TransportDEMENTIA²

General Information

PROGRAM

MS Finnmarken, Norway
September 2nd – 6th, 2016

Picture: Hypericum perforatum (photo: Paride Rizzo, IPK Gatersleben)

PAHNKELAB.EU

hurtigruten.de (photo: Christian Huehn)

WELCOME

Dear Ladies and Gentlemen.

Dear valuable friends.

I am very pleased to invite you all to the second meeting about ABC transporters and dementia. This time we have invited honourable speakers from different specialisations: PET imaging, mouse models, plant breeding and biochemistry, and also general talks about the blood-brain barrier and new methods.

Many of you may ask 'why plants ?'.
During the recent years we have hypothesised that ABC transporter activation could be one possibility to halt dementia symptoms that result from protein deposition in the brain. We have published mouse data from *Hypericum perforatum* treatment in 2013 and from *Sideritis scardica & S. euboea* treatment just recently. Both plants have also been tested in patients and have convinced us that these options should be investigated in greater detail.

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

Jens Pahnke

Hurtigruten Tour

The Hurtigruten tour will be from the 2nd till the 5th of September 2016. The name of our ship is ***MS Finnmarken***. The tour will be a round trip from ***Tromsø*** to ***Kirkenes***.

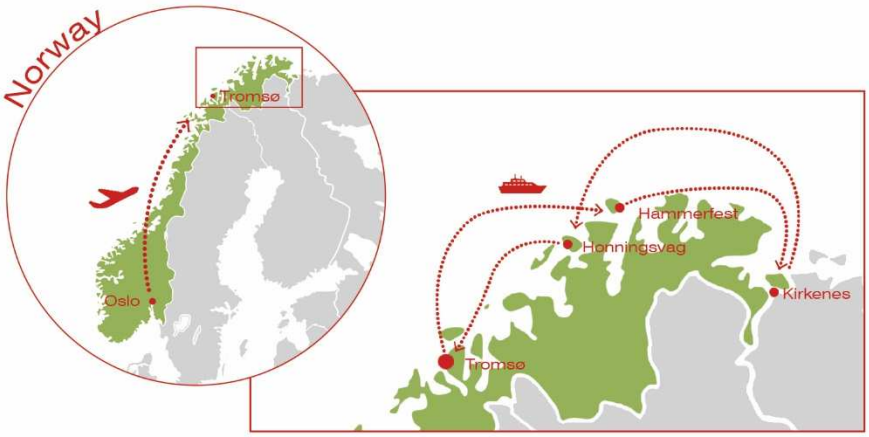
Breakfast, lunch, dinner, and all coffee breaks are included, while ***drinks have to be paid separately***. The crew on board accepts credit cards.

Breakfast:	7:00 – 10:00
Lunch:	12:00 – 14:30
Dinner:	2nd - 4th September at 20:30, 5th September at 18:30

If you have any wishes, problems or concerns, do not hesitate to contact ***Kristin Paarmann***.

E-Mail: Kristin.paarmann@medisin.uio.no

Phone: +47 230 71478 (office), +49 1578 1986 883, **+47 4012 0063** (mobile)



Flights

Every participant received a flight ticket and a reference number some weeks ago. If you ***did not get the reference number, contact Kristin Paarmann*** (contact details: page 3)
All flights to Tromsø **include a stop** at Oslos main airport at Gardemoen. Therefore, most participants will be on the same flight from Oslo to Tromsø. If your flight to Oslo and the connecting flight are operated by the same airline, please ensure that you ***check your baggage in until Tromsø***. In that case your baggage will be transported directly to Tromsø without you need to pick it up in Oslo and check it in again.

Bus transport to Hurtigruten ship (Tromsø)

We organized a collective bus transport from Tromsø airport to the Hurtigruten ship for all participants who arrive before 16:40 at Tromsø airport.
Participants who ***arrive later should take a cab***. If they forward us the receipt, they can get a refund. Public transports in Tromsø take **only** CASH while taxis etc. accept credit cards.



HOTEL STAY

From the ***5th to the 6th of September (Mo-Tu)*** participants will stay at Radisson Blu – Hotel Tromsø, which is located directly next to the ship at the harbor.

Breakfast time is 07:00 – 10:00.

Note: The hotel also offers a **Grab & Run takeaway breakfast** that includes tea and coffee in disposable cups along with fresh fruits and energy bars. If you want take this opportunity, **inform hotel staff when you check in**.

Radisson Blu Hotel Tromsø
www.radissonblu.com/Tromso
Sjøgata 7, 9259 Tromsø
Phone: +47 7760 0000

Bus transport to Tromsø airport

We organized two collective bus transports from Radisson Blu Hotel Tromsø to Tromsø airport on the ***5th of September***. Participants were assigned to the bus transports according to the departure of their flights. Bus transport from hotel to airport takes approximately ***15 minutes***. If you would like to change your departure, please contact us (contact details: page 3).

