheimer's and other neurodegenerative diseases are thriving around the globe.

The **Transport**DEMENTIA meeting series has always been the premier platform for researchers to share cutting-edge research and current findings spanning over various disciplines. Having started in 2015 in Oslo, the series is going into its 5th round under the headline

From Advanced Technologies to Applied Translational Medicine

TransportDEMENTIA5 focuses all aspects of chemical biology, molecular mechanisms, and clinical implications of membrane-bound transporter systems in human health and disease – and prioritizes fruitful scientific discussions of formal and informal nature.

We sincerely hope you will enjoy a unique experience with us in Tromsø !

The Organizing Committee.

TransportDementia~at~gmail.com

TD5

International Journal of
Molecular Sciences

IMPACT FACTOR 6.208

Indexed in: PubMed

an Open Access Journal by MDPI

TransportDEMENTIA5—From Advanced Technologies to Applied Translational Medicine

Guest Editors:

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Deadline for manuscript submissions:
31 December 2023

Message from the Guest Editors

Dear Colleagues,

It is our very pleasure to announce a Special Issue released by the *International Journal of Molecular Sciences* (*IJMS*) associated to the 5th meeting of our TransportDEMENTIA meeting series. The meeting will take place in the Capital of the Arctic, Tromsø, from August 28 until September 1, 2023. More information about the venue can be found on www.pahnkelab.eu/TD5.

The TransportDEMENTIA meeting series has established itself as a premier platform for cutting-edge research outlet amongst leading researchers from multiple disciplines. This year's topic "*From Advanced Technologies to Applied Translational Medicine*" will strongly combine chemical biology, molecular mechanisms, and clinical implications of membrane-bound transporter systems in human health and disease.

mdpi.com/si/162717

Special Issue

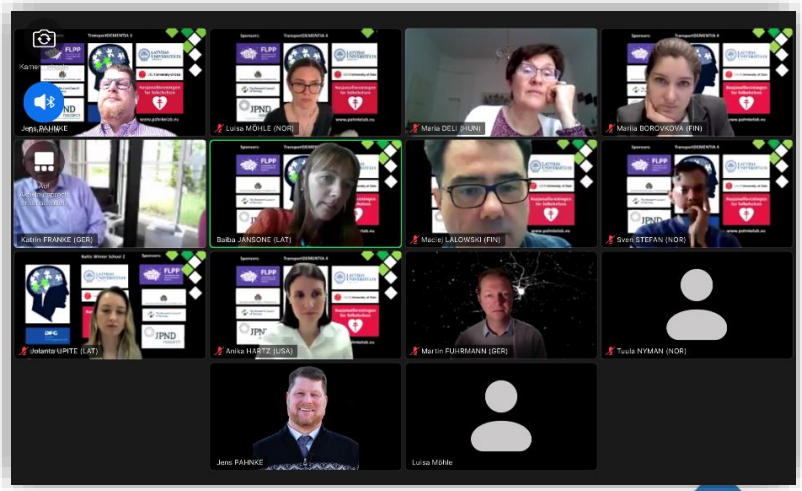
TD5

TD1 2015 - Oslo

TD2 2016 – Hurtigruten vessel “Nordkapp”

TD3 2017 – Svolvær, Lofoten

TD4 2021 - online



TD5 2023 – Tromsø

Scientific Program Overview

Monday, 28th August 2023

Consortium Meeting PETABC

Consortium Meeting TARIMAD

Tuesday, 29th August 2023

S1: The Role of ABC and SLC Transporters in Health and Disease

S2: New Advanced Technologies

S3: Multi-omics & Bioactivity Networks

S4: Translation between Fields

S5: Short Talks

Wednesday, 30th August 2023

S6: The Role of ABC and SLC Transporters in Drug Disposition and Discovery

S7: Improved Analytical Methods and New Assays

S8: The Role of ABC A1/A7 Transporters in Neurodegenerative Diseases / Lysosomal Transporters

S9: Structural, Functional, and Regulatory Aspects of Transport Processes

Thursday 31st August 2023

S10: Cellular and Animal Disease Models in Neurodegenerative Diseases

S11: ABC Transporters for Clinical Use

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Social Program Overview

Monday, 28th August 2023

20:00 Welcome Dinner at Scandic Ishavshotel

21:30 Hotel bar discussions

Tuesday, 29th August 2023

13:00 Tour through Tromsø

19:00 Dinner at Scandic Ishavshotel

22:15 Hotel bar discussions

Wednesday, 30th August 2023

20:00 Dinner at Hilltop Restaurant

21:30 Northern Light Watch from Hilltop depending of the weather

Thursday, 31st August 2023

13:00 Fjord Safari and RIB by PUKKA tours

19:00 Farewell Dinner and Award Party at Scandic Ishavshotel

Detailed Scientific Program

MONDAY – 28th August 2023

16.00 – 18:00 **Registration**

18:00 – 19:30 **Consortium Meeting PETABC & TARIMAD**

20:00 **Welcome Dinner at SCANDIC ISHAVSHOTEL**

22:00 **Open End Networking at the Hotel bar or in town**

TUESDAY – 29th August 2023

07:30 – 08:50 **Breakfast / Late Registration**

08:50 – 09:00 **TransportDEMENTIA5 – *Opening***
(Jens Pahnke – *University of Oslo, Norway*)

SESSION 1 – Chair: Baruch Kanner (20+5 min)

09:00 – 10:30 **The Role of ABC and SLC Transporters in Health and Disease**

09:00 – 09:25 **Kazumitsu Ueda**
(University of Kyoto, Japan)

"Mechanism and Physiological Roles of ABC Cholesterol Transporters"

09:25 – 09:50 **Jörg Gsponer**
(University of British Columbia, Canada)

"Phase Separation and Clustering of an ABC Transporter in Mycobacterium Tuberculosis"

09:50 – 10:10 **Inna Radzishevsky**
(Israel Institute of Technology (Technion), Israel)

"Neonatal Brain Development Critically Depends on Serine Supply by SLC38A5 at the Blood-brain Barrier"

10:10 –10:30 **Baruch I. Kanner**
(Hebrew University, Israel)

"Molecular Mechanism of Transport in the SLC6 Family"

10:30 – 10:45 **Catch a coffee**

SESSION 2 – Chair: Caterina Guiot (20+5 min)

10:45 – 12:00 **New Advanced Technologies**

10:45 – 11:10 **Matias Zurbriggen**
(University of Düsseldorf, Germany)

"Optogenetic Control of Biological Processes: From Photoreceptor Engineering to Their Implementation in Microbial, Animal, and Plant Systems"

11:10 – 11:35 **Shai Rahimipour (ZOOM)**
(Bar-Ilan University, Israel)

"Early Diagnosis and Treatment of Alzheimer's Disease by Targeting Toxic Soluble Abeta Oligomers"

11:35 – 12:00 **Caterina Guiot**
(University of Turin, Italy)

"Iron Overload in Brain: Transport Mismatches, Microbleeding Events, and How Nanochelating Therapies May Counteract Their Effects"

12:00 **Lunch & Networking**

13:00 – 15:30 **Explore the city of Tromsø** (individual)

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SESSION 3 – Chair: Jens Pahnke (20+5 min)

16:00 – 17:10 **Multi-omics & Bioactivity Networks**

16:00 – 16:25 **Radosveta Koldamova (ZOOM)**
(University of Pittsburgh, United States)

"Multi-transcriptomics Reveals Brain Cellular Responses to Peripheral Infection in Alzheimer's Disease Model Mice"

16:25 – 16:50 **Iliya Lefterov (ZOOM)**
(University of Pittsburgh, United States)

"Contribution of Extracellular Vesicles (EV) to the Restoration of Age-related Brain Transcriptomes and Cognition"

16:50 – 17:10 **Daniel M. Michaelson**
(Tel Aviv University, Israel)

"Counteracting the pathological effects of APOE4 in vivo, by activation of the lipidating protein ABCA1"

17:10– 17:30 **Coffee Break & Networking**

SESSION 4 – Chair: Lucía Chavez Gutierrez (20+5 min)

17:30 – 18:55 **Translation between Fields**

17:30 – 17:55 **Dietmar Thal**
(University of Leuven, Belgium)

"Necroptosis and Pyroptosis in Alzheimer's Disease: From Signal Transduction towards Solute Translocation"

17:55 – 18:20 ***Angelo Peschiaroli***
(Consiglio Nazionale delle Ricerche, Italy)

"Elucidating the Role of ABCC1 in Squamous Carcinogenesis"

18:20 – 18:45 **Lucía Chavez Gutierrez**
(University of Leuven, Belgium)

"Molecular bases of age at disease onset in Familial Alzheimer's Disease"

19:00 – 20:30 **Dinner at SCANDIC ISHAVSHOTEL**

SESSION 5 – Chair: Jens Pahnke (10 + 2 min)

20:30 – 22:10 **Short Talks competition (10 min each)**

20:30 – 20:40 **Jingyun Wu** (University of Oslo, Norway)

20:45 – 20:55 **Katja Stefan** (University of Lübeck, Norway)

21:00 – 21:10 **Magdalena Kurtyka** (University of Mainz, Germany)

21:15 – 21:25 **Tudor Emanuel Fertig** (Victor Babes Institute, Romania)

21:30 – 21:40 **Lara De Deyn** (University of Antwerpen, Belgium)

22:00 **Open End Networking at the Hotel bar**

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WEDNESDAY – 30th August 2023

07:30 – 08:50 **Breakfast & Networking**

08:50 – 09:00 **Daily information** (Jens Pahnke)

SESSION 6 – Elena Puris (20+5 min)

09:00 – 10:40 **The Role of ABC and SLC Transporters in Drug Disposition and Discovery**

09:00 – 09:25 **Gergely Gyimesi**
(University of Bern, Switzerland)

"The extended SLC Atlas: towards a unified view"

09:25 – 09:50 **Mikko Gynther**
(University of Heidelberg, Germany)

"Targeting Transporters for Drug Delivery to the Brain: How Can We Do Better?"

