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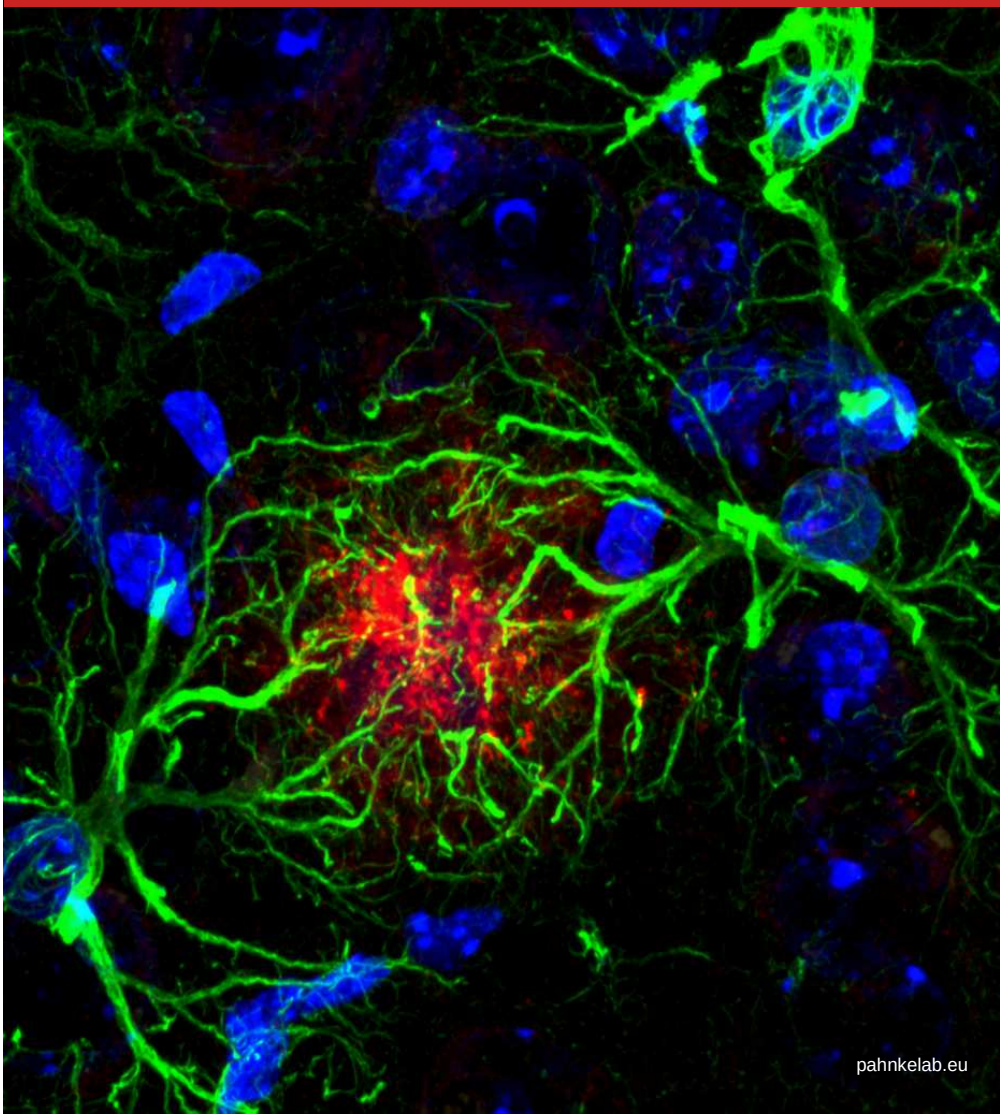
TransportDEMENTIA

General Information

PROGRAM

OSLO
DECEMBER 9 – 11, 2015





WELCOME

Dear Ladies and Gentlemen.

Dear friends.

We have the great opportunity to invite YOU and other internationally well-known researchers to Oslo to discuss a new era in dementia research.

During the recent years huge efforts have been made to unravel the pathogenesis of cerebral proteopathies. Amongst many routes to success, the blood-brain barrier and its transport molecules appear to be the most promising way in preventing and treating neurodegenerative diseases in near future. First successful steps have been made and, soon, the first Phase IIa study using ABC transporter activating compounds will start.

This meeting is funded by the Norges Forskningsrådet (The Research Council of Norway) and the Oslo University Hospital (OUS). We aim to gather world-leading experts in the nice capital of Norway to present most recent research results and, more importantly, to discuss new grant applications, new routes of research, and to generate more intense collaborations with Norway between those who already collaborate internationally.

Yours sincerely, Jens Pahnke

Holmenkollen Park Hotel

Address:	Kongeveien 26 0787 Oslo Norway
Phone:	+47 22 92 20 00
E-mail:	holmenkollenpark@scandichotels.com
Web:	www.holmenkollenparkhotel.no/en
Check-in:	15:00 (If your arrival is before 15:00, we will try to make sure that you get into your room earlier.)
Check-out:	12:00
Breakfast:	every day from 7:00-10:00

Taxi transport

Arrival at Oslo

After arrival at Oslo airport (Gardemoen) you should go to taxi information desk in the arrival hall. It is on the left side after you passed the customs zone (see picture below).

There you have to mention your name and that we pre-booked a taxi for you from ***Christiana Taxi***. The taxi driver will contact you at the taxi information desk. **Please be aware that you have to show your boarding pass, if you are asked for it.**

Departure from Hotel

Taxi transport from hotel to airport on 11th of December will be on schedule as you can see below.