Departure	names	
6:30	Claus Pietrzik	
	Wolfgang Härtig	
	Peter Brust	
	Ildiko Dunay	
	Hans-Gert Bernstein	
	Paride Rizzo	
	Martin Fuhrmann	
8:15	Oliver Langer	Surya Prakash Rai
	Thomas Wanek	Ludger Wessjohann
	Aikihiro Matsudo	Henrik Biverstål
	Maciej Lalowski	Axel Abelein
	Matthias Koepp	Pitt Niehusmann
	Helle Wangensteen	Jolanta Upite
	Cecilia Santos	
	Jean-Francois Ghersi-Egea	
	Anika Hartz	
	Isabel Goncalves	
	Jens Bankstahl	
	Jens Pahnke	
	Markus Krohn	
	Thomas Brüning	
	Kristin Paarmann	
	Mirjam Brackhan	

Friday September, 2nd

	Arrival
16:40	Bus transport from Tromsø airport to MS Finnmarken
17:30	Put out to sea
19:00-19:30	***Jens Pahnke*** (Oslo) Welcome
19:30-20:15	**Special topic** ***Anika Hartz*** (Lexington, Kentucky) ABCB1 News: The Transporter and the Amyloid
20:30	Dinner

Saturday September, 3rd

7:00-10:00	Breakfast
10:15-11:00	**Special topic** ***Martin Fuhrmann*** (Bonn) The role of hippocampal GABAergic neurons in a mouse model of Alzheimer's disease
11:15-14:45	**Explore Honningsvag**
12:00-14:30	Lunch
14:45-15:15	***Thomas Wanek*** (Wien) PET imaging of ABCG2 function in a preclinical model of Alzheimer´s disease
15:15-15:45	***Jens Bankstahl*** (Hannover) Serial molecular in vivo imaging of insult-induced epilepsy development
15:45-16:00	Break
16:00-16:30	***Peter Brust*** (Leipzig) Use of animal PET/MR for radiotracer development and molecular imaging
16:30-17:00	***Matthias Koepp*** (London) Functional imaging of drugs and drug-transporter function in dementia and epilepsy

17:00-17:15	Coffee break
17:15-17:45	***Wolfgang Härtig*** (Leipzig) Age-dependent alterations of the neurovascular unit after experimentally induced ischemic stroke
17:45-18:15	***Claus Pietrzik*** (Mainz) Clearance at the BBB, a potential target for Alzheimer's disease therapy?
18:15-18:30	Break
18:30-19:30	***DFG project meeting: PET imaging to assess blood brain function in Alzheimer's disease***
19:30-20:30	***DFG project meeting: The role of the blood-brain barrier and Alzheimer´s disease: Interaction of LRP1 and ABC transporter function***
20:30	Dinner

Sunday September, 4th

7:00-10:00	Breakfast
10:00-14:30	**Explore Kirkenes**
12:00-14:30	Lunch
14:30-15:15	**Special topic** ***Timothy Sharbel*** (Saskatoon, Saskatchewan) Attenuating sex to feed the world
15:15-15:45	***Paride Rizzo*** (Gatersleben) The hidden potential of the placental tissue of Hypericum perforatum.
15:45-16:00	Break
16:00-16:30	***Helle Wangensteen*** (Oslo) Ethnopharmacology and traditional medicine – tools to find new medicinal agents
16:30-17:00	***Ludger Wessjohann*** (Halle) Metabolomics-based identification of bioactive compounds
17:00-17:15	Coffee break

17:15-17:45	***Henrik Biverstål*** (Riga) Use of small fragments of the Amyloid-beta peptide to prevent amyloid aggregation
17:45-18:15	***Maciej Lalowski*** (Helsinki) Assessing brain dynamics and Aß transport in the brain using mass spectrometry and systems biology approaches.
18:15-18:30	Break
18:30-19:30	***JPND project meeting: PROP-AD*** *http://pahnkelab.eu/funding/prop-ad-jpnd/*
19:30-20:30	***Leibniz SAW project meeting - Hypericum perforatum against Alzheimer***
20:30	Dinner

Monday September, 5th

7:00-10:00	Breakfast
10:00-14:30	**Explore Hammerfest**
12:00-14:30	Lunch
14:30-15:15	**Special topic** ***Jean-Francois Ghersi-Egea*** (Lyon) Neuroprotective and neuroimmune functions of the blood-CSF barrier. Relevance to brain development and perinatal diseases.
15:15-15:45	***Hans-Gert Bernstein*** (Magdeburg) Vascular and extravascular distribution of the ATP-binding cassette transporters ABCB1 and ABCC1 in postmortem human brain: Reduced expression of ABCB1 in the habenula of schizophrenia patients
15:45-16:00	Coffee break
16:00-16:30	***Markus Krohn*** (Oslo) Mice with human ABC transporters – new tools for better translation

16:30-17:00	***Final note***
17:00-17:15	Coffee break
17:15-18:15	***JPND project meeting: NeuroGem*** http://pahnkelab.eu/funding/jpnd-neurogem/
18:30	Dinner
23:45	Landing in Tromsø

Tuesday September, 6th

00:00	Check-in Radisson Blu Hotel Tromsø
	Grab & Run takeaway breakfast (announce at check-in)
7:00-10:00	Regular breakfast
6:30	1st bus transport to Tromsø airport
8:15	2nd bus transport to Tromsø airport

Getting to know Norway

Since this is not only a scientific but also a cultural event, we collected here some facts about Honningsvag, Kirkenes, and Hammerfest. The participants will have the opportunity to get to know these towns.

Honningsvåg with its 2,800 inhabitants is the capital of the North Cape. Walking through Honningsvåg you'll find excellent shops, Arctic dining experiences and other exciting activities. Check out the Perleporten Kulturhus (the local cultural centre), the *Once Upon A Dream* art gallery, and the Artico Ice Bar. A visit to the church is highly recommended: it was the only building left standing in Honningsvåg at the end of World War II.

Kirkenes is located in the extreme northeastern part of Norway on the Bøkfjord, a branch of the Varangerfjord, near the Russian border. We're about 400 kilometres north of the Arctic Circle and actually as far east as St. Petersburg. Most of the approximately 7,000 inhabitants are of Norwegian background, while a minority is Sami. Others originate from Finland and some 500 immigrants have recently arrived from Russia.