09:50 – 10:15 **Lukas Gorecki**
(University Hospital Hradec Králové, Czech Republic)

"Step by Step in Finding Novel ABCC1 Activators for the Treatment of Alzheimer's Diseases: An Organic Synthesis Approach"

10:15 – 10:40 **Sven Marcel Stefan**
(University of Lübeck, Germany)

"Step by Step in Finding Novel ABCC1 Activators for the Treatment of Alzheimer's Diseases: A Computational Chemistry Approach"

10:40 – 11:00 **Coffee Break & Networking**

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SESSION 7 – Chair: Mikko Gynther (20+5 min)

11:00 – 12:15 **Improved Analytical Methods and New Assays**

11:00 – 11:25 **Elena Puris**
(University of Heidelberg, Germany)

"Altered Protein Expression of ABC and SLC transporters in Isolated Cerebral Microvessels and Brain Cortex of Familial Alzheimer's Disease Animal Models"

11:25 – 11:50 **Dominika Olešová**
(Slovak Academy of Sciences, Slovakia)

„Progression of tau pathology in transgenic rat model for tau pathology revealed by joined lipidomic and metabolomic approach"

11:50 – 12:15 ***Aleš Kvasnička***
(University Olomouc, Czech Republic)

"Comprehensive metabolomic and lipidomic study of patients with tauopathies"

12:15 **Group photo**

12:15 – 13:30 **Lunch & Networking**

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SESSION 8 – Chair: Joseph Mindell (20+5 min)

13:30 – 15:10 **The Role of ABCA1 & A7 Transporters in Neurodegenerative Diseases / Lysosomal Transporters**

13:30 – 13:55 **Jens Pahnke**
(University of Oslo, Norway)

"Effects of ABCA7-Deficiency in Different Animal Models of Neurological Diseases - Unravelling Unexpected Functions"

13:55 – 14:20 **Lena Duchateau**
(University of Antwerp, Belgium)

"Using Transcript and CSF Biomarker Analysis to Better Understand the Pathophysiology of ABCA7 Expression-reducing Mutations in Alzheimer's Disease"

14:20 – 14:45 ***Fabien Gosselet***
(University of Artois, France)

"***Inflammation on the Neurovascular Unit: Impact on Cholesterol Metabolism and Amyloid Clearance"***

14:45 – 14:10 **Joseph Mindell**
(National Institute of Neurological Disorders and Stroke, USA)

"***Mechanism of ClC-7 transporter inhibition by the lysosomal phospholipid PI(3,5)P2"***

15:10 – 15:30 **Coffee Break & Networking**

TD5

SESSION 9 – Chair: Anika Hartz (20+5 min)

15:30 – 17:10 **Structural, Functional, and Regulatory Aspects of Transport Processes**

15:30 – 15:55 **Oded Lewinson**
[Israel Institute of Technology (Technion), Israel]

"Conformational Dynamics of ABC Transporters: From Single Molecules to In Vivo Studies"

15:55 – 16:20 **Muhammad Rafehi**
(University Medical Center Göttingen, Germany)

"How to Tanslate the Bioactivity Network of Drugs into Druggability of Orphan Targets"

16:20 – 16:45 **Amer Alam (ZOOM)**
(University of Minnesota, United States)

*"**Insights into the Interplay of Membrane Lipids and Structural Transitions in Human ABCA7"***

16:45 – 17:10 **Anika Hartz**
(University of Kentucky, United States)

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

17:15-17:25 **Short talks competition**
Mishel Zaichenko (Imperial College London, UK)

POSTER SESSION - Competition

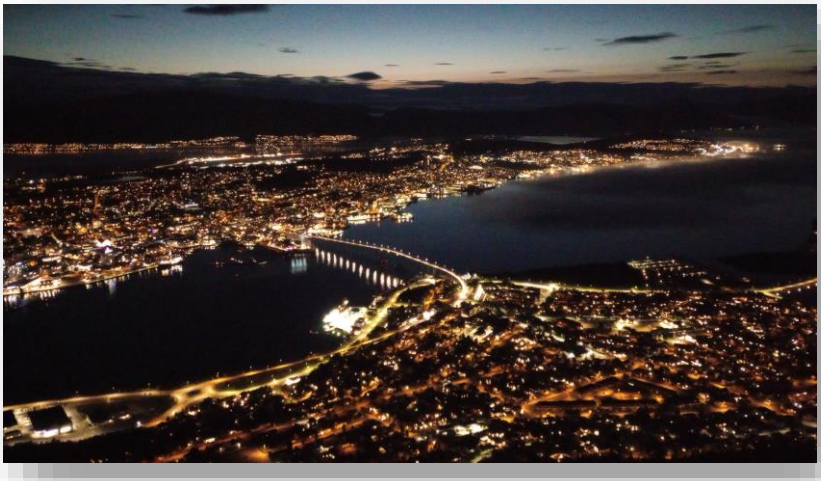
17:15 – 18:00 **Discussions & Networking at the Posters**

18:00 – 19:00 **individual walking / bus / driving to cable car (fjellheisen)**

Address: Sollivegen 12, 9020 Tromsdalen

20:00 – 21:30 **Dinner on HILLTOP RESTAURANT**
(separate booking, not included in registration fee)

01:30 **Last cable car down to town**



THURSDAY – 31st August 2023

07:30 – 08:50 **Breakfast & Networking**

08:50 – 09:00 **Daily information** (Jens Pahnke)

SESSION 10 – Chair: Jens Pahnke (20+5 min)

09:00 – 10:15 **Cellular and Animal Disease Models in Neurodegenerative Diseases**

09:00 – 09:25 **Tamir Ben Hur**
(Hebrew University Medical Center, Israel)

"When the Infectious Environment Meets the Alzheimer's Disease Brain"

09:25 – 09:50 **Shani Stern**
(University of Haifa, Israel)

"Reduced Synaptic Activity and Dysregulated Extracellular Matrix Pathways in Midbrain Neurons from Parkinson's Disease Patients"

09:50 – 10:15 **Dan Frenkel (ZOOM – 10 min) & Maria Natan (10 min)**
(Tel Aviv University, Israel)

"Do Glia Cells Have an Expiration Date?"

"Elucidating the outcome of expression of mutated presenilin 1 (PS1) in microglia cells on their inflammatory profile and β-amyloid clearance activity"

10:15 – 10:30 **Coffee Break & Networking**

SESSION 11 – Chair: Tamir Ben Hur (20+5 min)

10:30 – 12:00 **ABC Transporters for Clinical Use**

10:30 – 11:55 **Oliver Langer**
(Medical University of Vienna, Austria)

"Measurement of Cerebral P-gp, MRP1, and BCRP Function in a Beta-amyloidosis Mouse Model with PET"

10:55 – 11:20 **Severin Mairinger**
(Medical University of Vienna, Austria)

"[^{11}C]Metoclopramide, a PET Tracer with Improved Sensitivity to Measure Decreases in P-glycoprotein/ABCB1 Activity at the Blood-brain Barrier"

11:20 – 11:45 **Matthias Jackwerth**
(Medical University of Vienna, Austria)

"First-in-human Experience with 6-Bromo-7-[^{11}C]methyl-purine, a PET Tracer to Measure Cerebral MRP1 Activity"

11:45 – 12:00 **Peter Brust**
(University of Lübeck, Germany)

"Development of [^{18}F]FACH – the First ^{18}F-labeled MCT1/MCT4 Lactate Transport Inhibitor"

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from 12:00 **Lunch & Networking**

12:30 – 19:00 **FJORD SAFARI – RIB TOURS** *(PUKKA travels – pre-booking)*
Kirkegata 1, 9008 Tromsø (200m from hotel)

Summer Sail Safari 1 12:30-15:30 (12 guests)
Summer Sail Safari 2 16:00-19:00 (12 guests)
RIB1 12:45-14:45 (12 guests)
RIB2 15:30-18:00 (12 guests)

TD^5

WRAP-UP & AWARDS

19:00 – 20:30 **Farewell Dinner & Networking**

20:30 **TransportDEMENTIA^5 – *Closing – Competition awards***
(Jens Pahnke – *University of Oslo, Norway*)

21:00 **open end Farewell Party at the Hotel Bar and the Pub**

The winners: **Best short talk – Jingyun Wu (PhD student)**
Best poster – Ofir Sade (MSc student)

Abstracts of Talks and Poster Presentations

Amer Alam

University of Minnesota
The Hormal Institute

United States

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Insights into the Interplay of Membrane Lipids and Structural Transitions in Human ABCA7

Phospholipid extrusion by ABC subfamily A (ABCA) exporters is central to cellular physiology, although the specifics of the underlying substrate interactions and transport mechanisms remain poorly resolved at the molecular level. Here we report cryo-EM structures of lipid-embedded human ABCA7 in an open state and a nucleotide-bound, closed state at resolutions between 3.6-4.0 Å. The former reveals an ordered patch of bilayer lipids traversing the transmembrane domain (TMD), while the latter reveals a lipid-free, closed TMD with a small extracellular opening. These structures offer a structural framework for both substrate entry and exit from the ABCA7 TMD and highlight conserved rigid-body motions that underlie the associated conformational transitions. Combined with functional analysis and molecular dynamics (MD) simulations, our data also shed light on lipid partitioning into the ABCA7 TMD and localized membrane perturbations that underlie ABCA7 function and have broader implications for other ABCA family transporters.

Session 9: Structural, Functional, and Regulatory Aspects of Transport Processes
Wednesday – 30th August 2023, 16:20 – 16:45 (ZOOM

Tamir Ben-Hur

Dept. of Neurology
Hadassah Brain Labs
Hebrew University Medical Center

Israel

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When the Infectious Environment Meets the Alzheimer's Disease Brain

Misfolded proteins' deposition triggers a chain of events, leading to neurodegeneration in Alzheimer's disease (AD). Little is known on external environmental effects on the neurodegenerative process. Various infectious agents were linked with AD development. Infectious agents-derived pathogen associated molecular patterns (PAMPs) activate microglia, key mediators of neurodegeneration. We hypothesized that systemic pathogens may accelerate neurodegeneration in AD, mediated by microglia. We examined the effect of an infectious environment and of microbial toll-like receptor (TLR) agonists on cortical neuronal loss and on microglial phenotype in wild-type (wt) versus transgenic 5xFAD mice. 5xFAD mice grown in a natural ('dirty') environment displayed earlier cortical neuron loss than in a specific pathogen-free environment. Environmental exposure had no effect on cortical neuron density in wt mice. To model the effects of infectious environment, we injected systemically bacterial endotoxin, a TLR4 agonist, or zymosan and lipoteichoic acid, TLR2 agonists. Microbial TLR agonists penetrated the CNS and caused cortical neuronal death in 5xFAD, but not wt mice. We used the selective retinoic acid receptor alpha agonist Am580 to regulate microglial activation. Am580 attenuated iNOS expression, without canceling basic immune response of primary 5xFAD microglia. Intracerebroventricular delivery of Am580 in 5xFAD mice reduced iNOS+ microglia, increased TREM2+ microglia, and prevented TLR-induced neurodegeneration. Thus, exposure to systemic infections accelerates neurodegeneration in brains displaying amyloid pathology. AD brains exhibit increased susceptibility to microbial TLRs' neurotoxicity, accelerating neuronal death. These reciprocal effects may lead to a vicious cycle fueling AD pathogenesis. Microglial modulation protects the brain from microbial TLR agonists-induced neurodegeneration.

Session: Cellular and Animal Disease Models in Neurodegenerative Diseases
Thursday – 31st August 2023, 09:00 – 09:25

TD5

Peter Brust

Lübeck Institute of
Experimental Dermatology
University of Lübeck

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Development of [^{18}F]FACH – the First ^{18}F-labeled MCT1/MCT4 Lactate Transport Inhibitor

Overexpression of monocarboxylate transporters (MCTs) has been shown for a variety of human cancers (*e.g.*, colon, brain, breast, and kidney) and inhibition resulted in intracellular lactate accumulation, acidosis, and cell death. Thus, MCTs are promising targets to investigate tumor cancer metabolism with positron emission tomography (PET). Here, preclinical data about the development of [^{18}F]FACH – a PET radiotracer for imaging of the MCT1/MCT4 lactate transport will be presented.