DEPARTURE	NAMES
03:10	Shai Rahimipour
04:40	Kristaps Jaudzems
05:15	Dietmar Thal
06:30	Claus Pietrzik Cecilia Santos Oliver Langer Thomas Wanek Gabor Kovacs Anika Hartz
07:00	Saleh Ibrahim
07:30	Charalampos Tzoulis Kristoffer Haugarvoll Lasse Melvær Giil Fabien Gosselet Heidrun Potschka Joana Palha Margarida Correia-Neves
08:15	Baiba Jansone Roxana Carare Matthias Köpp Wolfgang Löscher Andreas Noack Kerstin Römermann Bogdan Popescu Ingolf Cascorbi
09:00	Ludger Wessjohann Peter Brust
09:30	Henrik Biverstål Simone Tambaro Axel Leppert Axel Abelein
10:00	Dan Frenkel Thomas van Groen Inga Kadish Maceij Lalowski
12:00	Fabrizio Piazza
13:00	Jörg Gsponer
15:30	Maria Deli

Contact

We hope you will have no trouble on your journey, but if you have any problems, call +47 230 71478 (office) or mobile +49 1578 1986 883 (Kristin) or Jens (+47 4780 4637, +49 176 4560 9359).

For problems that are not quite so urgent, write an E-Mail to kristin.paarmann@medisin.uio.no

WEDNESDAY DECEMBER, 9TH

Arrival

18:30	***Jens Pahnke*** (Oslo) Introduction
18:45-19:20	***Ole Petter Ottersen*** (Rector of the University of Oslo) Aquaporins and the brain's drainage
19:20-19:55	***Wolfgang Löscher*** (Hannover) ABC Transporter in brain diseases
20:00-22:00	Scientific Dinner

THURSDAY DECEMBER, 10TH

Breakfast

9:00-9:20	***Roxana Carare*** (Southampton) The anatomical structure of the BBB and the perivascular clearance
9:20-9:40	***Maria Deli*** (Szeged) In vitro models of the BBB
9:40-10:00	***Inga Kadish*** (Birmingham) RAs function in BBB integrity and permability
10:00-10:20	***Thomas van Groen*** (Birmingham) Function of pericytes in Aβ efflux from the brain
10:20-10:40	***Joana Palha*** (Braga) The choroid plexus transcriptome in health and in disease

Coffee break (20 min)

11:00-11:20	***Heidrun Potschka*** (München) ABC transporter regulation in human brain capillaries
11:20-11:40	***Ingolf Cascorbi*** (Kiel) Regulation of ABC transporters by non-coding RNAs
11:40-12:00	***Rada Koldamova*** (Pittsburgh) ABCA1, ApoE and ApoA-I and Aβ clearance through BBB: mouse models
12:00-12:20	***Claus Pietzik*** (Mainz) The role of LRP1 in Aβ clearance from the brain across the blood-brain barrier
12:20-12:40	***Anika Hartz*** (Lexington) ABCB1 News: The Transporter and the Amyloid
12:40-15:00	Lunch and recreation (2h20min)
15:00-15:20	***Markus Krohn*** (Oslo) ABCC1 in neurodegenerative diseases
15:20-15:40	***Danny Frenkel*** (Tel Aviv) The role (and source) of TGF-β on ABC expression in the brain and in EC
15:40-16:00	***Fabien Gosselet*** (Lens) ABCA7 in Alzheimer's disease: focus at the blood-brain barrier
16:00-16:20	***Shai Rahimipour*** (Ramat Gan) Novel anti-amyloidogenics to treat various amyloidogenic diseases
16:20-16:40	***Iliya Lefterov*** (Pittsburgh) Therapeutic potential of activated Nuclear Receptors in brain
	Coffee break (20 min)

17:00-17:20	***Gabor Kovacs*** (Wien) Neuropathological aspects of alpha-Synucleinopathies
17:20-17:40	***Dietmar Thal*** (Leuven) Amyloid β-protein aggregate maturation and perivascular clearance
17:40-18:00	***Oliver Langer*** (Wien) PET Imaging of efflux transporter function
18:00-18:20	***Charalampos Tzoulis*** (Bergen) Mitochondrial DNA homeostasis: a common mechanism for neurodegeneration
18:20- 18:40	**Bogdan Popescu** (Bucharest) Tight junction proteins in Alzheimer's disease and vascular dementia
	Coffee break (20 min)
19:00-19:20	***Jörg Gsponer*** (Vancouver) How to find common regulators and disease genes?
19:20-19:40	***Saleh Ibrahim*** (Lübeck) Mitochondria and brain diseases
19:40-20:00	***Anton Tonchev*** (Varna) Neurogenesis in ischemia and neurodegeneration
20:00-20:20	***Jens Pahnke*** (Oslo) Meetings essentials and outlook – Funding opportunities
20:30-22:30	Scientific Dinner

FRIDAY DECEMBER, 11TH

Discussions & Departure

Jens Pahnke

Translational Neurodegeneration and Neuropathology Lab

University of Oslo, Oslo, Norway

December 9, 2015
18:30

December 10, 2015
20:00 – 20:20

During the last years we have focussed 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 since a few weeks now.

ABC transporter-deficiency seems to be the major mechanism that is leading 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.

Prof. Ole Petter Ottersen

Rector of UiO

Institute of Basic Medical Sciences, Department of Medicine

University of Oslo, Oslo, Norway

Title: Aquaporins and the brain's drainage

December 9, 2015
18:45 – 19:20

Ole Petter Ottersen graduated from the University of Oslo as Cand. med. (MD) in 1980, and gained his doctorate in medicine in 1982.

He became professor of the Department of Anatomy in 1992.From 1997 to1999, Professor Ottersen was academic head of the Department of Anatomy; from 2000-2002 he was Vice-Dean of Research at the Medical Faculty, and from 2002 to 2009 he headed the Centre for Molecular Biology and Neuroscience – one of Norway's centres of excellence.

Professor Ottersen has received a number of awards for his research, including the Anders Jahre Medical Prize for young scientists in 1990 and the Anders Jahre Award for Medical Research (main award) in 2008.

Previous positions:

Director, Centre of Molecular Biology and Neuroscience (Center of Excellence sponsored by Nowegian Research council; www.cmbn.no)

Coordinator, Nordic Centre of Excellence in Molecular Medicine (WIRED)

Chief Editor of Neuroscience (Official Journal of the International Brain Research Organization)

Publications:

More than 350 research papers (331 listed in PubMed). Since 2002 Professor Ottersen has been included in the Institute of Scientific Information list of Highly Cited scientists (http://hcr3.isiknowledge.com/formSearch.cgi).