In Kirkenes you will notice strong bonds and cultural influences from Russia. A prominent example is the Russian Monument – a memorial for the liberation of Sør-Varanger by the Red Army in the autumn of 1944. There is a Russian market in Kirkenes once a month. Road signs are written in both Norwegian and Russian. The Russian border can be visited either by bus riverboat, or ATV/Quad. The Grenselandmuseet exhibits permanent and temporary exhibitions from the border area. The Art Museum Savio is built up around the well-known Sami artist John Andreas Savio (1902-1938), with art depicting the Sami reindeer herders, culture and nature in the north.

Since it was founded, **Hammerfest** has defended its position as the world's northernmost town. It lies roughly at the same latitude as the northernmost parts of Siberia and Alaska. In spite of the extreme northern location there is no permafrost

here. Still, Hammerfest often experiences heavy snowfall in winter. The people living here enjoy 24 hours of daylight in summer - and during some parts of the winter the sun does not rise above the horizon.The construction of the large liquefied natural gas site on Melkøya has resulted in an economic boom and new optimism in Hammerfest in recent years. Shopping is a traditional activity. The widespread myth that polar bears roam the streets of Norway originated in Hammerfest. A huge example of the species can usually be seen outside one of the shops in the town, and is a constant source of delight to visiting photographers. The Salen Restaurant, offers a panoramic view of the surrounding area. One chain of the Struve Geodetic Arc, now on the UNESCO World Heritage List, is located at Fuglenes in Hammerfest. Hammerfest is also a centre of Sami culture and home to the Royal and Ancient Polar Bear Society, a museum displaying the history of Arctic hunting.

www.hurtigruten.co.uk

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Jens Pahnke

Translational Neurodegeneration and Neuropathology Lab

Department of Neuro-/Pathology

University of Oslo, Norway

September 2nd, 2016
19:00 – 19:30

During the last years we have focused our research on ABC transporter function in neurodegenerative diseases, with special emphasis on Alzheimer's disease. We have discovered ABCC1 as one major Aβ exporting transporter in 2010 and developed ABCC1-activating treatment that is approaching a phase II study very soon. Besides chemical activation of ABC transporters, we have searched world-wide for new compounds in the field of natural and traditional medicine. The discoveries in that field have already made its way into the treatment of dementia patients. Using traditional formulations, it is much faster to legally deliver useful compounds to patients. Our most recent combination of special extractions of Hypericum perforatum and Sideritis scardica is available as a nutritive additive.
ABC transporter-deficiency seems to be one of the major mechanisms that lead to various neurodegenerative diseases with protein/peptide depositions. ABC transporters also modulate the clinical progression in inherited neurodegenerative diseases / dementias, so that the activation can be used also for effective treatment in this disease group.
ABCA1, ABCA7, ApoE, LRP1, ABCB1, and ABCC1 have recently been shown to be the key players in the Alzheimer's concert for treatment and diagnostics. Thus, we have started initiatives to combine efforts from different labs in multinational research projects for PET imaging, ABC transporter signalling and regulation, ethnopharmacology, and natural medicine that are funded by various agencies (http://pahnkelab.eu/funding/).

Anika Hartz

University of Kentucky

Sanders-Brown Center on Aging

Department of Pharmacology and Nutritional Sciences

Title: ABCB1 News: The Transporter and the Amyloid

September 2nd, 2016
19:30 – 20:15

Special topic

Memory loss in Alzheimer's disease is in part due to high levels of toxic amyloid-beta in the brain. This phenomenon is a consequence of impaired amyloid-beta removal from brain to blood. The blood-brain barrier transporter P-glycoprotein is critical for removing amyloid-beta from the brain, but in Alzheimer's disease P-glycoprotein is degraded and not functional. We specifically designed two novel therapeutic strategies to 1) restore P-glycoprotein function, and 2) prevent P-glycoprotein breakdown. We pursue these strategies to prevent amyloid-β brain accumulation and to lower amyloid-β brain burden with the ultimate goals of improving memory loss and delaying onset and slowing progression of Alzheimer's disease.

Martin Fuhrmann

Research Group Leader

Neuroimmunology & Imaging

German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany

Title:
The role of hippocampal GABAergic neurons in a mouse model of Alzheimer's disease

September 3rd, 2016
10:15 – 11:00

Special topic

Alzheimer's disease (AD) is characterized by cognitive decline and neuronal network dysfunction, but the underlying mechanisms remain unknown. In the hippocampus microcircuit activity during learning and memory processes is tightly controlled by O-LM interneurons. We investigated the effects of beta-amyloidosis on O-LM interneuron structural and functional connectivity combining two-photon in vivo imaging of synaptic morphology, awake Ca2+-imaging and retrograde mono-transsynaptic rabies tracing. We found a severely impaired synaptic rewiring that occurred on the O-LM interneuron input and output level in the vicinity of Aβ-plaques. Synaptic rewiring that occurred upon fear learning on O-LM interneuron's input level was affected in mice with AD-like pathology. This process required the release of acetylcholine from septo-hippocampal projections. We identified decreased cholinergic action on O-LM interneurons in APP/PS1 mice as a key pathomechanism that contributes to memory impairment in a mouse model with potential relevance for human AD.