Session 11: ABC Transporters for Clinical Use
Thursday – 31th August 2023, 11:45 – 12:00

Lucía Chavez Gutierrez

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Belgium

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Molecular bases of age at disease onset in Familial Alzheimer's Disease

γ-Secretases (GSEC) are intramembrane proteases controlling numerous signaling processes in pathophysiology. GSECs cleave many type I membrane proteins sequentially within their transmembrane domains (TMD) to release soluble fragments into the intracellular and extracellular compartments. This process, referred to as regulated intramembrane proteolysis, is essential in physiology and its dysregulation is tightly associated with disease. Mutations in GSEC that lead to its dysfunction cause Alzheimer's disease with early onset. Our research has shed mechanistic insights into Alzheimer's disease etiology by demonstrating that pathogenic mutations in GSEC promote the generation of longer, aggregation-prone amyloid-ß (Aβ) peptides from the amyloid precursor protein (APP) by destabilizing GSEC-APP (enzyme-substrate) interactions. Furthermore, our studies have recently shown that the molecular composition of Aß product profiles generated by mutant GSECs not only informs about pathogenicity, but can also be used to experimentally predict the age at disease onset (AAO). The significant link between mutation-driven changes in Aβ product length and Alzheimer's onset has motivated recent analysis addressing the structural strategies and kinetic mechanisms in GSEC that determine Aβ length. Our novel findings offer insights into how APP is processed by GSECs, as well as define the binding pocket of small allosteric compounds which modulate GSEC to promote efficient APP processing. These insights may open novel avenues to tackle toxic Av production in AD therapy.

Session 4: Translation between Fields
Tuesday – 29th August 2023, 17:55 – 18:20

Lara De Deyn

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Belgium

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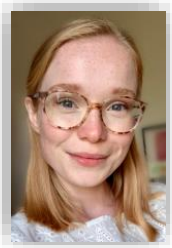

Poster & Short talk Transcript analysis of the important Alzheimer's disease risk gene, ABCA7, and its effect on AD using long and short read snRNA sequencing

Alzheimer's disease (AD) is a complex neurodegenerative disease characterized by the progressive deterioration of cognitive abilities and memory. One significant risk gene associated with AD is the ATP-binding cassette subfamily A member 7 (ABCA7). This gene exhibits both repeat expansion and rare premature termination codon mutations, with risk effect sizes comparable to the strongest genetic risk factor for AD, APOE ε4. While they are predicted to lead to loss-of-function, understanding the impact of these mutations on AD risk is challenging, due to a complex transcriptional architecture that may modulate the effect of these mutations, as well as due to cell type and tissue specific differences in expression and splicing.

In this study, we utilized a unique cohort and employ long and short read single-nuclei RNA sequencing techniques to investigate differential patterns of ABCA7 expression and splicing across various cell types, brain regions and ABCA7 genotypes in relation to AD. Furthermore, we explore the effect of ABCA7 perturbation on transcriptome-wide gene expression to identify pathways through which ABCA7 contributes to AD risk. The first outcomes of this research will be presented at the upcoming conference, offering novel insights into cellular heterogeneity and may contribute to our understanding of the pathological mechanisms underlying ABCA7 mutations in AD.

Session 5: Short Talks
Tuesday – 29th August 2023, 21:45 – 21:55

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

Lena Duchateau

Center for Molecular Neurology, VIB - University of Antwerp

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Using Transcript and CSF Biomarker Analysis to Better Understand the Pathophysiology of ABCA7 Expression-reducing Mutations in Alzheimer's Disease

ABCA7 is one of the most compelling risk genes for Alzheimer's disease (AD). Expression-reducing mutations, more specifically premature termination codon (PTC) mutations and a VNTR repeat expansion have been found to increase risk for AD. However, much remains unknown about the exact role of ABCA7 in the brain, and the pathomechanisms behind these mutations. During my PhD, I have leveraged several technologies to get a better insight into this pathophysiology. By studying CSF biomarkers of carriers of both PTC and VNTR expansion mutations, I discovered reduced Aβ1–42 levels in mutation carriers. This was even more pronounced in expansion carriers alone, where also reduced Aβ1–40, sAPPβ and YKL-40 levels were observed. These results suggest that expression-reducing mutation carriers have increased amyloid burden, and expansion carriers have reduced inflammation levels. To better understand the role of NMD escape, different isoforms and alternative splicing in ABCA7, and their potential role as modifiers of expression and disease severity, ONT long-read sequencing was used in a group of healthy and diseased PTC carriers and non-carriers. We found that ABCA7 splicing is much more complex than thought, with increased splicing in carriers and AD patients, and that NMD escape and rescue splicing could influence ABCA7 expression. Finally, we are performing spatial and single-nuclei sequencing on brain samples of mutation carriers and non-carriers, to learn more about cell-type specific and spatial differences of ABCA7 expression and isoforms. An initial pilot study pinpointed the *choroid plexus* as a region of particular interest with very high ABCA7 expression.

Session 8: The Role of ABC A1/A7 Transporters in Neurodegenerative Diseases
Wednesday – 30th August 2023, 13:55 – 14:20

TD5

Tudor Emanuel Fertig

Victor Babes Institute of Pathology, Bucuresti

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Poster & Short Talk Electron tomography reveals changes at the basement membrane of the mouse blood-brain barrier

Aging associates structural and functional changes of the blood-brain barrier (BBB) involving cellular degradation, disruption of molecular transport pathways and altered permeability. These changes lead to decline of cognitive function and/or neurodegenerative diseases. Key changes occur at the basement membrane of blood capillaries (BM), such as thickening and increased stiffness due to accumulation of extracellular matrix components or accumulation of advanced glycation end products. However, these changes remain poorly understood and relatively difficult to study.

In this work, we used transmission electron tomography (ET) to investigate changes of the BM in aging mice. We found the BM doubles in thickness between 6 and 24 months of age. Interestingly, lipid droplets clustered on the glial side of the BM of aged mice, which further increased BM thickness and altered its morphology. Using ET we showed that the lipid-rich regions organized in small pockets formed by the end-feet of astrocytes. These findings suggest an imbalance of the lipid metabolism preceding morphological changes of the BM, which may favour the accumulation of abnormal proteins accelerating neurodegeneration in aging.

Session 5: Short Talks
Tuesday – 29th August 2023, 21:30 – 20:40

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

Dan Frenkel

Dept. of Neuroscience
George S. Wise Faculty of Life Sciences
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Israel

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Do Glia Cells Have an Expiration Date?

Glia cells are essential for the maintenance of the brain activity and metabolism. During aging, glia cells, such as microglia and astrocytes, show markers of cellular senescence. Senescent cells exhibit altered activity towards chronic neuroinflammation. Senescent cells also show an impairment to support neurons resulting in chronic stress and neurodegeneration. We showed that aged astrocytes have an impairment to support neurons and present neurotoxic markers. We have established new mouse models to assess the role of senescent glia cells in aging and in progression of neurodegenerative diseases such as Alzheimer's disease.

Session 10: Cellular and Animal Disease Models in Neurodegenerative Diseases
Thursday – 31st August 2023, 09:50 – 10:00 (ZOOM)

Sylvie van Genderen

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POSTER Lipid Transporters and Beyond: the Effect of the Lipid Transporter ABCA7 on the Insulin-signaling Pathway

Fifty million people are diagnosed with Alzheimer's disease worldwide, which is expected to double in the next ten years. All patients are characterized by the deposition of the amyloid-b protein, neurofibrillary tangles composed of hyperphosphorylated tau, and neurodegeneration. Loss-of-function polymorphisms of the ABCA7 gene, which translates to a lipid transporter, are known to increase the risk of developing the disease up to 4-fold. The insulin hormone is crucial in the brain's energy metabolism, synaptic function, lipid synthesis, and degradation of amyloid-b. We, therefore, hypothesize a change in the regulation of the insulin-signaling pathway due to ABCA7 expression changes. LC-MS/MS was used to examine the protein expression in the guanidine fraction of the brain in 50, 100, and 200-day-old mice. Four groups of mice were compared; C57BL/6J mice, APP/PS1 mice, APP/PS1-hA7ko, and hA7ko. 7000 proteins were identified using this technique. Afterward, these results were validated using qPCR and imaging techniques. Results demonstrate a possible protective effect of an ABCA7 knockout via the insulin-signaling pathway at early time points of the disease, but as amyloidosis progresses, these effects were abolished. Further research needs to be conducted to determine if the ABCA7 transporter can be used as a diagnostic marker or a therapeutic target for Alzheimer's disease in the future.

Poster Session

Wednesday – 30th August 2023, 17:15 – 18:30

TD5

Fabien Gosselet

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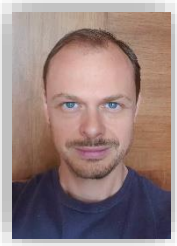

Inflammation on the Neurovascular Unit: Impact on Cholesterol Metabolism and Amyloid Clearance

The blood-brain barrier (BBB) is composed of brain endothelial cells (BECs) that display special features restricting molecule and cell exchanges between brain and blood. BECs closely communicate with brain pericytes that are embedded in the same basal lamina and that contribute to the BBB formation and maintenance. β-amyloid peptide (Aβ) accumulation in the brain parenchyma occurs when a lack of elimination through the BBB happens. This major hallmark of Alzheimer's disease (AD) is also associated with tau protein hyperphosphorylation, lipid metabolism imbalance, and inflammatory processes. Tumor Necrosis Factor alpha (TNFa) is the major inflammatory molecule reported in AD. Noteworthy, its impacts on the BBB cells of human origin and in particular, on the cholesterol metabolism and Aβ peptide transport remain to be clarified. Using a human syngenic BBB model comprising BECs and brain pericytes, we demonstrated in different studies that TNFa modulates the expression of several genes implicated in AD and cholesterol metabolism such as LXR/ABCA1 axis, APOE lipid acceptor, LDLR & LRP1 receptors, and efflux pumps including ABCB1 (P-gp) as well as ABCG2 (BCRP). In addition, TNFa impairs the BBB permeability by affecting expression and localization of proteins forming the tight junctions. Altogether, these modifications lead to a decrease of amyloid clearance across the BBB, and an increase of the cholesterol efflux independently of LXR/ABCA1. Our studies reinforce the link between inflammation, BBB and cholesterol/amyloid metabolism, and suggest that inflammation might be targeted in AD to delay or stop the disease progression.

Session 8: The Role of ABC A1/A7 Transporters in Neurodegenerative Diseases
Wednesday – 30th August 2023, 14:20 – 14:45

Lukas Gorecki

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Step by Step in Finding Novel ABC Activators for the Treatment of Neurodegenerative Diseases: An Organic Synthesis Approach

Overproduction and accumulation of macromolecular amyloid beta (Aβ) proteins are hallmarks of Alzheimer's disease, a devastating neurological disorder. The natural balance and elimination of Aβ peptides is associated with several adenosine-triphosphate-(ATP) binding cassette (ABC) transporters, and pharmacological activation of these membrane-bound efflux pumps holds promise as a revolutionary approach in Alzheimer's disease (AD) treatment. ABCC1 (multidrug resistance-associated protein 1, MRP1) was demonstrated to be a key player in Aβ clearance in AD. A low number of functional activators of ABCC1 and related transporters has been reported in the literature, however, structure-activity relationships (SAR) are unknown and cannot be exploited for future therapeutic and diagnostic development. In this study, we aimed to develop novel activators of ABCC1. A small library of 52 diverse compounds belonging to the most pronounced chemical classes was prepared and biologically evaluated in various functional and ATPase assays. Three molecules of structural similarity showed a very strong activation of ABCC1 indicated by reduced intracellular concentrations of ABCC1 substrates and increased ATPase activity of this transporter. We synthesized 14 derivatives of these closely related molecules and were able to draw major conclusions in terms of their SAR. Taken together, this systematic organic synthesis approach has provided crucial insights into the medicinal chemistry of ABCC1 as potential therapeutic target in AD.