Wolfgang Löscher

Department of Pharmacology, Toxicology and Pharmacy, University of Veterinary, Medicine Hannover and Head, Center for Systems Neuroscience Hannover, Germany

Title: ABC transporters in brain diseases

December 9, 2015
19:20 – 19:55

ABC drug efflux transporters that are expressed at the blood–brain barrier limit the ability of many drugs to access the brain. Limited response to drug treatment is an important hurdle in the therapy of many brain disorders, including brain cancer, epilepsy, schizophrenia, depression and infection of the brain with HIV. Consequently, there is a pressing need to develop new and more effective treatment strategies. Mechanisms of resistance that operate in cancer and infectious diseases might also be relevant in drug-resistant brain disorders. There is increasing evidence that drug efflux transporters such as P-glycoprotein have an important role in drug-resistant brain disorders, and this information should allow more efficacious treatment strategies to be developed. Furthermore, ABC transporters seem to play a role in the pathogenesis of some brain diseases, particularly Alzheimer's disease. Thus, insufficient Aβ export, physiologically facilitated by the ABC transporter superfamily at the brain's barriers, seem to plays a fundamental role in disease initiation and progression, thus providing novel targets for treatment and prevention.

The Löscher group in Hannover, Germany, is working on three topics within the field of epilepsy research: 1. mechanisms involved in epileptogenesis after brain insults as new targets for pharmacological intervention; 2. mechanisms of pharmacoresistance in epilepsy (and other brain disorders); 3. new targets for antiepileptic (anti-seizure) and antiepileptogenic drugs. In addition, we are working on mechanisms of electroconvulsive therapy in pharmacoresistant depression. We are using diverse methods and technologies for

our studies, including behavioral phenotyping, molecular and biochemical methods, in vivo and ex vivo neuropharmacological, electrophysiological, neurochemical, and neuropathological methods, and in vivo imaging techniques. The main research interests of the Löscher group are described in a recent review in Nature Reviews Drug Discovery (Löscher et al., 2013).

Roxana Carare

Clinical Anatomy, University of Southhampton Southampton, UK

Title: The anatomical structure of the BBB and the perivascular clearance

December 10, 2015
9:00 – 9:20

Roxana Carare is a medically qualified Associate Professor in clinical anatomy and experimental neuropathology in the University of Southampton. Having graduated in general medicine in 1994 in Bucharest, Roxana completed her PhD in experimental neuropathology in 2006, in the University of Southampton, UK. The main international recognition for Roxana Carare has come from the neuroanatomy and neuropathology interdisciplinary research she leads, demonstrating the unique lymphatic drainage pathways by which fluid and soluble amyloid are eliminated from the brain along basement membranes within the walls of cerebral capillaries and arteries. The focus of Roxana's research is to manipulate the pathways to improve the clearance of amyloid and interstitial fluid from the ageing brain, preventing neurodegenerative diseases. Roxana is part of the International Scientific Steering Committee of Vas-Cog, Cerebral Amyloid Angiopathy, Alzheimer's Society Romania. Roxana regularly reviews for neuroscience, neuropathology and Alzheimer's disease journals, for national and international funding agencies, as well as for the European Commission. The Carare team has won prestigious British and International awards, most recently Roxana has received a Dementia Research Leader award from Alzheimer's Society UK. Of Romanian heritage, Roxana is Honorary Consul of Romania, Advisor for Age UK Southampton and Patron of Libra Foundation.

Maria Deli

Institute of Biophysics, Biological Research Centre, Biological Barriers Research Group
Szeged, Hungary

Title: *In vitro* models of the BBB

December 10, 2015
9:20 – 9:40

Culture models of the blood-brain barrier (BBB) are important tools to study physiological functions, transport mechanisms, drug delivery and pathomechanisms. Co-cultures using two or three cell types, brain endothelial cells, glial cells and pericytes, and recently dynamic models and lab-on-a-chip devices have been developed to better mimic the in vivo complexity of the BBB. We designed and manufactured an integrated biochip with transparent gold electrodes for the investigation of the BBB with several functions and measurements: co-culture of two or three types of cells; fluid flow; visualization of the entire cell layer by microscopy; real-time transcellular electrical resistance monitoring; permeability measurements. Two BBB models, hCMEC/D3 human brain endothelial cell line and primary rat triple co-culture were studied in both static and dynamic conditions.

Biography and research interest
Maria Deli is a scientific advisor and head of the Biological Barriers Research Group of the BRC in Szeged, Hungary. The team examines solid vesicular nanoparticles for targeted drug delivery to the nervous system. The safe and reversible opening of intercellular junctions by lipids and peptides to increase drug penetration are also tested. Another major research topic of the group is BBB injury/dysfunction in pathologies, including Alzheimer's disease with the aim to identify protective molecules. In a joint interdisciplinary project with the Biomolecular Electronics research group we work on the development of new dynamic human co-culture models of the BBB and BCSFB in the frame of the H2020 BtRAIN network.

Inga Kadish

University of Alabama at Birmingham, Dept. Cell, Developmental and Integrative Biology
Birmingham, Alabama, USA

Title: Function of pericytes in Aβ efflux from the brain

December 10, 2015
9:40 – 10:00

The overall goal of my research is to elucidate the role of white matter pathology in the development of age-related cognitive deficits. Currently, our studies have shown two significant pathological changes in white matter with aging: malfunctioning of oligodendrocytes and demyelination of axons. These changes will lead to a "functional" disconnection in the brain leading to cognitive disturbances.

My second research interest is the role of vascular pathology in Alzheimer's disease, specifically hypertension and the relation between white matter infarcts and AD pathology. Our studies have shown that small ischemic infarcts both increase Aß deposition and decrease cognition. Further, we have begun investigating the role of obesity, and/or caloric restriction and hunger (by using synthetic ghrelin agonist) in the development of cognitive deficits in aging and AD. We have demonstrated that hunger has similar positive effects on aging and AD as caloric restriction has, i.e., ghrelin agonist treated animals has less age and disease related inflammation in the brain. We are also studying whether dietary composition (i.e., high fat versus high protein versus high carbohydrates) has importance beyond the known effect of high fat intake to increase AD pathology and cognitive deficits.

