Improvement of the Research Competitiveness in
Neuroscience at Ernst-Moritz-Arndt University of Greifswald

Adult Brain Regeneration After Injuries

First International Workshop: March 25-27, 2010
Greifswald, Germany

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Neuroscience at Ernst-Moritz-Arndt University of Greifswald

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Neuroscience at Ernst-Moritz-Arndt University of Greifswald

The Neuroscience Group at the Medical Faculty of the University of Greifswald promotes interdisciplinary investigations from the level of gene expression in single neurons to imaging of localized regions of the human brain and neurorehabilitation. Ongoing studies encompass: behavioral neuroscience; neurorehabilitation; functional neuroimaging and sensorimotor integration; molecular neurophysiology; molecular and cellular mechanisms underyling recovery of brain tissue and function after stroke; adult brain neurogenesis and tissue regeneration.

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GREIFSWALD

Improvement of the Research Competitiveness in Neuroscience at Ernst-Moritz-Arndt University of Greifswald

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Welcome to Greifswald!

Aurel Popa-Wagner,
Project Coordinator

Christof Kessler,
Clinic Director

Christine Pöhlke,
Workshop Manager

Dear Participant at the Workshop „Adult Brain Regeneration after Injuries", Welcome to Greifswald, once an influential religious centre and a member in the Hanseatic League, today a vivid University town at the beautiful shore of the Baltic Sea. The Ernst-Moritz-Arndt University, one of the oldest universities in Germany, and the University Hospital established a climate of collaborative research which is strongly supported by the European Union which is committed to improve the research capacity of our neuroscience group.

We are indeed very pleased that you have joined us for our first workshop focused on Adult Brain Regeneration after Injuries. During the next three days, we will get insights into basic mechanisms of neuronal de- and regeneration after brain lesioning, including a special session devoted to brain imaging. And there will be ample time for a small poster presentation and fruitful discussions, too.

We also welcome our sponsors and exhibitors who helped us with this event.

Enjoy your time in Greifswald.

Aurel Popa-Wagner, Christof Kessler and Christine Pöhlke (Organizing committee)

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Program

All talks in the university library, lecture hall.

Thursday, March 25,16:45

Welcome:	Heyo Kroemer, Dean of Medical Faculty, Ernst-Moritz-Arndt-University Aurel Popa-Wagner
17:00 - 18:00	Keynote Lecture Glial cells generate neurons – new approaches to neuronal repair Magdalena Goetz, Munich
18:00 – 18:45	bHLH proteins and cellular differentiation in the adult central nervous system Olivier Raineteau, Zurich
20:00	Dinner at „Alter Fritz“

Friday, March 26.

Session 1:	**Translational stroke research, Chair: Matthias Endres**
9:00 – 9:30	From animal studies to clinical trails – problems and solutions in translational stroke research Jens Minnerup / Wolf Schaebitz, Muenster
9:30 – 10:00	Evaluation of therapeutic and diagnostic procedures using an ovine stroke model Johannes Boltze, Leipzig
10:00 – 10:30	Neuromodulation with pleiotropic and multimodal drugs – future approaches to treatment of neurological disorders Dafin Muresan, Cluj
10:30 – 11:00	Post-stroke depression in a mouse model Matthias Endres, Berlin
11:00 – 11:30	Coffee break

Session 2: Stem cell transplantation, Chair: Zaal Kokaia

11:30 – 12:00 Transplantation of stem cells after experimental stroke in rats
Holger Braun, Magdeburg

12:00 – 12:30 Stem cell transplantation vs. Post-stroke neurogenesis
Zaal Kokaia, Lund

12:30 – 13:30 Lunch break in the conference room of the neurology

13:30 – 14:15 Poster presentation in the foyer of the University Library

14:30 – 15:15 *Special Lecture*
Telomeres and stem cell aging: possible roles in neurodegeneration
Karl Lenhard Rudolph, Ulm

Session 3: Functional relevance of adult hippocampal neurogenesis,
Chair: Nora Abrous

15:30 – 16:15 Adult neurogenesis after postnatal injuries
Georg Kuhn, Gothenburg

16:15 – 16:45 Coffee break

16:45 – 17:30 Functional relevance of adult hippocampal neurogenesis: the influence of spatial learning on neurogenesis
Nora Abrous, Bordeaux

17:30 – 18:15 Qualitative changes in learning after differential regulation of adult hippocampal neurogenesis
Alexander Garthe / Gerd Kempermann, Dresden

18:15 – 19:00 *Special lecture*
Motoneuron pathology: death signalling and therapeutic perspectives
Cédric Raoul, Marseille

20:00 Dinner at „Gasthaus zur Sonne“

Saturday, March 27.