Session 6: The Role of ABC and SLC Transporters in Drug Disposition and Discovery
Wednesday – 30th August 2023, 09:50 – 10:15

Anna Maria Górska

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POSTER Alzheimer's Disease Biomarkers in ISF and CSF – a Proteomics Approach

Proteomics using high-performance liquid chromatography (nanoLC) coupled to tandem mass spectrometry (nanoLC-MSMS) has developed into a powerful technology that is used in different areas of biomedical research, clinical diagnostics, and biotechnology. One of the most important applications of MS-based proteomics is the potential discovery of new biomarkers in human cerebrospinal fluid (CSF) for neurodegenerative disorders. Application of MS-based proteomics in basic research using animal models of Alzheimer's disease (AD) representing the crucial elements, such as deposition of amyloid-β and tau aggregates, of the pathological processes observed in AD patients, allows for detection and quantification of thousands of proteins in mouse brain tissue and CSF samples related to disease progression. The field of CSF proteomics is constantly expanding. However, studies of mouse CSF proteome is limited due to samples collection and small samples volumes. The CSF serves as a reservoir for the interstitial fluid (ISF), and extensive communication between ISF and CSF helps for the removal of waste products from the brain ISF. It was estimated that ~20% of CSF originates from the brain ISF. Such an exchange between CSF and ISF is crucial for the preservation of homeostasis in the brain. Microdialysis is a technique allowing for monitoring extracellular analytes in ISF and give a physiological important information that cannot be obtained from in vitro experiments. Combining proteomics analysis of those two systems will give us better inside view of mutual communication and function of both compartments. Moreover, establishment of ISF and CSF analyses in case of studying AD progression will give us better possibilities to select promising biomarkers.

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

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Iron Overload in Brain: Transport Mismatches, Microbleeding Events, and How Nano-chelating Therapies May Counteract Their Effects

Iron overload in many brain regions is a common feature in aging and in most neurodegenerative diseases. Physiological and pathological situations can be investigated using compartmental models mimicking the iron trafficking across the blood-brain barrier (BBB) and the cerebro-spinal fluid (CSF)-brain exchange membranes located in the choroid plexus. Elevated iron concentrations in the different compartments is either related to altered protein-mediated transport or by the abnormal presence of free iron ions in the cerebral intracellular fluid, that can be produced by BBB breakdown and hemoglobin degradation. *In silico* models can investigate alteration of iron homeostasis and also simulate the iron concentration in the brain environment and the effect of intracerebral iron chelation, suggesting potential doses and timing to recover the physiological state. As a matter of fact, novel formulations of non-toxic nanovectors with chelating capacity are already tested in organotypic brain models and are able to move from *in silico* to *in vivo* experiments.

Session 2: New Advanced Technologies
Tuesday – 29th August 2023, 11:35 – 12:00

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Phase Separation and Clustering of an ABC transporter in *Mycobacterium tuberculosis*

Phase separation drives numerous cellular processes, ranging from the formation of membrane-less organelles to the cooperative assembly of signalling proteins. Features such as multivalency and intrinsic disorder that enable condensate formation are found not only in cytosolic and nuclear proteins, but also in membrane-associated proteins. The ABC transporter Rv1747, which is important for *Mycobacterium tuberculosis* (Mtb) growth in infected hosts, has a cytoplasmic regulatory module consisting of 2 phosphothreonine-binding Forkhead-associated domains joined by an intrinsically disordered linker with multiple phospho-acceptor threonines. Here we demonstrate that the regulatory modules of Rv1747 and its homolog in *Mycobacterium smegmatis* form liquid-like condensates as a function of concentration and phosphorylation. The serine/threonine kinases and sole phosphatase of Mtb tune phosphorylation-enhanced phase separation and differentially colocalize with the resulting condensates. The Rv1747 regulatory module also phase-separates on supported lipid bilayers and forms dynamic foci when expressed heterologously in live yeast and *M. smegmatis* cells. Consistent with these observations, single-molecule localization microscopy reveals that the endogenous Mtb transporter forms higher-order clusters within the Mycobacterium membrane. Collectively, these data suggest a key role for phase separation in the function of these mycobacterial ABC transporters and their regulation *via* intracellular signaling.

Session 1: The Role of ABC and SLC Transporters in Health and Disease
Tednesday – 29th August 2023, 09:25 – 09:50

Gergely Gyimesi

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The extended SLC Atlas: towards a unified view

The Solute Carrier (SLC) gene superfamily represents the largest and most diverse group of transmembrane transporter proteins involved in maintaining cellular homeostasis of metabolites and ions. Their heterogeneity poses a significant challenge to their identification, classification and annotation. Due to the absence of conserved sequence or structural signature motifs, we hypothesized that yet unidentified SLC transporters could exist in the human genome. In our work, we undertook a systematic meta-analysis of available data and literature in order to discover SLC-like proteins not yet in the official nomenclature. We derived a set of eight criteria defining "SLC-likeness" in terms of properties that can be extracted from available databases. Manual curation of TCDB protein families and corresponding Pfam models was carried out based on their textual description on the corresponding web sites in order to exclude those that violate any of our SLC-likeness criteria. The following sequence similarity searches in seven clinically relevant organisms revealed 3669 SLC-like proteins, including ~120 potentially SLC-like proteins in human in addition to the previously annotated SLCs. Classification into families gave ~40 "novel" SLC-like protein families. Subsequent literature search on the found human proteins revealed that 53 of the "novel" SLC-like proteins could be assigned a small-molecule substrate. Currently, several of these "novel" SLC-like families are being included into the SLC nomenclature in collaboration with the Human Gene Nomenclature Committee (HGNC). A complete view of the human "SLC-ome" will play an instrumental role in understanding human physiology and can potentially be exploited for therapeutic benefits.

Session 6: **The Role of ABC and SLC Transporters in Drug Disposition and Discovery**
Wednesday – 30th August 2023 09:00 – 09:25

Mikko Gynther

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Targeting Transporters for Drug Delivery to the Brain: How Can We Do Better?

Limited drug delivery to the brain is one of the major reasons for high failure rates of central nervous system (CNS) drug candidates. The blood-brain barrier with its tight junctions, membrane transporters, receptors and metabolizing enzymes is a main player in drug delivery to the brain, restricting the entrance of the drugs and other xenobiotics. Current knowledge about the uptake transporters expressed at the BBB and brain parenchymal cells has been used for delivery of CNS drugs to the brain via targeting transporters. Although many transporter-utilizing prodrugs and nanocarriers have been developed to improve the uptake of drugs to the brain, their success rate of translation from preclinical development to humans is negligible. In order to find explanations for the current lack of success, we made a systematic summary of the progress in development of brain targeted transporter-utilizing prodrugs and nanocarriers. In addition, we applied CNS pharmacokinetic concepts for evaluation of the limitations and gaps in investigation of the developed transporter-utilizing prodrugs and nanocarriers. Finally, we give recommendations for a rational development of transporter-utilizing drug delivery systems targeting the brain based on CNS pharmacokinetic principles.

Session 6: **The Role of ABC and SLC Transporters in Drug Disposition and Discovery**
Wednesday – 30th August 2023 09:25 – 09:50

Anika Hartz

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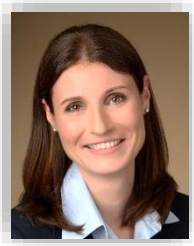

Blood-Brain Barrier Dysfunction in Alzheimer's Disease: An Environmental Health Perspective

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. Our study funded by a UK-CARES grant and a NIHR01 showed that the xenoestrogen bisphenol A (BPA) triggers barrier dysfunction and causes cognitive impairment in vivo in mice. We also found barrier dysfunction, high oxidative stress levels, and high BPA levels in human brain samples from CAA patients compared to cognitively normal individuals suggesting a potential role for BPA in AD. Data from our ongoing study indicate that the FDA-approved estrogen receptor blocker Fulvestrant reduces BPA-induced barrier dysfunction, Aβ capillary levels, and memory deficits in vivo. Based on our existing data, we are currently in the process of developing therapeutic strategies to repair barrier dysfunction to lower Aβ brain burden with the ultimate goal of improving memory loss and delaying onset and slowing progression of Alzheimer's disease.

Session 9: Structural, Functional, and Regulatory Aspects of Transport Processes
Wednesday – 30th August 2023 16:45 – 17:10

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First-in-human Experience with 6-Bromo-7-[^{11}C]methyl-purine, a PET Tracer to Measure Cerebral MRP1 Activity

There is evidence that multidrug resistance-associated protein 1 (MRP1/ABCC1) may contribute to the clearance of beta-amyloid from the brain. Positron emission tomography (PET) imaging with 6-bromo-7-[^{11}C]methylpurine ([^{11}C]BMP) allows for measuring the activity of MRP1 in vivo. [^{11}C]BMP PET experiments revealed an increase in cerebral MRP1 activity in APP/PS1-21 mice as compared with age-matched wild-type mice. The aim of the Austrian sub-project (FFG #882717) of the PETABC project is to use [^{11}C]BMP for the first time in humans and apply this radiotracer to assess cerebral MRP1 activity in AD patients. As a first task, test-retest scans with [^{11}C]BMP will be performed in young healthy volunteers. As a second task, the effect of MRP1 inhibition with probenecid on the disposition of [^{11}C]BMP will be assessed and as a third task AD patients and age-matched control subjects will be examined.
In this talk, the necessary steps for performing a first-in-human study with a new radiotracer will be summarized and first human PET data will be presented.

Session 11: ABC Transporters for Clinical Use
Thursdau – 31st August, 2023 11:20 – 11:45

Baruch I. Kanner

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Molecular Mechanism of Transport in the SLC6 Family

Inhibitors of the sodium- and chloride-coupled neurotransmitter transporters from the SLC6 family define a key therapeutic strategy to treat clinical depression, ADHD, neuropathic pain and certain forms of epilepsy. These transporters shape synaptic transmission by removing the neurotransmitter from the synaptic cleft and thereby terminate the signal. Moreover, dysfunction of synaptic transmission has been implicated in the pathophysiology of Alzheimer's Disease. In this talk I'll give an overview of our knowledge on the molecular mechanism of active neurotransmitter transport by SLC6 members. Our insights are obtained by functional and structural studies by several groups. The first cloned SLC6 transporter is the GABA transporter GAT1 on which our laboratory has carried out extensive functional studies. The strategy was to obtain "insightful" mutants and characterize them by biochemical and functional approaches. The results could be very well explained by structures obtained by different groups. One of the hallmarks of transport is that their binding pocket can be alternately open to either side of the membrane. In the SLC6 transporters this is achieved by a relative movement of the bundle, consisting of four transmembrane helices relative to the scaffold of eight such helices. We will discuss additional movements of other structural elements required for alternating access and the role of chloride. Glutamate is the only neurotransmitter transported by SLC1 rather than SLC6 transporters which remarkably achieve alternating access by a different mechanism, namely by an elevator-like movement of the transport domain relative to the scaffold.