Thomas van Groen

University of Alabama at Birmingham, Dept. Cell, Developmental and Integrative Biology
Birmingham, Alabama, USA

Title: Function of pericytes in Aβ efflux from the brain

December 10, 2015
10:00 – 10:20

It is clear that the vasculature plays a role in the removal of Aβ from the brain, and it has been suggested that the LRP1 receptor is a major player in the removal of Aβ across the BBB. Sequestration of plasma Aβ or removal through the liver/kidneys enhances the peripheral Abeta 'sink action'. Indirect removal of Aβ from the brain would involve the perivascular space around blood vessels for Aβ transport out of the brain. It is less clear which cells in the brain participate in the Aβ efflux, LRP1 is located on the vascular smooth muscle cells, and on pericytes. In our studies we have demonstrated that in our treated AD mouse models the major outflow of Aβ from the brain is through pericytes.

Joana Palha

The Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho Braga, Portugal

Title: The choroid plexus transcriptome in health and in disease

December 10, 2015
10:20 –10:40

We have been studying the choroid plexus as an active participant in the communication between the periphery and the brain, in physiological conditions (including aging), in response to peripheral stimuli such as inflammation and in the context of diseases of the central nervous system including multiple sclerosis and Alzheimer's disease.

We found that the choroid plexus responds quickly and transiently to an acute peripheral inflammatory stimulus, but in an attenuated form if the inflammatory stimulus is repeated in time. As such, it seems that the choroid plexus is able to adapt to inflammation. Future studies should address how that may relate to the predisposition to diseases of the central nervous system.

Using the mouse as the model, for aging and for Alzheimer's disease, we found longitudinal differences in the expression of various genes, with particular interest on those of IFN type I and II responses and on genes involved in the circadian rhythm. Ongoing studies intend to further dissect how this may have implication in disease pathology. Using the experimental autoimmune encephalomyelitis (EAE) mouse model of multiple sclerosis we found that particular proteins secreted by the choroid plexus may be involved in pathology, which we are presently investigating further. Of interest, we translated the finding on lipocalin 2 to the clinics, and found identical CSF lipocalin 2 profiles in patients with multiple sclerosis, which we are presently validating as a marker of disease.

The neurosciences research domain of the Life and Health Sciences Research Institute (ICVS) at the Medical School at the University of Minho (Braga, Portugal) is organized around projects and not groups, which has allowed us the build ideas based on the team member's expertise interested in particular topics. As such, not only the studies on the choroid plexus have motivated colleagues from other fields of interest, such as psychiatric disorders (so plans are to extend some of the choroid plexus studies into mood disorders), but also the basic and translational research may feed more easily into the clinics. As such, a longitudinal cohort is being built with the idea to search for predictors of healthy aging in individuals older than 55 years of age. In addition, we have established cohorts of patients with multiple sclerosis, in the various phases of the disease, for the study of potential novel biomarkers of disease diagnostic/progression/remission; some of which originating from the choroid plexus and already being evaluated. Similarly for patients with Alzheimer's disease.

As for basic and translational research, several models of disease are well established within the neuroscience research domain, mostly on psychiatric disorders (stress, depression, bipolar depression, schizophrenia, addiction), neurological disorders (multiple sclerosis, Alzheimer's disease and polyglutamine disease), and particular expertise is available on neurogenesis, glial research, electrophysiology and behavior phenotyping (specific novel apparatus for addressing behavior in the natural setting have been built with companies; and all

state of the art equipment for evaluation of cognition, anxiety, mood, addiction, pain are well established).

Heidrun Potschka

Institute of Pharmacology, Toxicology and Pharmacy, Ludwig-Maximilians-University Munich, Germany

Title: ABC transporter regulation in human brain capillaries

December 10, 2015
11:00 –11:20

ABC transporters are dynamically regulated in response to endogenous and exogenous factors and compounds. Considering that efflux transport can have a major impact on brain distribution of CNS drugs, it is crucial to understand the mechanisms of transporter regulation. Therefore we study the impact of different signaling factors, which are activated by disease states, as well as the impact of drug exposure on the expression and function of ABC transporters in freshly isolated brain capillaries.

Respective studies are traditionally performed in rodent or pig capillaries. Data obtained raise the question about the translational value. Thus, it is of particular interest to study the regulation of ABC transporters in human brain capillaries isolated from neurosurgical specimen. Using this approach we have for instance identified key signaling factors which modulate transporter function in response to glutamate exposure, which can reach increased extracellular levels in different CNS diseases.

BBB research in our team is focused on disease- and drug-associated alterations in the barrier function. The interest is driven by the fact respective alterations can contribute to the pathophysiology of CNS diseases but can also have a major impact on pharmacosensitivity.

The methods applied in BBB research projects include transport assays in freshly isolated capillaries (incl. human), µPET studies of transporter function, brain microdialysis studies assessing BBB penetration of test compounds, and Omics technologies assessing the pattern of molecular alterations.

Ingolf Cascorbi

Institute of Experimental and Clinical Pharmacology, Christian Albrechts University Kiel, Germany

Title: Regulation of ABC transporters by non-coding RNAs

December 10, 2015
11:20 –11:40

There is increasing evidence that epigenetic modification contributes to the modulation of efflux transporter expression. Despite alteration of DNA methylation or histone-acetylation, deregulated microRNA expression patterns in tumour or inflammatory tissue have been identified to interfere with drug response. Attempts to modify the expression of selected microRNAs have partly led to intriguing improvements of chemotherapy response. Down-regulation of certain microRNAs could abolish the suppression of gene expression as exemplified by imatinib resistance of BCR/ABL-over-expressing K-562 cells through up-regulation of ABCG2 (BCRP).