Research Interest:
Alzheimer's disease is characterized by the extracellular deposition of Aβ and the intracellular aggregation and formation of fibrils consisting of the hyperphosphorylated protein tau. Additionally, synapse and neuron loss are hallmarks of AD, which correlate well with cognitive decline. These and other changes presumably affect the integrity of individual neurons, micronetworks and ultimately lead to neuronal network dysfunction that underlies learning and memory impairment. One

possible explanation for neuronal network dysfunction represents an imbalance between excitation and inhibition, which destabilizes the network and contributes to aberrant neuronal activity. Indeed, encephalogram (EEG) recordings in AD patients revealed phases of abnormal epileptiform activity. However, the cellular and sub-cellular mechanisms that contribute to an imbalance between excitation and inhibition and how this might influence learning and memory impairment remain unexplored. In fact we are just starting to understand how learning and memory works in healthy brains on cellular and sub-cellular levels. Models of neurodegenerative diseases like AD may help to understand learning and memory processes if we use them as a defect example. Based on this background research in my lab focuses on the synaptic and neuronal network processes involved in learning and memory and how are they impaired in AD? In order to address these questions we use state of the art in vivo imaging techniques and combine them with electrophysiological, histological and biochemical techniques in transgenic mice and rats. Moreover, we use optogenetics to specifically activate or inactivated neuronal subsets.

Thomas Wanek

Health & Environment Department

AIT Austrian Institute of Technology GmbH

Seibersdorf, Austria

Title: PET imaging of ABCG2 function in a preclinical model of Alzheimer´s disease

September 3rd, 2016
14:45 – 15:15

A major hallmark of Alzheimer's disease (AD) is the accumulation of senile plaques containing beta-amyloid (Aß) in the brain. Several lines of evidence suggest that reduced Aß clearance from the brain underlies Aß accumulation. Adenosine triphosphate-binding cassette (ABC) transporters that are expressed in endothelial cells of the blood-brain barrier (BBB) may play an important role in excreting Aß from brain into the blood.

A number of studies suggest that ABC transporter function at the BBB may be impaired in AD patients as compared with age-matched control subjects. P-glycoprotein (ABCB1) cooperates closely with another ABC transporter at the BBB, breast cancer resistance protein (ABCG2). Given this cooperative action between ABCB1 and ABCG2 and previous data suggesting that ABCG2 may be up-regulated at the BBB of AD patients as possible compensatory mechanism for ABCB1 down-regulation, the role of ABCG2 in AD is currently of high interest.

In the present talk we will present an overview about the in vivo function of ABCG2 at the BBB of an AD mouse model and age-matched wild-type control animals using the non-invasive nuclear imaging method positron emission tomography (PET).

Jens Bankstahl

Head of Preclinical Molecular Imaging

Department of Nuclear Medicine

Hannover Medical School

Title: Serial molecular *in vivo* imaging of insult-induced epilepsy development.

September 3rd, 2016
15:15 – 15:45

As in vivo neuro-imaging markers are mostly targeting brain alterations that are common in various brain diseases, a wide variety of syndromes can profit from recent advances in preclinical molecular imaging. In the present talk, an overview of current molecular imaging approaches in models of acquired brain diseases, i.e. epilepsy, will be given. Animal models of epileptogenesis reflect brain pathology of insult-induced epilepsies in many aspects. Particularly, they show distinct brain inflammation and blood-brain barrier alterations, which are suggested to be key processes mediating insult-induced epileptogenesis. Non-invasive molecular imaging (i) can identify these processes as epileptogenesis biomarkers that hold potential for translation to the clinic, (ii) helps to define appropriate time windows for potential epilepsy-preventing pharmacotherapy, and (iii) functions as a tool to survey treatment effects.
J. P. Bankstahl, who is head of Preclinical Molecular Imaging of the Department of Nuclear Medicine, Hannover Medical School (MHH), has worked in the fields of epilepsy research and molecular imaging over the last 10 years. He received his PhD in the lab of W. Löscher (University of Veterinary Medicine Hannover), where he also spent four years as a postdoc and was trained as a neuropharmacologist. During an FP7-funded project (EURIPIDES), he was intensively trained in molecular imaging at the Austrian Institute of Technology. He has profound knowledge in animal models of epilepsy and has provided significant contribution to the understanding of transporter function at the blood-brain barrier (BBB) as a mechanism of

pharmacoresistance in epilepsy. In a current FP7-funded project (EPITARGET), imaging approaches are extended towards neuro-inflammation, BBB integrity, brain metabolism or changes in neuro-receptor expression during epilepsy development. The Preclinical Molecular Imaging Lab at MHH is equipped with two high-end small animal scanners, an Inveon dPET/CT (Siemens) and an eXplore SPECZT/CT 120 (TriFoil Imaging) and is closely associated to the MHH Central Animal Facility which runs a recently built non-nuclear imaging lab (Head: M. Meier), equipped with a small-animal 7 Tesla MRT Pharmascan (Bruker), a high-performance ultra-sound system (VisualSonics) and a new FMT system (Perkin Elmer). Furthermore, the Department of Nuclear Medicine is well-appointed with new state-of-the-art clinical PET/CT and SPECT/CT scanners. It is also fully equipped for all aspects of PET and SPECT radiochemistry (cyclotron, hot-cells, automated radiochemical synthesis systems) and has over 36 years of experience in the development of radio-labeled radiopharmaceuticals. In addition, strategic partnerships have been established with two global high-tech companies, Siemens and GE, for the development of new imaging solutions as well as the evaluation of new tracers.

Peter Brust

Head Neuroradiopharmaceuticals

Helmholtz-Zentrum Dresden-Rossendorf in Leipzig

Title: Use of animal PET/MR for radiotracer development and molecular imaging.