Session 1: The Role of ABC and SLC Transporters in Health and Disease
Tuesday - 29th August 2023, 10:10 – 10:30

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Multi-transcriptomics Reveals Brain Cellular Responses to Peripheral Infection in Alzheimer's Disease Model Mice

Peripheral inflammation has been associated with various neurodegeneration, including Alzheimer's Disease (AD). In this study, we employed an AD mouse model nasally infected with *Staphylococcus aureus* to assess the impact of chronic or acute peripheral inflammation on brain transcriptome and amyloid pathology. The chronic exposure increased the diffuse and compact amyloid plaques and blood cytokine levels. Following a short-term exposure, single-cell and spatial transcriptomics uncovered cell type- and spatial-specific transcriptional changes indicating a dysregulation of the brain barriers, including the blood-brain and the blood-cerebrospinal fluid barriers. Brain macrophages exhibited increased Apoe expression and macrophage-specific genes were upregulated at ventricular areas of infected mice. In addition, we report an increase of disease associated microglia genes around the Aβ plaques, together with dis-balances in neuronal expression in response to peripheral inflammation. Overall, results enlighten the mechanisms linking peripheral inflammation to AD.

Session 3: Multi-omics & Bioactivity Networks
Tuesday - 29th 2023 16:00 – 16:25 (ZOOM)

TD5

Aleš Kvasnička

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Comprehensive metabolomic and lipidomic study of patients with tauopathies

Background: Tauopathies are neurodegenerative diseases, including Alzheimer's disease (AD), characterized by the abnormal deposition of tau protein causing neuroinflammation and neuronal death. However, the pathophysiology and effective treatment of tau protein dysregulation are not fully elucidated. Therefore, we performed comprehensive metabolomic and lipidomic analyses of tauopathies and AD to identify new potential biomarkers and understand metabolic changes between different tauopathy cohorts. *Methods:* We used targeted LC-MS/MS analysis to analyze cerebrospinal fluid (CSF) from patients with different tauopathies Samples were obtained from patients suffering from AD (n=19), progressive supranuclear palsy (PSP, n=12) patients, a semantic variant of primary progressive aphasia (PPA1, n=7), a non-fluent agrammatic variant of primary progressive aphasia (PPA2, n=6) patients, corticobasal degeneration (CBD, n=5) and behavioural variant of frontotemporal dementia (FTD, n=7). The results were subjected to multivariate and univariate statistical analysis.
Results: We identified 95 polar metabolites in CSF and found a significant increase in free carnitine and several acylcarnitines in all tauopathy cohorts compared to controls. Moreover, 213 lipids (15 lipid classes) were identified in CSF where levels of phosphatidylcholines, their glycerophospholipid plasmalogens and lyso-species, and cholesteryl esters were increased, particularly in AD, FTD, CBD, PPA1, and PPA2.
Conclusion: Our results demonstrate systematic dysregulation of metabolism related to different tauopathies and AD on the level of polar metabolites and lipids, which could serve as potential biomarkers.

Session 7: Improved Analytical Methods and New Assays
Wednesday – 30th August 2023, 11:50 – 12:05

Poster Session
Wednesday – 30thAugust 2023, 17:15 – 18:30

Magdalena Kurtyka

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Poster & Short talk SLC7A1 is a novel candidate for the transport of therapeutics across the blood-brain barrier

After decades of extensive research, the delivery of therapeutics into the brain still poses a great challenge due to the blood-brain barrier (BBB) selectivity. Most molecules require carrier- or receptor-mediated transport systems to cross the BBB. Directed transport is achieved by the polarity of the endothelial cells with different receptor compositions of the blood- (luminal) and brain- (abluminal) faced membrane. These transport systems form attractive routes for the delivery of drugs into the central nervous system (CNS), yet the number of known brain endothelium-enriched receptors allowing the transport of molecules into the brain is scarce. In this study, we combined transcriptomic analysis of human and murine brain endothelium and performed a complex screening of BBB-enriched genes according to established selection criteria. As a result, we propose the high-affinity cationic amino acid transporter 1 (SLC7A1) as a novel candidate for drug delivery across the BBB. Using in situ hybridization assay, we demonstrated SLC7A1 gene expression enrichment in both human and mouse brain microvasculature. Moreover, we detected SLC7A1 protein expression in isolated murine brain capillaries and cultured primary brain endothelial cells. In order to prove SLC7A1 functionality as a transporter, we performed a transcytosis assay with isolated murine primary brain endothelial cells, using the radiolabelled anti-SLC7A1 antibody. Our data demonstrate that SLC7A1 may function as a transcytosis transporter. Yet, more studies, particularly in vivo, need to be performed to further validate its therapeutical potential for the transport of therapeutics into the brain.

Session 5: Short Talks
Tuesday – 29th August, 2023, 21:15 – 21:25

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

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Measurement of Cerebral ABCB1, ABCC1, and ABCG2 Function in a β-amyloidosis Mouse Model with PET

Adenosine triphosphate-binding cassette (ABC) transporters, *i.e.*, P-glycoprotein (P-gp/ABCB1), multidrug resistance-associated protein 1 (MRP1/ABCC1), and breast cancer resistance protein (BCRP/ABCG2), may contribute to the clearance of beta-amyloid from the brain. There is evidence from several studies employing different techniques (immunohistochemical staining, Western blot, quantitative proteomics) that beta-amyloidosis can lead to changes in the abundance of cerebral ABC transporters. It is not fully understood, whether these changes in the abundance of ABC transporters have functional consequences leading to changes in the brain clearance of beta-amyloid. Positron emission tomography (PET) imaging with radiolabeled substrates of ABC transporters enables the non-invasive assessment of the function of ABC transporters *in vivo*. We have used PET imaging with a range of different radiotracers to assess changes in the function of P-gp, MRP1, and BCRP in the brain of a frequently used β-amyloidosis mouse model (APP/PS1-21 mice) relative to age-matched wild-type mice. My talk will summarize the data we have obtained so far.

Session 11: ABC Transporters for Clinical Use
Thursay – 31st August 2023, 10:30 – 10:55

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Contribution of Extracellular Vesicles (EV) to the Restoration of Age-related Brain Transcriptomes and Cognition

We demonstrate that infusions of young serum significantly improved age-associated memory deficits. RNA-seq analysis of the choroid plexus demonstrated EV-mediated effects on genes involved in barrier function and trans-barrier transport. Comparing the differentially expressed genes to the recently published chronological aging clocks revealed a reversal of transcriptomic aging in the choroid plexus. The hippocampal transcriptome demonstrated a significant upregulation of the anti-aging gene Klotho following young serum treatment and an abrogated effect after EV depletion. Transcriptomic profiling of Klotho knockout and heterozygous mice showed downregulation of genes associated with transport, exocytosis, and lipid transport, while upregulated genes were associated with activated microglia. The results of our study indicate the significance of EVs as vehicles to deliver signals from the periphery to brain and the importance of Klotho in maintaining brain homeostasis.

Session 3: Multi-omics & Bioactivity Networks
Tuesday – 29th August 2023, 16:25 – 16:50 (ZOOM)

Oded Lewinson

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Conformational Dynamics of ABC Transporters: From Single Molecules to *In Vivo* Studies

ABC transporters are members of an ancient superfamily of transport proteins that play diverse and vital roles in all kingdoms of life. They couple the energy derived from ATP hydrolysis to the transport of a wide range of biomolecules. Although they share a common basic architecture, they have evolved to perform many different functions. In this talk, I will present recent results that explain how this common architecture is fine-tuned by conformational dynamics and allosteric connectivity to give rise to distinct transport mechanisms and functional adaptations.

Session 9: Structural, Functional, and Regulatory Aspects of Transport Processes
Wednesday – 30th August, 2023 15:30 – 15:55

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[^{11}C]Metoclopramide, a PET Tracer with Improved Sensitivity to Measure Decreases in ABCB1 Activity at the Blood-Brain Barrier

Background: P-glycoprotein (P-gp/ABCB1) plays an important role in the clearance of beta-amyloid (Aβ) peptides across the blood-brain barrier (BBB). Positron emission tomography (PET) with radiolabelled P-gp substrates has shown promise to non-invasively measure P-gp activity at the human BBB, but its applicability is limited by insufficient sensitivity to detect moderate, yet physiologically relevant changes in cerebral P-gp activity. We compared the sensitivity of the newly developed radiotracer [^{11}C]metoclopramide with (*R*)-[^{11}C]verapamil and [^{11}C]*N*-desmethyl-loperamide to measure decreased cerebral P-gp activity, by using wild-type (wt), heterozygous Abcb1a/b$^{(+/-)}$ and homozygous Abcb1a/b$^{(-/-)}$ mice as models with controlled levels of cerebral P-gp expression.
Methods: wt, Abcb1a/b$^{(+/-)}$ and Abcb1a/b$^{(-/-)}$ mice underwent [^{11}C]metoclopramide PET scans. Brain uptake of [^{11}C]metoclopramide was expressed as the area under the brain time-activity curve (AUC_{brain}) and compared with data previously obtained with (*R*)-[^{11}C]verapamil and [^{11}C]*N*-desmethyl-loperamide in the same mouse strains. Immunohistochemistry was used to quantify cerebral P-gp expression levels in the three mouse strains.
Results: wt, Abcb1a/b$^{(+/-)}$ and Abcb1a/b$^{(-/-)}$ mice had normal, intermediate and no cerebral P-gp expression, respectively. All three radiotracers had significantly higher AUC_{brain} values in Abcb1a/b$^{(-/-)}$ versus wt mice (2.5- to 5.7-fold, $p<0.0001$). [^{11}C]Metoclopramide also had significantly higher AUC_{brain} values in Abcb1a/b(+/−) versus wt mice (1.46-fold, $p<0.001$), while for (*R*)-[^{11}C]verapamil and [^{11}C]*N*-desmethyl-loperamide AUC_{brain} values were unchanged in Abcb1a/b$^{(+/-)}$ as compared with wt mice.
Conclusions: [^{11}C]Metoclopramide was the only radiotracer capable of detecting an approximately 50% reduction in cerebral P-gp expression, which suggested adequate sensitivity to measure moderate, physiologically relevant decreases in cerebral P-gp activity (*e.g.*, in AD patients).