The interaction of miRNA with ABC-transporter mRNA however may also vary due to alterations of the 3'-UTR or changes of the mRNA secondary structure. Hence, the interaction of transcription factors, genetic variants, 5-UTR length and miRNA pattern contributes significantly to the transporter phenotype that is finally decisive for the function of efflux transporters.

Research at Cascorbi Lab, Institute of Experimental and Clinical Pharmacology, Christian Albrechts University of Kiel, Germany

Our main research is focused on pharmacogenomics and epigenomics of drug metabolizing enzymes and drug transporters in oncology, transplantation medicine, epilepsy and Alzheimer. Further aspects relate to association analyses of adverse drug events such as clozapine-induced agranulocytosis and to the role of genetic variants in neuropathic pain.

Currently we are investigating the expression profile of genes and miRNA along the gut in bariatric surgery, mechanisms of tyrosine kinase inhibitor resistance in CML.

A recently accomplished project dealt with epigenetic changes in therapy-resistant epilepsy in humans. In cooperation with Heidrun Potschka, Munich, miRNA profiling of murine models of therapy-resistant epilepsy are currently analysed.

Research networks: Cluster of Excellence, Inflammation at Interfaces; BMBF P2N biobank

Further partners of cooperation in Kiel are Ralf Baron, Dept.of Neurology; Andre Franke, Inst. of Clinical Molecular Biology; Christian Röder, Inst. of Experimental Cancer Research; Ulrich Stephani, Dept.of Neuropediatrics. Cooperation partners in Germany: Werner Siegmund, University of Greifswald, Matthias Schwab, IKP Stuttgart, Heidrun Potschka, TU Munich

International partners: Ann Daly, Newcastle, UK; Magnus Ingelman-Sundberg, Stockholm, Sweden; Deanna Kroetz, UCSF, USA; Patrick F. Sullivan, UNC, USA

Rada Koldamova

School of Public Health, University of Pittsburgh Pittsburgh, Pennsylvania, USA

Title: ABCA1, ApoE and ApoA-I and Aβ clearance through BBB: mouse models

December 10, 2015
11:40 –12:00

We study the role of ABCA1 transporter and brain apolipoproteins in Amyloid- β clearance and aggregation. Or research is focused on the link between APOE lipidation and its functionality in terms of AD pathogenesis. We are using mouse models of AD expressing human APOE isoforms, Abca1, Apoe and Apoa-I knockout mice. The goal is to elucidate the effect of Abca1/ApoE/ApoA-I axis on the formation of Aβ oligomers, Aβ efflux through the BBB and how those affect cognitive impairment.

Claus Pietrzik

Institute of Pathobiochemistry, University Medical Center of the Johannes Gutenberg University Mainz, Germany

Title: The role of LRP1 in Aβ clearance from the brain across the blood-brain barrier

December 10, 2015
12:00 – 12:20

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. With a novel Slco1c1-CreERT2 mouse, we generated the first brain endothelial-specific LRP1 knockout mouse to accurately evaluate LRP1-mediated Aβ BBB-clearance in vivo. Selectively deleting Lrp1 in brain endothelium of C57BL/6 mice strongly reduced brain efflux of injected [125I] Aβ1-42. In another model, the 5xFAD mouse model of AD, brain endothelial-specific Lrp1 deletion resulted in reduced plasma Aβ and elevated soluble brain Aβ leading to aggravated spatial learning and memory deficits, thus, emphasizing the importance of systemic Aβ elimination via the BBB.

Anika Hartz

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

Title: ABCB1 News: The Transporter and the Amyloid

December 10, 2015
12:20 – 12:40

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.

The blood-brain barrier is the vasculature that separates blood from brain. The primary role of this barrier is to ensure nutrient supply to the brain and, at the same time, to protect the brain from potentially toxic xenobiotics, including therapeutic drugs. Recent studies show that brain disorders affect the blood-brain barrier, which itself may play a role in brain pathology such as Alzheimer's disease. This is a new paradigm in the field that is not well understood.

My current research is focused on mechanisms that regulate blood-brain barrier function in Alzheimer's disease. We develop novel therapeutic strategies to improve blood-brain barrier function to reduce memory loss and delay onset and slow progression of Alzheimer's disease.

Markus Krohn

Translational Neurodegeneration and Neuropathology Lab, University of Oslo Oslo, Norway

Title: ABCC1 in neurodegenerative diseases

December 10, 2015
15:00 – 15:20

Among ABC transporters, and possibly beyond, ABCC1 deficiency has the strongest effect on amyloid burden in mouse models of Alzheimer's disease. Currently, we are evaluating the role of ABCC1 as disease modifier in different neurodegenerative diseases and its usability in diagnostics and as treatment target. However, the search for activating agents reveals several uncertainties regarding substrate recognition of ABCC1 and substrate interaction which we aim to resolve in current and future projects.

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 especially for ABCC1.

Dan Frenkel

Life Science Faculty, Department of Neurobiology, Sagol School of Neuroscience Tel Aviv, Israel

Title: The Role of Pathological Elevation in Astrocyte Transforming growth factor beta 1in Mediating Cerebral Amyloid Angiopathy

December 10, 2015
15:20 – 15:40

Astrocyte-endothelial cell (EC) interaction plays a major role in the function of the neurovascular unit. Dysfunction in their interaction may lead to amyloid accumulation in blood vessels, a condition known as cerebral amyloid angiopathy (CAA), which can lead to a major hemorrhagic stroke and cognitive impairment. Transforming growth factor beta 1 (TGF-β1) is a pleiotropic cytokine involved in both neurodegenerative and neuroprotective mechanisms. TGF-β1 expression levels correlate positively with the degree of cerebrovascular amyloid in Alzheimer's disease (AD) cases. Furthermore, expression of TGF-β1 under GFAP promoter in mice leads to an age-related deposition of amyloid, such as β-amyloid (Aβ), around cerebral blood vessels. We demonstrated that TGF-β1 affects EC and peripheral inflammation cross talk, which led to a reduction in expression of transporter proteins and secreted factors such as chemokines and cytokines that may affect development of cerebrovascular amyloid deposition. The investigation of TGF-β1-mediated cellular pathways in EC may provide useful therapeutic intervention targets for cerebrovascular amyloidosis that can be found in different neurodegenerative diseases such as Alzheimer's disease.