September 3rd, 2016
16:00 – 16:30

Positron emission tomography (PET) is an in vivo molecular imaging tool which is widely used in nuclear medicine for early diagnosis and treatment follow-up of many brain diseases. PET uses biomolecules as probes, which are labeled with radionuclides of short half-lives, synthesized prior to the imaging studies. These probes are called radiotracers. Fluorine-18 is a radionuclide that is routinely used in the radiolabeling of receptor ligands for PET because of its favorable half-life of 109.8 min. The delivery of such radiotracers into living subjects provides images of transport, metabolic, and neurotransmission processes on the molecular level. Successful radiotracer design as required for PET provides molecular probes which are useful not only for imaging of human brain diseases. They also allow molecular imaging studies in various small-animal models of disease, including genetically-engineered animals. Furthermore, they provide a powerful tool for in vivo pharmacology during the process of pre-clinical drug development to identify new drug targets, to investigate pathophysiology, to discover potential drug candidates, and to evaluate the pharmacokinetics and pharmacodynamics of drugs *in vivo*.
Peter Brust studied animal physiology and neurobiology at the University of Leipzig, Germany. He had been working in the field of BBB research for more than ten years before he moved into experimental PET as a postdoc at Montreal Neurological Institute and Johns Hopkins University in Baltimore. His group in Leipzig has been focused on the development of radiopharmaceuticals for brain PET imaging for almost two decades. Four newly developed radioligands for imaging of depression and

dementia have been translated into human application within the last eight years. Related to the program-bound project funding within the Helmholtz society the main emphasis of the group has recently moved into tumor research trying to visualize molecular switches which are involved in tumor development and progression. An example of a successful radiotracer development has recently been described in a video of Beilstein TV (https://www.hzdr.de/db/Cms?pOid=41787&pNid=3112; www.beilstein.tv/).

Matthias Koepp

Epilepsy Imaging Group
Institute of Neurology
UCL London

Title: Functional imaging of drugs and drug-transporter function in dementia and epilepsy

The link between AD and epilepsy is best described as "shared risk factor association" originating from common underlying risk factors (depression, traumatic brain injury), which are predisposing to the development of both conditions. Classic pharmacological approaches to the treatment or prevention of cognitive decline, and/or epilepsy have failed to substantially reduce their medical and financial burden. In general, we do not know the exact mechanisms underlying epilepsy in AD, or vice-versa. Addressing common pathways and related morbidities represents an innovative way to develop new, potentially preventative therapies, which has been stagnating for both neurodegeneration and epilepsy, partly due to a lack of clinically validated, sensitive and specific biomarkers to identify the relevant disease-mechanism and drug-response in individual patients. Biomarkers for early detection and disease monitoring are the pre-requisite to develop innovative, mechanisms-based treatment strategies for both epilepsy and dementia within a personalised health care framework. We will present data from epilepsy patients undergoing surgery to determine the role of tau- load for cognitive decline in the elderly, and suggest strategies to validate novel PET tracer to detect pathological tau. In addition, imaging biomarkers have been developed for assessment and prediction of drug-response to levetiracetam, a highly effective anti-epileptic drugs which also has shown benefit in people with MCI. Many epilepsy patients rank cognitive impairment as the most relevant complaint and, vice versa, consider the side-effect profile of specific AEDs as more important than achieved seizure control

by these drugs. Currently, we have no means to predict how a patient will respond to a drug, both in terms of efficacy and cognitive side-effects. Rather than waiting for side-effects to occur in order to assess efficacy and tolerability through trial-and-error, for therapeutic guidance, we ultimately need a measurement that can be used as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy.

September 3rd, 2016
16:30 – 17:00

Wolfgang Härtig

Paul-Flechsig-Institute for Brain Research

University of Leipzig

Title: Age-dependent alterations of the neurovascular unit after experimentally induced ischaemic stroke.

September 3rd, 2016
17:15 – 17:45

Essential prerequisites for the improved translation of preclinical data into the clinics are improved animal models and analyses of the entire neurovascular unit (NVU) also performed at Leipzig University in cooperation of the Paul Flechsig Institute for Brain Research with Dominik Michalski from the Department of Neurology and Martin Krueger from the Institute of Anatomy.

Current own histochemical studies comprise semiquantitative analyses of NVU components, e.g., vessels, neuronal markers, microglia/macrophages, astrocytes, oligodendroglia as well as the extracellular matrix after ischaemia in the forebrains of mice. Ongoing investigations of the ECM predominantly concern perineuronal nets known as polyanionic, chondroitin sulphate-rich surroundings of certain neurons. Considering the age-dependency of ischaemia-induced alterations, 3- to 12-month-old mice are studied. To model the frequent co-morbidity of patients displaying both stroke and dementia, comparative analyses include both ischaemia-affected wild-type mice and triple-transgenic (3xTg) mice with age-dependent Alzheimer-like alterations.

Additional ultrastructural analyses are focused on the blood-brain barrier with emphasis on endothelial cells damaged after stroke - induced by different models in rodents.

Claus Pietrzik

Institute of Pathobiochemistry

University Medical Center of the Johannes Gutenberg University Mainz

Title: Clearance at the BBB, a potential target for Alzheimer's disease therapy?