Session 11: ABC Transporters for Clinical Use
Wednesday – 31st August 2023, 10:55 – 11:20

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Counteracting the pathological effects of APOE4 in vivo, by activation of the lipidating protein ABCA1

Objectives: The overall objective of this study was to determine whether the low molecular weight and brain permeable drug-able ABCA1 activator developed in our laboratory, can reverse the hypolipidation of apoE4 in vivo and the associated apoE4 driven brain pathological effects.
Methods: ABCA1 agonists, which reverse the hypolipidation of APOE4, were developed by High-Throughput Screening utilizing functional and ABCA1 binding assays. These include cholesterol efflux, counteracting the impaired ability of APOE4
to digest senile plaques in vitro, as well as binding of the hits to the extracellular domain (ECD1) of ABCA1. This yielded several hits and a lead compound (N1) which activates cholesterol efflux, senile plaque digestion and bind the ECD1of ABCA1 with affinities of 2-4 μM. These in vitro findings will be presently extended to the in vivo level as outlined below.
Results: We first analyzed the extent to which the hypolipidation of APOE4 *in vivo* can be reversed by direct injection of N1 into the brain. This revealed that N1 reverses the hypolipidation of APOE4 in the brain, thus demonstrating that N1 can affect the lipidation of apoE4, both in vitro and when applied directly into the brain.
We next investigated whether N1 can enter the brain when applied externally, and affect the lipidation of apoE4. This revealed that intranasal application of N1 for several weeks completely reversed the hypolipidation of APOE4. Furthermore, this was associated with reversal of the pathological effects of apoE4 on key parameters. (e. g. it decreased the apoE4 driven hyperphosphorylation of tau, and increased the levels of APOE receptor - APOER2 back to control APOE3 levels.
Conclusions: Taken together, these finding provide a proof of concept for the validity of the presently proposed approach of contracting the pathological effects of APOE4 by treating with ABCA1 activators.

Session 3: Multi-omics & Bioactivity Networks
Wednesday – 28th August 2023, 16:50 – 17:10

Joseph Mindell

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Mechanism of ClC-7 transporter inhibition by the lysosomal phospholipid PI(3,5)P2

Lysosomes process cellular waste and coordinate cellular responses to metabolic challenge, and have been increasingly connected to multiple neurodegenerative diseases. Central to lysosomal homeostasis are key signaling phosphoinositide lipids which regulate lysosomal membrane dynamics and which have been implicated in the pathophysiology and therapy of such diseases as cancer, ALS, and prion disease. In particular, the lipid phosphoinositol 3,5-bisphosphate (PI(3,5)P2), synthesized by the enzyme PIKfyve, is specific to lysosomes and interacts with multiple lysosomal membrane proteins. PI(3,5)P2 was recently demonstrated to modulate lysosomal pH, critical for digestive function, by directly inhibiting the chloride proton antiporter ClC-7. However, the molecular basis of this inhibition is unknown. Here we show that PI(3,5)P2 binding to ClC-7 inhibits transporter function by inducing close association between transmembrane and cytoplasmic domains. Mutations that disrupt the domain interface show increased transport activity and loss of PI(3,5)P2 inhibition in electrophysiology experiments. Cryo-EM structures reveal that binding of PI(3,5)P2 induces close association between the cytosolic domain and the TMD whereas this cytoplasmic region is unresolved in the absence of PIP2 or in the presence of a disease-causing mutation, a model also supported by molecular dynamics simulation. These results suggest a model in which PI(3,5)P2 binding results in tight association between the ClC-7 cytosolic and transmembrane domains, inhibiting transport.

Session 8: ABCA1/7 and Lysosomal Transporters
Wednesday – 30th August 2023, 14:45 – 15:10

Maria Natan

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Poster + Short talk **Elucidating the outcome of expression of mutated presenilin 1 (PS1) in microglia cells on their inflammatory profile and β-amyloid clearance activity**

Alzheimer's disease (AD) is the most common type of dementia, and it affects over 50 million people worldwide. The majority of genetic early familial AD cases (75%) relate to the PS1protein. PS1 is highly expressed in microglia as compared to other cells in the brain. Microglia had been suggested to have an important role in AD due to its function in β-amyloid plaques clearance and increased neurotoxicity. We have previously reported that PS1 plays an important role in microglia activity (Farfara et al., Ann Neurology, 2011). We further assessed the outcome of mutation in PS1, which is affiliated with AD, on microglia activity. We established a microglia cell line that is over expressing human PS1 (hPS1) and AD-related, mutated, human PS1 (mhPS1) protein. Our findings may elucidate the contribution of PS1 protein in microglia to AD development and progression.

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

Session 10: Cellular and Animal Disease Models in Neurodegenerative Diseases
Thursday – 31st August 2023, 10:00 – 10:10

Dominika Olešová

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Progression of tau pathology in transgenic rat model for tau pathology revealed by joined lipidomic and metabolomic approach

Tauopathies are a group of neurodegenerative disorders characterized by cerebral atrophy, hyperphosphorylation, abnormal aggregation of tau filaments into intracellular neurofibrillary tangles and chronic neuroinflammation. A role of lipid metabolism dysregulation in aging and neurodegeneration is well established, however still poorly understood. To investigate the impact of tau pathology on lipid metabolism, we have performed a thorough targeted lipidomic and metabolomic analysis of brain tissue, cerebrospinal fluid (CSF) and plasma of transgenic rats expressing human truncated tau. Specific biofluid markers of tau pathology (total-tau and neurofilament-light-chain) and tau hyperphosphorylated and aggregated forms in brain tissue were measured to examine the effect of tau pathology on metabolic profiles. Presence of neurofibrillary pathology resulted in substantially dysregulated lipid metabolism in brain tissue and even more in the CSF. The most profound change was in phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, lysophosphatidyl-choline and sphingomyelin subclasses. However, neither of the changes in CSF nor brain lipidome were reflected in the plasma. Further analysis showed that lipid changes correlate with the tau pathology in brain tissue. Moreover, we found that tau pathology induces formation of lipid droplets in vitro and in vivo . Our results results highlight the importance of lipid metabolism in tau pathology alone, but also main hallmarks of neurodegenerative disesases such as neuroinflammation, glial activation and hyperphoshorylation.

Session 7: Improved Analytical Methods and New Assays
Wednesday – 30th August 2023, 11:25 – 11:50

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Effects of ABCA7-Deficiency in Different Animal Models of Neurological Diseases - Unravelling Unexpected Functions

A while ago, the ABC transporter A7 has been discovered as important AD risk factor. It is linked to cholesterol & lipid transport. We supposed that ABCA7 is together with ABCA1 and APOE4 a general modulator that may also be involved in the pathogenesis or initiation of other neurodegenerative/neurological diseases. Therefore, we generated a new, humanized ABCA7 mouse model that also enables Cre-inducible, location-specific knockout of the inserted human ABCA7 cDNA in the Abca7 mouse locus. Using this inducible, humanized model, we generated β-amyloidosis AD (APPPS1 [1]), Multiple Sclerosis (EAE) and Huntington's disease (zQ175dn [2]) models that are deficient for ABCA7 (A7ko).

The talk will present up-to-date results of the characterization (phenotypical, biochemical, morphological, and proteomics, metabolomics and lipidomics mass spec) of these new models and will present insides into the function of ABCA7 and its related effects in AD, HD and MS.

[1] Radde *et al.* 2006 EMBO, doi: 10.1038/sj.embor.7400784
[2] Wu J *et al.* 2022 IJMS, doi: 10.3390/ijms232314763

Session 8: The Role of ABC A1/A7 Transporters in Neurodegenerative Diseases
Wednesday – 30th August 2023, 13:30 – 13:55

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Elucidating the Role of ABCC1 in Squamous Carcinogenesis

The ABC transporter ABCC1 (also known as MRP1) regulates the extracellular efflux of several endogenous metabolites, including pro-inflammatory biolipids. Here we reported several evidence showing that ABCC1 is a novel target gene of the transcription factor ΔNp63 exerting an oncogenic role in squamous cell carcinoma (SCC). By gain or loss of function experiments and ChIP assay, we demonstrated that in ΔNp63 directly controls the expression of ABCC1 by binding a p63 DNA consensus motif localized in the first intron of ABCC1 gene. ΔNp63 and ABCC1 levels are positively correlated at mRNA and protein levels during physiological (epidermal differentiation) and pathological (SCC) processes. At functional level, we found that genetic (CRISPR-Cas9), chemical (MK-571) or siRNA-mediated inhibition of ABCC1 affects SCC proliferation, ROS homeostasis and the extracellular efflux of GSSG and proinflammatory lipids. Accordingly, we found that the in vivo genetic deletion of ABCC1 affects the cellular response to the pro-inflammatory agent TPA and delays squamous carcinogenesis. Collectively, these data uncover the ABCC1-ΔNp63 axis as a novel oncogenic route in SCC.

Session 4: Translation between Fields
Tuesday – 29th August 2023, 17:55 – 18:20

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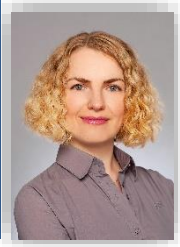

Altered Protein Expression of ABC and SLC transporters in Isolated Cerebral Microvessels and Brain Cortex of Familial Alzheimer's Disease Animal Models

Membrane transporters, such as ATP-binding cassette transporters (ABC) and solute carriers (SLCs), mediating passage of nutrients, metabolites and drugs, across the blood-brain barrier (BBB) and brain parenchymal cells have been shown to play roles in Alzheimer's disease (AD) pathogenesis. However, there is a lack of information on quantitative changes in transporter protein expression in AD patients and animal models, in particular, with the emphasis on sex-specific alterations in transporter expression. In the present study, we investigated the changes in absolute protein expression of five ABC and thirteen SLC transporters in the isolated cerebral microvessels and brain cortical tissues in two commonly used animal models of AD, such as TgF344-AD rats and 5xFAD mice, while comparing to age-matched wild-type controls. Moreover, we studied sex-specific alterations in transporter expression in the brain cortical tissue of the TgF344-AD rats and 5xFAD mice. To achieve the goal, we used state-of-the-art liquid chromatography tandem mass spectrometry (LC-MS/MS)-based quantitative targeted absolute proteomic analysis. The study revealed significant changes in protein expression of several ABC and SLC transporters in the isolated cerebral microvessels and brain cortical tissue, which were model- and sex-specific. In order to evaluate the relevance of the animal models to mimic AD-related changes in patients, alterations in protein expression in the models were compared to published quantitative data in AD brains. The study provides new knowledge for elucidation of molecular mechanisms underlying AD. In addition, the study gives first insight on sex-specific changes in transporter expression in brain cortices of AD models.

Session 7: Improved Analytical Methods and New Assays
Wednesday – 30th August 2023, 11:00 – 11:25

Inna Radzishevsky

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Neonatal Brain Development Critically Depends on Serine Supply by SLC38A5 at the Blood-brain Barrier

Brain L-serine is critical for neurodevelopment and is thought to be synthesized solely from glucose, without any influence from blood L-serine. In contrast, we found that the influx of L-serine across the blood-brain barrier (BBB) is essential for brain development. We identified endothelial SlC38A5 (sodium-coupled neutral amino acid transporter 5, SNAT5), formerly known as a glutamine transporter, as an L-serine transporter at the BBB expressed during early postnatal life. Young SlC38A5 knockout (KO) mice develop microcephaly and exhibit a selective decrease in brain L-serine and the neuromodulator D-serine, without changes in other brain or serum amino acids. The brains of these mice also show accumulation of neurotoxic deoxysphingolipids, abnormal synaptic size, mitochondrial damage, and reduced neurogenesis. SLC38A5-KO pups exhibit increased ultrasonic vocalizations and motor impairments that are rescued by administration of L-serine at concentrations that replenish the serine pool in the brain. Our findings underscore the crucial role of SLC38A5 in supplying L-serine across the BBB for synaptic and mitochondrial maintenance and brain development.