Fabien Gosselet

LBHE Laboratoire de Physiopathologie de la Barrière Hémato-Encéphalique, Université d'Artois, Arras Lyon, France

Title: ABCA7 in Alzheimer's disease: focus at the blood-brain barrier

December 10, 2015
15:40 – 16:00

The overall goal of my research is to elucidate the role of the blood-brain barrier (BBB) in the brain homeostasis and in neurodegenerative diseases. In particular, I investigate the close relationships between amyloid transport across the BBB and the complex brain cholesterol metabolism. Using in vitro BBB models from mice, rat, bovine and human, and in situ techniques, I currently focus my attention on the ABC transporters such as ABCA1, ABCB1, ABCG2, and ABCG1 and I decipher their potential contribution in these both processes, thus demonstrating that daily, they actively participate in the regulation of the amyloid and cholesterol pools.

Recently, several genome wide-association studies (GWAS) have established that polymorphisms in ABCA7 gene confer a higher risk to develop AD. For this reason, one of my current project aims to delineate the role of this ABC transporter at the BBB level. In my talk, I will show my preliminary data regarding the loss-of-function of Abca7 at the BBB level.

Shai Rahimipour

Department of Chemistry,
Bar-Ilan University
Ramat-Gan, Israel

Title: Novel anti-amyloidogenics to treat various amyloidogenic diseases

December 10, 2015
16:00 – 16:20

One of the major goals of my group is to better understand and treat disorders that are linked to aberrant protein folding and assembly. Our research strategy is interdisciplinary, aiming at utilizing self-assembly processes to design new modalities for arresting amyloid formation in different diseases. We also use self-assembly processes to enhance biological activity by inducing multivalency. The main thrust of my group's research is summarized below.

Drug Discovery, Design, and Delivery Research for Amyloidogenic Diseases. My group seeks to develop a supramolecular-based platform that can be used as a general scaffold for the design and discovery of novel anti-amyloidogenic compounds with potential application in the treatment of various amyloidogenic diseases, such as Alzheimer's disease, Parkinson's disease and type II diabetes. Very recent biochemical and biophysical studies have shown that pathogenic amyloids share common structural and functional features despite being composed of different proteins and amino acids. The similarities between the different amyloids are so great that soluble aggregates of diverse amyloidogenic proteins, such as insulin, islet amyloid polypeptide, and a-synuclein, can cross-react with each other and be equally recognized by polyclonal antibodies raised against prefibrillar assemblies of amyloid β (Aβ) peptides, which are responsible for Alzheimer's disease. Astonishingly, we have recently found that there are immense structural and functional similarities between different amyloids and the self-assembled cyclic D,L-β-peptides

that we recently discovered. These similarities led our cyclic peptide to cross-react with toxic soluble oligomers of Aβ, α-syn, insulin and tau-derived peptide and inhibit their aggregation and toxicity. We believe that these studies may shed light on the etiology of misfolded proteins and provide additional insights that can be used to tackle poorly understood topics in the field of misfolded protein diseases, such as the infectious nature of the amyloids and their ability to spread from cell-to-cell. These insights may eventually unravel the mechanism by which proteins begin to misfold to form toxic intermediates, and enhance our ability to intervene in such processes.

Developing New Chemical Methods to Induce Multivalency – Application in the Field of Amyloidogenic Diseases Research. My group is also involved in developing new chemical methods to induce a multivalency effect, which is frequently used by nature to dramatically increase the bioactivity of ligands with low individual activity. These methods include the development of a new and straightforward sonochemical method to generate nano- and micro-sized particles bearing multiple copies of a bioactive element covalently attached to their surface. We used this technology to show that particles expressing multiple copies of the peptide KLVFF can strongly bind Aβ, inhibit its aggregation, and reduce its cytotoxicity. The anti-amyloidogenic activity of these particles was found to be significantly higher than that of an equimolar concentration of soluble KLVFF—most probably because of the multivalent presentation of the KLVFF peptide. We also showed that such

surface-modified nanoparticles can dramatically increase the phagocytosis of Aβ even with defected microglia cells and reduce the inflammation associated with Aβ. Initial in vivo toxicity experiments on rats suggest that the particles are biocompatible even after intravenous injection of large doses. Bio-distribution and pharmacokinetic studies are now in progress.

Utilizing Multivalency and Supramolecular Chemistry in the Field of Inflammatory Disease Research: Type II Diabetes and Multiple Sclerosis. Various aspects of oxidative cellular stress are associated with the pathogenesis of several devastating human diseases, including diabetes, Alzheimer's disease, Parkinson's disease, and multiple sclerosis. It is well known that the generation of reactive oxygen species (ROS) in abnormal amounts or an impairment of the cells' anti-oxidative protective systems can lead to cellular and tissue damage.

We demonstrated that the multivalent presentation of histidine residues induced by the abiotic self-assembly of cyclic D,L-β-peptides can lead to the generation of multifunctional agents that catalytically decompose intracellular ROS and induce cell protection. In particular, we showed that treatment of muscle cells with such permeable His-rich cyclic peptides protects the cells against the oxidative stress that is induced by hyperglycemic conditions and increases the uptake of glucose from the periphery by increasing the translocation of GLUT1 and GLUT4. In neuronal cells, we were able to show that these peptides exhibit potent anti-inflammatory, anti-oxidant, and

anti-excitotoxic activity, and protect the neurons against axonal damage. In a pilot study carried out in collaboration with Teva Pharmaceutical Industries Ltd., we were able to demonstrate that the discovered cyclic peptides exhibit potent neuroprotecting activity in an animal model of multiple sclerosis (experimental autoimmune encephalomyelitis) and significantly ameliorate the related symptoms.