September 3rd, 2016
17:45 – 18:15

According to the neurovascular hypothesis, impairment of the low-density lipoprotein receptor-related protein-1 (LRP1) in brain capillaries of the blood-brain barrier (BBB) contributes to neurotoxic amyloid-beta (Aβ) brain accumulation and drives Alzheimer's disease (AD) pathology. However, conflicting findings on LRP1's involvement in Aβ transport and its expression in brain endothelium have questioned the role of LRP1 at the BBB. As global knockout of Lrp1 in mice is lethal, there is a lack of appropriate models to study the function of LRP1. Moreover, the relevance of systemic Aβ clearance remains unclear, as no BBB-specific knockout models had been available. We therefore engineered mice with selective knockout of Lrp1 in the brain endothelium (Lrp1BE–/–). We found that endothelial LRP1 is a major receptor for Aβ BBB clearance leading to cognitive impairment in the 5xFAD mouse model of AD. Using our inducible Lrp1BE–/– mice, we are investigating the role of LRP1 in the import of Aβ peptides across the BBB into the brain. To prevent such detrimental transport effects we have generated LRP1 specific antibodies, blocking the binding of Aβ peptides to the receptor. Application of these antibodies in vitro reduced the transcytosis of radiolabeled Aβ 1-42 from blood to the brain side by approx. 50%. This inhibition correlates with studies through Lrp1 deficient endothelium, suggesting full blockage of Aβ binding to the receptor. These antibodies will be used in an in vivo setting to evaluate the therapeutic strength of receptor blockage at the BBB preventing Aβ entry into the brain.

Tim Sharbel

Research Chair in Seed Biology

Global Institute for Food Security in Saskatoon, Saskatchewan, Canada

Title: Attenuating sex to feed the world

September 4th, 2016
14:30 – 15:15

Special topic

An organism's choice to reproduce with or without sex has long puzzled evolutionary biologists. Apomixis, a natural form of reproduction in plants whereby seeds are produced asexually, has evolved repeatedly from sexual ancestors in many taxa. Apomixis is of interest on a number of levels, ranging from population genetics to evolution, but also from an applied perspective, as it represents a disruptive technology which could significantly change agricultural practices (e.g. fixing heterosis in hybrid crops). The switch from sex to apomixis is hypothesized to result from deregulation of developmental pathways leading to sexual seed development, and the trigger for deregulation involves the global genomic effects of hybridization and polyploidy.

We study apomixis in wild plant populations, and use evolutionary theory to guide our experimental approaches. High-throughput methods are employed to understand population-level phenotypic (seed production) and genetic (polyploidy, genetic structure) variability. These data are then used to design targeted experiments, whereby candidate genes for apomixis are identified using tissue-specific "omics" methods in particular genotypes. These candidates are then used (1) in transformation experiments to attempt apomixis induction in sexual plants, and (2) in population-level studies to understand the origin and evolution of apomixis with respect to sexuality in natural populations.

Paride Rizzo

Post-doctoral researcher

Leibniz Institute for Crop Plant Research, Gatersleben, Germany

Title: The hidden potential of the placental tissue of Hypericum perforatum

September 4th, 2016
15:15 – 15:45

Hypericum perforatum (Saint John's wort) arose in the last decades as a commercially interesting species due to his high content in several metabolites characterized by important biological activity like hypericin and hyperforin. Hypericin and more in general Hypericum extracts, have been proposed to have antidepressant activity (Zhai et al. 2015; Ramalhete et al. 2016) and possible applications in anti-tumor immunology (Abhisheck et al. 2011). A recent study even suggests a possible use of the SJW extracts in the treatment of neurodegenerative diseases (Hofrichter et al., 2013).
The possible applications of SJW extracts attracted the interest of many research programs especially focusing on the metabolites contained in the dark and translucent glands typical of this species.
The aim of the project is to characterize different reproductive tissues at different developmental stages in order to find patterns in the distribution and the timing of differentiation of the dark glands. The characterization work performed up to now, shows clear phenotypic differences between different Hypericum accessions that can be used in the frame of transcriptomic and metabolomics analyses that will build novel knowledge regarding gland differentiation and the biosynthetic processes of many key metabolites of the genus Hypericum.

Helle Wangensteen

School of Pharmacy, Department of Pharmaceutical Chemistry – Pharmacognosy,

University of Oslo, Norway

Title: Ethnopharmacology and traditional medicine – tools to find new medicinal agents

September 4th, 2016
16:00 – 16:30

My research interest is to isolate and identify secondary metabolites (e.g. alkaloids, flavonoids or terpenoids) in medicinal plants that can support the traditional use of the plants as medicines. I studied pharmacy at University of Oslo and graduated in 2001 with a master degree in pharmacognosy and pharmacology, and obtained my PhD degree in pharmacognosy in 2007. Since then I have worked mainly with African medicinal plants and ethnopharmacology but also some Norwegian plants. Recently we have identified an alkaloid in an African tree with antimalarial activity against Plasmodium falciparum in drug-like concentrations. We also found that other substances in the tree have insecticidal and larvicidal effects against the malaria vector Anopheles gambiae. Such information gives scientific support for the traditional use against malaria. However, it can also bring more knowledge about natural products as sources for the development of new medicines, both as mixtures of natural products or as single entities. I have recently been introduced to the Alzheimer research area and the use of herbal products against this disease. I believe there are natural products that have a potential against Alzheimer's, either as single molecules or as combinations of substances that may have multi-target actions.

Ludger A. Wessjohann

Director

Leibniz Institute of Plant Biochemistry (IPB), Halle, Germany

Title: Metabolomics Based Identification of Bioactive Compounds News from St. John's Wort and Beyond

September 4th, 2016
16:30 – 17:00

Natural products are at the basis of some 40% of our current drugs although they make up less than 1% of the tested compounds. Plant metabolites are especially effective as neuro-active or anticancer drugs with up to 70% of all market drugs derived from or inspired by them. However, identification of the active principle is cumbersome and often fails if additive or synergistic effects are responsible. Our group was the first one to apply a reverse metabolomics strategy to facilitate identification of the respective bioactive components avoiding dereplication procedures. This new methodology is now applied on CNS active compounds.
The common St. John's wort (Hypericum perforatum L.) is a current project example. It is a well-known medicinal herb used for the treatment of mild to moderate depressions. Prominent secondary metabolites include flavonoids, naphthodianthrones such as hypericin, and polyprenylated phloroglucinols such as hyperforin. The genus Hypericum comprises more than 450 species widely occurring in temperate regions and tropical highlands. Many species are used locally as traditional medicine against a variety of diseases. However, only a small proportion has been phytochemically characterized. We applied untargeted metabolomic approaches to investigate the secondary metabolite diversity within the genus and to select species for the discovery of unknown natural products.
Our present research focuses on the identification of secondary St. John's wort metabolites connected to anti-Alzheimer properties observed for selected St. John's wort extracts, but

also extents to other plant species and applications, like e.g. learning, taste or stroke protection.