Session 1: The Role of ABC and SLC Transporters in Health and Disease
Tuesday - 29th August 2023, 09:50 – 10:10

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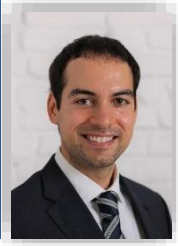

How to Translate the Bioactivity Network of Drugs into Drugability of Orphan Targets

Medicinal polypharmacology is a young field at the intersection of medicinal chemistry, chemical biology, clinical pharmacology, and molecular medicine. It acquires, visualizes, processes, and utilizes data on polypharmacology of molecules to shape the polypharmacological profile of the drugs of the future. From a therapeutic perspective it is generally accepted today that the clinical outcome of drug treatment is the result of multiple interactions with multiple targets rather than a single drug-single target interaction. Even the controlled engagement of multiple targets is considered a valid strategy to overcome disease, pulling away polypharmacological drugs from their 'dirty drug' image. From a basic research perspective, polypharmacological drugs hold the key to unlock yet undruggable orphan targets by addressing conserved structural motifs amongst even phylogenetically distant protein families through the 'conservatism of nature'. ATP-binding cassette (ABC) and solute carrier (SLC) transporters are protein superfamilies consisting of 48 and >400 subfamily members that exert (poly)specific translocation of solutes, metabolites, and/or xenobiotics between membranes. Most of these transporters are undruggable although associated with both prevalent and orphan human diseases. By applying medicinal polypharmacology, we assembled a small compound library of 31 polypharmacological drugs and used these to mediate between both superfamilies, identifying several candidate with very large broad-spectrum activity. These molecules are the anchor point for future exploration of yet undruggable orphan ABC and SLC transporters.

Session 9: Structural, Functional, and Regulatory Aspects of Transport Processes
Wednesday – 30th August 2023, 15:55 – 16:20

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Early Diagnosis and Treatment of Alzheimer's Disease by Targeting Toxic Soluble Aβ Oligomers

The aim of this study was to develop novel self-assembled cyclic D,L-alpha-peptide nanotubes as theranostic agents to diagnose early Aβ oligomers in pre-symptomatic stage of AD and diminish memory and cognition decline. Kinetic Thioflavin T, electron microscopy, NMR, and CD spectroscopy as well as immunochemical and biochemical methods were used to study the effect of aza-glycine insertion on cyclic D,L-alpha-peptide self-assembly, Aβ oligomer disruption, and toxicity. The *in vivo* PET imaging studies and therapeutic activity were performed in AD transgenic mice and *C. elegans*. Introducing an aza-glycine residue with extra hydrogen-bond donor to tune nanotube assembly and amyloid engagement, cyclic aza-peptide 1 interacted with early Aβ oligomers (1-3mers) and inhibited Aβ aggregation and toxicity at sub-stoichiometric concentrations. NMR studies revealed dynamic interactions between aza-peptide 1 and Aβ42 residues F19 and F20, which are pivotal for early dimerization and aggregation. In an AD mouse model, brain PET imaging using stable ^{64}Cu-labeled aza-peptide 1 gave unprecedented early amyloid detection in 44-day pre-symptomatic 5xFAD mice better than ^{11}C-PIB. No tracer accumulation was detected in the cortex and hippocampus of treated AD mice; instead, intense PET signal was observed in the thalamus, from where Aβ oligomers may spread to other brain parts with disease progression. Effectively crossing the BBB, the cyclic (aza-) peptides reduced Aβ oligomer levels, prolonged lifespan of AD transgenic *C. elegans*, and abated memory and behavioral deficits in AD mice. Thus, cyclic (aza-)peptides offer novel promise for early AD diagnosis and therapy by targeting the soluble oligomers.

Session 2: New Advanced Technologies
Tuesday - 29th August 2023, 11:10 – 11:35 (ZOOM)

Ofir Sade

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POSTER Detection of a-Synuclein Aggregates in Skin Biopsies of Parkinson's Disease Patients Using Super Resolution Microscopy

The main goal of this research is to establish a-Syn in skin biopsies as a comparative biomarker for the detection of PD pathology by utilizing super-resolution microscopy (SRM). This unique method, specifically direct Stochastic Optical Reconstruction Microscopy (dSTORM), provides the opportunity to investigate a-Syn aggregation at the single-molecule level, and perhaps overcome the challenge to identify sub-diffraction a-Syn aggregates already in early stages of their formation. We have previously quantified and characterized nano-sized a-Syn aggregates in brain slices from a transgenic mouse model and showed correlation between aggregates' size and disease severity and reversal by a specific drug, Anle138b. These a-Syn aggregates could not be detected using conventional microscopy, thus demonstrating the distinct advantage of SRM in detecting small a-Syn aggregates and providing proof of concept for the current study. We are currently in the process of combining the use of SRM with two computational analysis tools: cluster-identification and machine learning algorithms. The first combination provides quantitative analysis of the composition of a-Syn aggregates. For this purpose, we have developed an initial analysis platform, which provides access to two cluster-identification algorithms (DBSCAN and HDBSCAN), application of aggregate density thresholds, and noise reduction, which we will further develop. Preliminary analysis shows more phosphorylated a-Syn aggregates in PD patients than in healthy control (HC) subjects. The second combination enables us to identify correlations between aggregate properties (AP) with patients' clinical status (CS). Through this, we have found positive correlations between number of aggregates and number of molecules per aggregate to several clinical parameters.

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

Katja Stefan

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Poster & Short Talk ***In Silico*** **Identification and** ***In Vitro*** **Establishment of Novel ABCA1 Inhibitors**

ABCA1 is a 'difficult-to-drug' ABC transporter with only 14 known inhibitors in the literature with in part very poor inhibitory activity. However, ABCA1 is a lead ABC transporter in malignant, metabolic, and neurodegenerative diseases. Identification and characterization of novel inhibitors would be the first crucial step to take in the drug development pipeline to generate novel therapeutics and diagnostics for ABCA1, and potentially other ABCA transporters, such as ABCA7.

We summarized the entirety of knowledge with respect to ABCA transporter modulators (=small-molecule inhibitors and (potential) substrates) and analyzed 101 molecules for their molecular-structural composition by applying a novel drug discovery tool ('C@PA' – 'computer-aided pattern analysis'). We were able to identify key molecular-structural features that could be used in a virtual screening approach, resulting in 66 predicted and purchased unique molecules. Biological assessment using various ABCA1-expressing cell lines resulted in striking 62 hit molecules, extending the currently known ABCA1 inhibitor landscape by over 5-fold. One hit candidate showed a slightly weaker inhibitory power compared to the currently used reference inhibitor cyclosporine A, however, it was much more stable concerning its dose-dependent effect, and thus, was established as novel reference inhibitor to substitute cytotoxic and unreliable cyclosporine A. In essence, our findings did not only show the suitability of our computational approach to accurately predict novel bioactive molecules, but also provided a novel structural entity as potential starting point for the development of future ABCA1 (and other ABCA transporter) therapeutics and diagnostics.

Session 5: Short Talks
Tuesday – 29th August, 2023, 20:45 – 20:55

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

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Step by Step in Finding Novel ABCC1 Activators for the Treatment of Alzheimer's Diseases: A Computational Chemistry Approach

The identification of hit molecules with desired biological effect(s) against (a) target(s) of interest and their derivatization to elucidate structure-activity relationships (SAR) are key aspects in medicinal chemistry. The basis of this approach is the generation of libraries of structurally similar molecules to allow for evaluation of potential binding pocket(s) of the target protein(s) and potential binding mechanism(s). One downside of this approach is the lack of structural diversity of the molecule libraries that consists *per se* of related molecules. In the search for novel activators of the AD-related ABC transporter ABCC1, we developed a novel computational tool ('C@PS' – 'computer-aided pattern scoring') to generate new molecular-structural entities with unique composition to provide novel starting points for medicinal chemistry approaches. 175 ABCC1 activators reported in the literature were computationally analyzed for their molecular composition, and 244 partial structures and functional groups could be identified as distinctive for ABCC1 activation. Processing these structures and functional groups by introducing a scoring methodology allowed determining the importance the partial structures and functional groups for ABCC1 activation. Virtual screening of a virtual compound library consisting of ~15M molecules resulted in the rational selection of 49 candidates. Biological assessment revealed that 15 molecules demonstrated a significant activation of ABCC1 *in vitro*. Strikingly, all 15 molecules showed also activation of the ATPase, an indicator of increased numbers of transport cycles, and the two most promising candidates demonstrated the activation of ABCC1 in an alternative assay. Taken together, C@PS did not only provide novel molecular-structural entities for medicinal chemistry approaches, but also two very distinctive hit candidates with clinical potential.

Session 6: The Role of ABC and SLC Transporters in Drug Disposition and Discovery
Wednesday – 30th August 2023, 10:15 – 10:40

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Reduced Synaptic Activity and Dysregulated Extracellular Matrix Pathways in Midbrain Neurons from Parkinson's disease Patients

Several mutations that cause Parkinson's disease (PD) have been identified over the past decade. These account for 15–25% of PD cases; the rest of the cases are considered sporadic. Currently, it is accepted that PD is not a single monolithic disease but rather a constellation of diseases with some common phenotypes. While rodent models exist for some of the PD-causing mutations, research on the sporadic forms of PD is lagging due to a lack of cellular models. In our study, we differentiated PD patient-derived dopaminergic (DA) neurons from the induced pluripotent stem cells (iPSCs) of several PD-causing mutations as well as from sporadic PD patients. Strikingly, we observed a common neurophysiological phenotype: neurons derived from PD patients had a severe reduction in the rate of synaptic currents compared to those derived from healthy controls. While the relationship between mutations in genes such as the SNCA and LRRK2 and a reduction in synaptic transmission has been investigated before, here we show evidence that the pathogenesis of the synapses in neurons is a general phenotype in PD. Analysis of RNA sequencing results displayed changes in gene expression in different synaptic mechanisms as well as other affected pathways such as extracellular matrix-related pathways. Some of these dysregulated pathways are common to all PD patients (monogenic or idiopathic). Our data, therefore, show changes that are central and convergent to PD and suggest a strong involvement of the tetra-partite synapse in PD pathophysiology.

Session: Cellular and Animal Disease Models of Neurodegenerative Diseases
Thursday – 31st August 2023, 09:25 – 09:50

TD5

Laura Suominen

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POSTER *In vitro* Characterization of Rare Genetic Variants of ABCG2

Decreased function ABCG2 variants can result in increased drug plasma levels and brain accumulation. ABCG2 has over 400 rare missense variants that occur at <1% frequency. The transport activity and expression levels of most of the variants are unknown. Rare variants are, however, a plausible cause for inter-individual variability in drug pharmacokinetics. Thus, *in vitro* classification of these variants may help to design personalized drug treatments. A common variant (9% frequency in European population), Q141K, has a clinically significantly decreased transport activity compared to wild type ABCG2. Here, we use Q141K as a control variant for identifying decreased function variants. Our aim is to determine the activity of the rare variants *in vitro* in order to predict their effect on drug distribution into the brain.

We have studied the activity of 30 rare ABCG2 variants with inverted crude membrane vesicles using Lucifer Yellow as a substrate. These vesicles were also analyzed with targeted proteomics to determine ABCG2 abundance. Variants were transiently expressed in HEK293 cells using a baculovirus expression system. To our knowledge, 27 of these variants have not been characterized before. Out of the 30 variants, 14 showed similar or lower apparent transport activity compared to Q141K and were categorized as decreased function variants. Reduced protein levels could not explain all of the observed decrease in transport activity. Like the Q141K variant, the identified decreased function variants might lead to increased systemic drug exposure and brain permeability.