Iliya Lefterov

School of Public Health, University of Pittsburgh Pittsburgh, Pennsylvania, USA

Title: Therapeutic potential of activated Nuclear Receptors in brain

December 10, 2015
16:20 – 16:40

The research in my laboratory is focused on understanding the role of Nuclear Receptors RXR and LXR in the pathogenesis of Alzheimer's disease, and clearance of Aβ species from brain. Using AD-like mouse models expressing human APOE isoforms we also try to answer the question what is the role for small molecule receptor specific ligand activated RXR in adult neurogenesis and their therapeutic effect on behavior and memory in AD mice. Significant part of our research is directed toward the understanding the role of age, gene-gene, and gene-environment interactions in neuroinflammation, response to environmental toxicants and traumatic brain injury.

Gabor Kovacs

Institute of Neurology,
Medical University of Vienna
Vienna, Austria

Title: Neuropathological aspects of alpha-Synucleinopathies

December 10, 2015
17:00 – 17:20

Dementia with Lewy bodies, Parkinson's disease and multiple system atrophy are characterized by the deposition of disease-associated a-synuclein. In a recent study we evaluated immunostaining patterns, at light and electron microscopy level, and their correlation in human brain tissue with micro- and astrogliosis using a novel anti-a-synuclein antibody. In addition to neuronal immunoreactivities, we found disease-associated a-synuclein in perivascular macrophages, ependyma and cranial nerves. We documented ultrastructurally the pathway of processing of disease-associated a-synuclein within neurons and astroglial cells. We concluded that Lewy bodies themselves are not the most relevant morphological substrate that evokes tissue lesioning; furthermore, that both neurons and astrocytes internalize disease-associated a-synuclein in the human brain, reminiscent of what is seen in prion disease.

My work has been devoted to neurology and neuropathology (i.e. the study of tissue alterations in diseases of the nervous system for diagnostic and research purposes). My particular interests are in prion and neurodegenerative diseases. My achievements include first descriptions of several peculiar types of neurological diseases and tissue-related research on the pathogenesis of prion diseases. Currently I focus on the development of biomarkers for neurodegenerative diseases; on the understanding of phenotypic variability and selective vulnerability; and on the search for a link between development and ageing of the brain.

Dietmar Thal

Laboratory of Neuropathology, University of Ulm Ulm, Germany

Title: Amyloid β-protein aggregate maturation and perivascular clearance

December 10, 2015
17:20 – 17:40

Dietmar Thal's research is focused on the neuropathology of Alzheimer's disease and other neurodegenerative disorders. He set up a staging system for amyloid plaques that is currently recommended for use in the recommendation of the NIA-AA for the neuropathological diagnosis of Alzheimer's disease. He is furthermore interested in the biochemical characterization of Aß aggregates and in the clearance of Aß aggregates especially along perivascular drainage pathways.

Abstract: Amyloid β-protein (Aβ) is the major component of senile plaques and of deposits related to sporadic cerebral amyloid angiopathy (CAA) in Alzheimer`s disease (AD). Perivascular drainage of neuron-derived Aβ has been shown to be related to CAA and it is considered to represent a possible pathomechanism for the development of CAA. Recently, we showed that posttranslational modified forms of Aβ, namely N-terminal truncated and pyroglutamate-modified AβN3pE and phosphorylated pSer8Aβ, showed a distinct hierarchical sequence, in which they occur in AD-related Aβ deposits at the biochemical level. We reported that pSer8Aβ was mainly restricted to symptomatic AD whereas preclincal AD cases exhibited only non-modified Aβ and AβN3pE.

Here, we studied APP-transgenic mice (APP23 mice carrying the Swedish APP-mutation KM670/671NL driven by a neuron-specific Thy1 promoter) for the occurrence of posttranlational modified forms of Aβ to clarify whether perivascular drainaged of these Aβ-species takes place and causes CAA. These three Aβ-

species were detected in plaques and biochemically in APP23 mice. Interestingly, while no vascular Aβ deposits were seen at 5-month-old APP23 nor wildtype mice, 11-months-old APP23 mice exhibited CAA affected vessels exhibiting Aβ as well as AβN3pE and pSer8Aβ.

These results indicate that posttranslationally modified AβN3pE and pSer8Aβ are subject of perivascular clearance and result from posttranslational modification of neuron-derived Aβ on the APP23 mice. In so doing, generation of AβN3pE and pSer8Aβ is a central process and perivascular drainage is one pathway for its elimiation.

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Oliver Langer

Health & Environment Department, AIT Austrian Institute of Technology GmbH, Seibersdorf and

Department of Clinical Pharmacology, Medical University of Vienna Vienna, Austria

Title: PET Imaging of efflux transporter function

December 10, 2015
17:*40 – 18:00*

Adenosine triphosphate-binding cassette (ABC) transporters expressed at the blood-brain barrier (BBB) and at the blood-cerebrospinal fluid barriers, such as P-glycoprotein (ABCB1), breast cancer resistance protein (ABCG2) and multidrug resistance-associated proteins 4 and 1 (ABCC4 and ABCC1), control the exposure of brain parenchyma to exogenous and endogenous compounds and have been implicated in the pathophysiology of neurological disease, such as drug resistant epilepsy and Alzheimer's disease. Positron emission tomography (PET) in combination with radiolabelled transporter substrates can be used to non-invasively assess the function of cerebral ABC transporters in animals and humans. In the present talk I will give an overview of currently available PET protocols to measure efflux transporter function in the brain and some applications in animal disease models.

Oliver Langer studied pharmacy at the University of Vienna, where he graduated with a Master's degree in 1995. He then obtained a PhD degree at the Karolinska Institute in Stockholm, Sweden in 2000, where he specialized in the development of radiotracers for the imaging of neurotransmitter systems with positron emission tomography (PET). Since 2002 he has been employed at the Department of Clinical Pharmacology at the Medical University of Vienna, where he became Associate Professor ("Privatdozent") in Radiopharmaceutical Chemistry in 2006. In 2006, he became Senior Scientist at Austrian Institute of Technology in Seibersdorf, which is Austria's largest non-university research organization. In his research, he uses preclinical and clinical PET to address different questions related to drug

disposition and pharmacodynamics with a particular emphasis on studying drug transporters.