Henrik Biverstål

Latvian Institute of Organic Synthesis (Riga) and Karolinska Institute (Stockholm)

Title: Use of small fragments of the Amyloid-beta peptide to prevent amyloid aggregation

September 4th, 2016
17:15 – 17:45

Alzheimer´s disease is an incurable neurodegenerative disorder linked to misfolding and aggregation of the amyloid β-peptide (Aβ) [1]. What causes Alzheimer´s disease is not fully understood, but it is believed that the transition of unstructured monomeric Aβ into β-sheet rich oligomers and fibers is a key element [2]. A recent study reports the first familiar autosomal recessive APP mutation (APPA673V) that causes AD only in the homozygous state whereas heterozygous carriers may be unaffected [3], and another study reports the protective variant APPA673T [4]. The mutation A2V in hAβ already destabilizes aggregates in vitro when present as hexapeptide only (Aβ1-6A2V) through binding to full-length hAβwt and thus delays amyloid fibril formation [3]. In preliminary studies we also found plaque formation in vivo to be inhibited by this peptide. To exploit this mechanism as potential treatment, we are investigating hAβ42 incubated under different conditions to determine protocols that to produce oligomers or fibrils, respectively. Samples containing hAβ42 and hAβ40 together with Aβ1-6A2V, Aβ1-6A2T has been investigated by Thioflavin T assay to explore conditions to prevent Aβ aggregation. 15N-labeled Aβ40 together with Aβ1-6A2V, Aβ1-6A2T have been further analyzed by 15N-HSQC where we examined structural induction in the intrinsic disordered Aβ40 peptide by co-incubation with Aβ1-6A2V and Aβ1-6A2T. 15N-HSQC will also be used, together with Thioflavin T to investigate Aβ1-6A2V or Aβ1-6A2T can dissolve amyloid aggregates of the Aβ42 and Aβ40 peptide.

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Maciej Lalowski

Medicum, Meilahti Clinical Proteomics Core Facility, Finland.

Finish Proteomics Society, President

Title: Assessing brain dynamics and Aβ transport in the brain using mass spectrometry and systems biology approaches.

September 4th, 2016
17:45 – 18:15

Meilahti Clinical Proteomics Core Facility (MCP) is located at the Medicum Helsinki. With its expertise in clinical proteomics, quantitative mass spectrometry (MS), interactomics and systems biology the facility provides know-how, technical support and necessary instrumentation for various collaborative studies. The MCP is a part of Biocenter Finland (Finnish network of biocenters), including Infrastructure networks & technology platform services and has been chosen as a national consortium MS-Imaging Facility.

Detection of protein expression directly on tissue slices from fresh-frozen and formalin-fixed paraffin embedded tissue specimens can be achieved using Mass Spectrometric Imaging (MSI). One of major advantages over other imaging and analytical methods used in pharmaceutical research is that the technology is completely label-free and allows measuring hundreds of analytes simultaneously. Comparison of three methods currently used in biomedical and clinical research, namely immunohistochemistry, MALDI-MSI and liquid chromatography mass spectrometry (LC-MS), pointed to versatility of the imaging technology, which shares a feature of spatial resolution with IHC and capacity for multiplexing and quantitation with LC-MS 1. Matrix-Assisted Laser Desorption Ionisation Mass Spectrometric tissue profiling and Imaging (MALDI-MSI, reviewed by us in 2) is one of the MSI techniques allowing studies on distribution of various peptides/proteins and numerous biological compounds in normal and diseased tissues including cancer and neurodegenerative disorders, i.e. Alzheimer's disease.

The intra-Aβ Arctic mutation [p.E693G], leads to early onset Alzheimer's disease in the fifth decade of life. We compared the neuropathology in Arctic AD to that in sporadic and another familial (with PS1 mutation) AD using complementary biochemical techniques. Different types of Aß deposits in temporal cortex were examined using light, confocal and electron microscopy and MALDI mass spectrometry imaging (MSI) directly on tissues. These results demonstrated that combination of different biochemical techniques and classic IHC staining can result in novel type of information about AD pathology and Aß processing 3,4. Importantly, the distribution of different Aß peptides could be visualized by MALDI-MSI technology, which allowed recognition of molecular signatures directly on tissues.

Our recent research projects include analysis of proteome alterations in the brain of a Ppt1 1 knockout mouse model of CLN1 disease and its age-matched counterparts at different stages. For this purpose, we utilized a combination of laser capture microdissection- based label-free nano-liquid chromatography tandem mass spectrometry (nano-LC-MSE) and MALDI Mass Spectrometry Imaging (MALDI-MSI), to quantify/visualize the changes in protein expression of disease-affected brain thalamus and whole brain tissue slices, respectively. The identified changes in protein levels were further validated by quantitative interactomics 5, functional bioinformatics/network approaches, immunohistochemistry on brain tissues and querying literature knowledge from other neuronal ceroid lipofuscinosis models thus identifying various

functional modules affected in CLN1 disease which can be targeted therapeutically 6.