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

Dietmar Thal

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Necroptosis and Pyroptosis in Alzheimer's Disease: From Signal Transduction towards Solute Translocation

Necroptosis and pyroptosis are two 'inflammation-driven' forms of programmed necrosis that are initiated by signaling pathways and are executed by pore formation in the cell membrane. The necroptosis pathway is initiated by TNFa leading to the phosphorylation of RIPK1, then RIPK3, and finally MLKL forming the necrosome. Phosphorylated MLKL forms oligomers that build membrane pores causing cell death. Pyroptosis starts either by the activation of the inflammasome and caspase 1 or by LPS-induced activation of caspase 1 which cleaves gasdermin D (GSDMD) to its *N*-terminal fragment (GSDMD-NT). GSDMD-NT oligomerizes and forms membrane pores that either directly lead to cell death (pyroptosis) or facilitate release of IL-1β and IL-18. Here, we show that necrosome accumulation and accumulation of GSDMD-NT occur in the Alzheimer's disease (AD) brain and correlate with neuronal death. Necrosome accumulation is mainly located in neurons within granulovacuolar degeneration (GVD) bodies whereas GSDMD-NT is seen in astrocytes, microglial cells and single pyramidal neurons. In microglia, the activation of the pyroptosis pathway is linked to the inflammasome and cytokine release of IL-18 whereas neurons express caspase 4 as alternative GSDMD-cleaving enzyme and astrocytes express caspase 8. GVD shows in this context the strongest association with neuron loss. Taken together, our results show that both necroptosis and pyroptosis contribute to the process of neurodegeneration in AD with necroptosis presumably having the stronger effect on neuronal death. Pyroptosis is also activated in microglia, and astrocytes and accelerates the neurodegenerative process by inducing cytokine production and release by microglial cells. Support: FWO.

Session 4: Translation between Fields
Tuesday – 29th August 2023, 17:30 – 17:55

Maria Villa-Cruz

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POSTER ABC Transporters in Neuroinflammation - New Discoveries of Their Involvement in an EAE Model in Mice

ABC transporters are involved in inflammation. For example, the ABCA7 transporter plays a role in the binding of antigen-presenting cells and natural killer cells. Its deficiency affects the development and activation of these natural killer cells. ABCC1 transporter is involved in CCL2 release by astrocytes, thus controlling the migration of monocytes across the blood-brain barrier. This function is shared with the ABCB1 transporter, which is widely implicated in inflammation and exerts diverse functions in different cell types. Multiple sclerosis is a pathology mainly based on neuroinflammation, affecting oligodendrocytes and ultimately leading to axonal loss. Considering the aforementioned involvement of ABC transporters in inflammation, the role that modulation of these transporters may play in the development of this pathology deserves to be studied. Therefore, we performed an animal model reproducing the MS pathology in mice.
We performed the Experimental Autoimmune Encephalomyelitis by injecting myelin oligodendrocyte, in complete Freund's adjuvant, and pertussis toxin. We used WT, ABCA7ko, ABCB1ko, and ABCC1ko mice and assessed the clinical score every day from day 8 to 35 after induction.
We found a better clinical course of the transporters-deficient animals compared to the WT, especially the ABCB1ko and ABCC1ko mice, which presented lower cumulative and maximum scores compared to the WT.
These results suggest that ABC transporters play an important role in MS pathology, so its modulation may be useful to improve the development of this disease.

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

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Mechanism and Physiological Roles of ABC Cholesterol Transporters

ABCA1 is responsible for the generation of high-density lipoprotein (HDL). However, it is still unclear how ABCA1 loads more than 100 lipids onto APOA-I to generate discoidal nascent HDL particles. In addition, ABCA1 dysfunction or excess cholesterol is related to various diseases, such as atherosclerosis, autoimmune disease, diabetes cancer, and mental disease. Why? We found that ABCA1 exerts two independent activities, HDL generation and cholesterol flopping from the inner leaflet to the outer leaflet of the plasma membrane to generate 10 times concentration difference between the two leaflets. This allows Scap/SREBP in ER to monitor the local and temporal increase of cholesterol in the plasma membrane. In addition, we proposed that cholesterol functions as a signal in the plasma membrane. This may explain the pleiotropic adverse effects of ABCA1 dysfunction.

Mutations in the ABCA13 gene increase the susceptibility to schizophrenia, bipolar disorders, and major depression. However, little is known about the physiological role of ABCA13. We examined its biochemical activity and physiological role by using HEK293 cells expressing murine ABCA13 and *Abca13* KO mice. ABCA13 accelerates cholesterol internalization by endocytic retrograde transport and *Abca13* KO mice exhibited deficits of prepulse inhibition.

Session 1: The Role of ABC and SLC Transporters in Health and Disease
Tuesday – 29th August 2023, 9:00 – 9:25

Jolanta Upite

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POSTER Benefits and detrimental effects of sequence variants of Amyloid-β: towards the use of small peptides for aggregate dissolution therapy in dementia

Alzheimer's disease (AD) is a widespread neurodegenerative disease. Currently, available drugs are capable to improve only parts of the symptoms for a short period of time. AD is characterized by time- and location-specific accumulation of Aβ and hyperphosphorylated tau protein, and inflammatory changes including microglia and astrocyte activation. The most prominent neuropathological hallmark of AD are senile plaques that consist of toxic Aβ peptides. It has been discovered that the removal of toxic peptide monomers could be an innovative option for the treatment and prevention of dementia. Furthermore, it was first found in Italian and Island families that specific mutations in the N-terminal part of Aβ (position 2) lead to the protection of heterozygote carriers by reducing the aggregation propensity. Based on this information, our aim was to investigate whether specific amino acid changes could be used to dissolve higher order Aβ aggregates and to enhance clearance of Aβ from the brain into the bloodstream. For this study, we used 50-day-old male APP-transgenic mice. D-peptide hexamer peptides ($^{1\text{-}6}$hAβ^{A2V}, $^{1\text{-}6}$mAβ^{A2V}, $^{1\text{-}6}$hAβ^{A2T}, $^{1\text{-}6}$mAβ^{A2T}, wild-type human $^{1\text{-}6}$Aβ and wild-type mouse $^{1\text{-}6}$Aβ) were injected. Intracerebroventricular surgery with mini-osmotic pumps was performed to infuse the peptides for 42 days at a rate of 16 nmol/day and artificial cerebrospinal fluid, which served as the control. At the age of 100 days, brains were collected for immunohistological analysis. The previously developed toolbox (PMC8764605) to evaluate the process of potential treatment in relation to intracerebral injection channels after continuous long-term intracerebral injection was used.

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

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Poster & Short Talk An Enhanced Huntington's Disease Mouse Model And Its Potential Applications in HD Treatment

Huntington's disease (HD) is an inherited and autosomal-dominant neurodegenerative disease characterized by the disordered control of voluntary movement, psychiatric disturbance, and cognitive impairment. Firstly, we generated the zQ175dn HD mice and performed a temporal characterization of several behavioral and neuropathological features. The zQ175dn mice exhibited motor coordination dysfunctions and body weight loss at an early age of around 29 weeks. In addition, zQ175dn mice demonstrated muscular declines, anxiety-like behaviours, striatal atrophy, testicular atrophy and increased neuroinflammation after 36 weeks of age. Overall, the zQ175dn is a reliable knock-in mouse model that recapitulated robust and significant HD-like phenotypes at a heterozygous state and only at late stage of mouse life span, which is more relevant to human HD. This enhanced HD mouse model could provide a great value for preclinical studies. Secondly, our preliminary data showed that the chronic oral uptake of fingolimod, an immunomodulating medication mostly used for treating multiple sclerosis (MS), attenuated several HD neurological phenotypes in a sex-dependent way. Generally, treating zQ175dn mice at a pre-symptomatic stage (15 weeks of age) rescued the mice from brain atrophy, body weight loss, motor behaviours and testis atrophy etc.

Session 5: Short Talks
Tuesday – 29th August 2023, 20:30 – 20:40

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

TD5

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Poster & Short Talk The Role of Gut Microbiota in Alzheimer's Disease Progression: Implications for Novel Therapeutic Strategies

Alzheimer's disease is a debilitating neurodegenerative disorder with an unclear etiopathology. Recent research on the gut-brain axis has revealed bidirectional communication, implicating the involvement of gut microbiota in neurodegenerative diseases. This review aims to highlight the relationship between gut microbiota and the pathogenesis and progression of Alzheimer's disease through multiple mechanisms and pathways. Aging affects microbial diversity, leading to alterations in the gut microbiota composition of affected individuals prior to disease onset and during various stages of the disease. Murine models of Alzheimer's have been found to have gut dysbiosis, and the observed effects indicate that microbial changes occur before the onset of pathology and with the progression of the disease. Through decreased production of short-chain fatty acids, the gut barrier becomes more permeable, allowing for the translocation of endotoxins into circulation. Elevated levels of lipopolysaccharides in the serum and cerebral matter exacerbate the neuropathology of the disease by disrupting the blood brain barrier and causing neuroinflammation. Activation of microglia subsequently induces amyloidogenesis and modulates the deposition of more toxic monomers of amyloid-beta and tau through phosphorylation. Improvements in disease pathology and cognitive function following the transfer of a healthy microbiome implicate novel therapeutic strategies targeting the gut microbiome in AD. By reducing endotoxin levels and increasing other metabolites, the progression of the disease may potentially be modulated.

Session 9: Extra Short Talk in Competition
Tuesday – 30th August 2023, 17:15 – 17:25

Poster Session
Wednesday – 30th August 2023, 17:15 – 18:30

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Optogenetic Control of Biological Processes: From Photoreceptor Engineering to Their Implementation in Microbial, Animal, and Plant Systems

The development of a functionally different set of optoswitches has taken root and expanded the applicability of light as stimulus to control a plethora of cellular processes. These range from gene expression, protein stability, receptor function, subcellular localization of proteins, and organelles up to the generation of biohybrid materials to manipulate extracellular environments and regulate cell viability. We discuss here representative examples of the complete synthetic biology research process leading from the engineering and rewiring of the photoreceptors for the intervention of the molecular and cellular processes up to their application *in vivo*. We describe a wide family of tools sensitive to different wavelengths of the white light spectrum, namely UV-B, blue, green, orange, red/far-red. With hundreds of engineered photoreceptors and optoswitches being reported, we have now entered an era in which we can combine different systems to achieve orthogonal, independent control of various cellular processes using light of different colors sequentially or simultaneously. We implement these molecular tools into microbial, yeast/fungi, mammalian cells, and *in vivo* in animals. We have successfully introduced optogenetic into plants, by overcoming the intrinsic experimental limitations posed by the need of plants for light to grow. We use optogenetics to precisely control metabolic and signaling networks, and introduce novel functionalities in the organisms. These synthetic biology strategies open up unforeseen perspectives in fundamental and applied research, including the biomedical and biopharmaceutical fields and crop improvement.

Session 2: New Advanced Technologies
Tuesday – 29th August 2023, 10:45 – 11:10