Charalampos Tzoulis

Translational Science in Neurodegeneration and Aging, Department of Neurology, Haukeland University Hospital Bergen, Norway

Title: Mitochondrial DNA homeostasis - a common mechanism for neurodegeneration

December 10, 2015
18:*00 – 18:20*

His talk will give an overview on mitochondrial mechanisms in Parkinson's disease, focusing on the most promising ones with respect to understanding the disease mechanisms and move towards therapies. Furthermore he will present findings from his own research studying the link between mitochondrial DNA damage and Parkinson's disease.

Biography & Research

Charalampos Tzoulis is a neurologist and researcher at Haukeland University Hospital. Clinically, he specialized in neurogenetics and neurodegeneration. He leads a research group, Translational Science in Neurodegeneration and Aging (TSNA) (http://www.uib.no/en/rg/neurodegeneration), dedicated to molecular, genetic and clinical studies of neurodegeneration with a particular focus on Parkinson's disease. Their aim is to elucidate novel disease mechanisms and design neuroprotective and disease-modifying therapies for neurodegeneration.

Bogdan O. Popescu

Department of Neurology, Colentina Clinical Hospital

Laboratory of Molecular Medicine and Neuroscience 'Victor Babes' National Institute of Pathology Bucharest, Romania

Title: Tight junction proteins in Alzheimer's disease and vascular dementia

December 10, 2015
18:*20 – 18:40*

Various pathogenic mechanisms are involved in Alzheimer's disease (AD) and vascular cognitive impairment (VCI), with some overlap. There are many clinical and experimental studies clearly showing that blood brain barrier (BBB) is altered in these diseases. One important determinant of BBB properties is expression of tight junction proteins (TJPs), such as occludin and claudin species. We examined expression of TJPs in AD and VCI brains and we found significant changes compared with matched age controls. Moreover, we were able to show that Abeta changes barrier properties in experimental models in correlation with alteration of TJPs expression.

Blood-brain barrier (BBB) alteration in Alzheimer's disease was documented by numerous clinical and experimental studies. One of the determinants of BBB permeability /selectivity is expression of different tight junction proteins (TJP) in brain endothelial cells. Factors influencing TJP expression are not fully identified yet. In 3 studies on human brains we showed that expression of TJP occludin and claudin species are altered in Alzheimer's disease and vascular dementia. In 2 experimental studies we showed that β-amyloid influences expression of TJP in cell cultures and alter functional barrier properties of epithelial cells. Therefore, I think it would be worthy to explore possible new therapeutic targets for neurodegenerative diseases at the level of endothelial TJP.

Jörg Gsponer

**Michael Smith Laboratories,
University of British
Columbia
Vancouver, Canada**

Title: How to find common regulators and disease genes?

December 10, 2015
19:*00 – 19:20*

The computational integration of diverse and often large data sets is a corner stone of systems medicine and systems biology. My lab develops and applies computational tools for the systems-wide analysis of regulatory processes in eukaryotic cells and their alteration in disease states. One area in the focus of our research is proteostasis where we are aiming to (i) map and characterize the constituents of the proteostasis network and (ii) reveal how deficits in this network modulate the onset and progression of neurodegenerative disorders. I will present work focusing on both of these aims.

Saleh Ibrahim

Institute of Dermatology (LIED)
University Hospital of Schleswig-Holstein
Lübeck, Germany

Title: Mitochondria and brain diseases

December 10, 2015
19:*20 – 19:40*

Mitochondrial genome polymorphism/mutations have been linked to longevity and age-related diseases. However, dissecting the pathways controlled by those genes has been hampered by the lack of appropriate animal models. We recently identified 16 different functional variations in common inbred strains and developed a series of 24 conplastic strains carrying those mutations. The strains have identical nuclear genomes and differ only in individual mitochondrial genes (e.g. tRNA-Arg, COX3, ND1, ND5, ATP8). Phenotyping of the mice for basic traits e.g. mitochondrial functions has been completed. In collaboration with colleagues at different institutions we are currently using some of those strains to study longevity, and the following aging-related phenotypes: mitochondrial dysfunction, neuronal plasticity, circadian rhythm, as well as the development of age-related diseases (e.g. Autoimmunity, Alzheimer, Diabetes, Obesity, etc.). Latest results suggest a strong influence of single mtDNA mutations on basic mitochondrial functions, aging-phenoyptes and life span.

Anton B. Tonchev

Department of Anatomy, Histology and Embryology, Medical University of Varna, Varna, Bulgaria

Title: Neurogenesis in ischemia and neurodegeneration

December 10, 2015
19:*40 – 20:00*

Generation of new neurons persists in the normal adult mammalian brain, with neural stem/progenitor cells residing in at least two brain regions called neurogenic niches: the subventricular zone (SVZ) of the lateral ventricle and the subgranular zone (SGZ) of the dentate gyrus (DG). Adult neurogenesis is mostly studied using rodent models, while important differences had been demonstrated between rodent and primates neurogenic niches. Brain ischemia is best described injury which upgregulates neurogenesis by endogenous precursors, in rodent and monkey models. We found that the ischemic insult significantly increased the number of progenitor cells in monkey SGZ and SVZ, and an increased number of proliferating cells was observed in neocortex, striatum, and the ischemia-prone hippocampal CA1 sector. Less clear is the evidence of the neurogenesis levels in neurodegeneration. In human Alzheimer's disease (AD) as well as in mouse transgenic models the data is conflicting with some studies showing enhanced while others decreased indicators of neurogenesis. Unraveling the mechanisms regulating neurogenesis in the AD brain may be of therapeutic importance in the treatment of the disease.

We are currently studying the primate (money and human) neurogenic niches in terms of cell phenotypes classification based on transcriptome and morphological analyses. We further investigate human fetal and adult brains for the involvement of glial cells (especially astrocytes and microglia) in the regulation of progenitor cells in developing and adult brain.