Recent findings in mouse AD models demonstrated the occurrence of Aß immunopositive deposits in the brains of animals peripherally injected with amyloidogenic peptides and the induction and acceleration of senile plaque formation resulted by the intracerebral injection of Aß-containing brain extracts. These findings raise the possibility that soluble oligomeric Aß assemblies in the human brain act as potent Aß-seeders and are also present in the body fluids (plasma, CSF, brain parenchymal space). Within the recently launched collaborative JNPD project we are focusing on quantitative assessment of different routes of Aß penetration and its clearance from the brain.

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Jean-François Ghersi-Egea

FLUID Team and BIP Facility
Lyon Neurosciences Research Center
Lyon, France

Title: Neuroprotective and neuroimmune functions of the blood-CSF barrier. Relevance to brain development and perinatal diseases.

September 5th, 2016
14:30 – 15:15

Special topic

Oxidative and inflammatory challenges as well as exposure of the developing brain to chemical insults are major factors of neurological deficits in later life. The ability of blood-brain interfaces to efficiently protect the immature brain is therefore an important pathophysiological issue.
In this presentation I will focus on the neuroprotective mechanisms associated to the blood-CSF barrier, including multispecific efflux transporters and detoxification enzymes, as well as on the role of the choroid plexuses-CSF system in neuroimmune regulation and neuroinflammation. The special relevance of the blood-CSF barrier in controlling the fluid environment in which the brain matures during peri/postnatal development will be discussed. Dysfunctions of this barrier during different types of perinatal injuries and restauration strategies will also be presented.
The overall goal of my research team is to understand the implication of the blood-brain and blood-CSF barrier in the pathophysiology and pharmacology of adult and pediatric CNS diseases. To this end we use animal models of diseases, and various ex vivo and cellular models of brain barriers developed by a technology facility associated to our team.

Hans-Gert Bernstein

Department of Psychiatry and Psychotherapy, University of Magdeburg, Germany

Title: Vascular and extravascular distribution of the ATP-binding cassette transporters ABCB1 and ABCC1 in postmortem human brain: Reduced expression of ABCB1 in the habenula of schizophrenia patients

September 5th, 2016
15:15 – 15:30

ATP-binding cassette (ABC) transporters play an increasing role in the understanding of neurodegenerative and neuropsychiatric diseases, such as Alzheimer's, Parkinson's and schizophrenia. First, we studied the regional and cellular localization of ABCB1 and ABCC1 proteins in the adult human brain. Both transporters have similar but not identical expression patterns. In brain regions with an established blood-brain barrier (BBB), ABCB1 and ABCC1 were ubiquitously expressed in endothelial cells of the microvasculature and in a subset of larger blood vessels. Remarkably, both transporters were also found in fenestrated capillaries in circumventricular organs where the BBB is absent. Moreover, ABCB1 and ABCC1 were also expressed in various non-endothelia cells such as pericytes, astrocytes, choroid plexus epithelia, ventricle ependymal cells, and neurons. With regard to their neuronal expression it was shown that both transporters are located in specific nerve cell populations, which are also immunopositive for three putative cell markers of purinergic cell signaling, namely 5'-nucleotidase, adenosine deaminase and nucleoside triphosphate diphosphohydrolase-2. Therefore, neuronal expression of ABCB1 and ABCC1 might be linked to adenosinergic/purinergic neuromodulation. Since there is increasing evidence that microvascular abnormalities and malfunction of the blood-brain barrier (BBB) significantly contribute to schizophrenia pathophysiology, we investigated ABCB1 protein expression immunohistochemically in twelve human post-mortem brain regions known to play a role in schizophrenia, in patients with schizophrenia and controls. In ten out of twelve brain regions

under study, no significant differences were found with regard to the numerical density of ABCB1-expressing capillaries between all patients with schizophrenia and control cases. The left and right habenular complex, however, showed significantly reduced capillary densities in schizophrenia patients. In addition, we found a significantly reduced density of ABCB1-expressing neurons in the left habenula. Reduced ABCB1 expression in habenular capillaries might contribute to increased brain levels of proinflammatory cytokines in patients with schizophrenia, while decreased expression of this protein in a subpopulation of medial habenular neurons (which are probably purinergic) might be related to abnormalities of purines and their receptors found in this disease. Our results clearly show that in schizophrenia ABCB1 deficits are found in other brain regions than those described in Alzheimer´s disease.

Markus Krohn

Translational Neurodegeneration and Neuropathology Lab

University of Oslo, Oslo, Norway

Title: Mice with human ABC transporters – new tools for better translation

September 5th, 2016
15:45 – 16:30

I did my studies in Biology 1997-2002 at the University of Greifswald, Germany. After finishing diploma thesis I worked for two years at the Institute for Animal Physiology in Greifswald before starting PhD work at the Institute of Pathology in 2005. I finished my PhD thesis entitled "The role of ABC transporters in Alzheimer's disease" in 2010 after moving to the Neurodegeneration Research Lab at the University of Rostock, Germany, in 2007. During the following years I have been working at the German Center for Neurodegenerative diseases in Magdeburg, the University of Magdeburg and since 2015 at the Translational Neurodegeneration and Neuropathology Lab in Oslo.

My research aims the improvement of AD mouse models, the role of the choroid plexus in neurodegeneration, understanding function and manipulation of ABC transporters and defining activating agents specially for ABCC1. Currently, I am investigating mouse models with humanized ABC transporters A7, B1 and C1.

This meeting is funded by the Norges Forskningsrådet (The Research Council of Norway) and the Oslo University Hospital (OUS).