Session 4: Molecular mechanisms of brain degeneration,
Chair: Liliana Minichiello

9:00 – 9:30 Axonal de- and regeneration in the central nervous system
Paul Lingor / Mathias Baehr, Goettingen

9:30 – 10:00 Brain degeneration and regeneration
Ludwig Aigner, Salzburg

10:00 – 10:30 Molecular basis of Neurodegeneration
Liliana Minichiello, Edinburgh

11:00 – 11:30 Coffee break

Session 5: Imaging after injuries, Chair: Adi Mizrahi

11:30 – 12:00	Neuron-glia interactions- imaging dynamics after CNS injuries Frank Kirchhoff, Goettingen
12:00 – 12:30	Becoming a new neuron in the adult brain- insights from live imaging Adi Mizrahi, Jerusalem
12:30 – 13:00	Focus on blood vessels: imaging of vascular structure and function Marc van Zandvoort, Maastricht
13:00	Concluding remarks: Aurel Popa-Wagner
13:30	Farewell lunch
14:30 – 16:00	MARS meeting

Sponsors

Brief Profiles

Adi Mizrahi

Adi Mizrahi is the head of the teaching program in the department of Neurobiology at the Alexander Silberman Inst. of Life Sciences of the Hebrew University of Jerusalem, Israel. Research conducted in the lab investigates how neurons and circuits are maintained and changed in the adult mammalian central nervous system. The work is focused within two primary senses of the rodent brain – olfaction and audition. The goal is to understand how these brain circuits change in the face of the never-ending behavioral demands of the animal. The approach is to use molecular tools to tag and manipulate neurons in combination with live imaging and electrophysiology to readout brain structure and function, in vivo.

Nora Abrous

Nora Abrous is head of the team "Neurogenesis and Pathophysiology" in the Neurocenter Magendie in Bordeaux, France. She obtained Ph.D.s in Neurosciences at the University of Bordeaux. After 2 years of post doc in the laboratory of SB Dunnett (Cambridge, UK) she obtained a tenure track at INSERM. NoraAbrous's primary research interest was the study of neuronal plasticity in the context of grafting embryonic dopaminergic neurons in animal models of Parkinson disease. Then she focused on the property of the adult brain to create new neurons. In particular, she studied role of adult-born neurons in memory processing and in the appearance of age-related memory disorders.

Ludwig Eigner

Ludwig Aigner is the director of the Institute of Molecular Regenerative Medicine, Paracelsus Medical University Salzburg, Austria. His main research topics are the morphological and molecularbiological analysis of axotomy resistent retinal ganglia cells, the role of Smad7 in stem and progenitor cells in the adult brain and the molecular regulation of proliferation and differentiation of retinal progenitor cell populations by TGFbeta.

Johannes Boltze

Johannes Boltze is the leader of the Neurorepair group at the Fraunhofer institute of cell therapy and immunology in Leipzig, Germany. His areas of research interests are ischemic stroke, therapy development, stem cells (adult and fetal, ESCs with limitations), large animal models, stem cell biology, MRI, PET, quality and assurance in preclinical stroke research.

Holger Braun

Holger Braun is a senior scientist at the Leibniz Institute for Neurobiology (IfN) in the projects about neuropharmacology in Magdeburg, Germany. His research interests are stem cells including MSC and iPS; neuronal differentiation under in vitro and in vivo conditions, the role of microglia and T-cells in brain pathologies.

Matthias Endres

Matthias Endres is the director of the Center for Stroke Research Berlin, Germany (Integrated Center for Research and Treatment funded by the BMBF) starting June 2008 and also the Head of the Department of Neurology at the Charité Campus Benjamin Franklin. Endres´ research focus is vascular mechanims of stroke protection, endothelial NO synthase as target for stroke protection (statins, exercise), angiogenesis and vasculogenesis, neurodegeneration and neuroregeneration, neuronal cell cycle, DNA damage and repair and mild ischemia and apoptosis

Frank Kirchhoff

Frank Kirchhoff is a research group leader at the Max Planck Institute for Experimental Medicine since 2000 in Goettingen, Germany. After studying biochemistry in Hannover and receiving his PhD in neurobiology at the University of Heidelberg he finished his Habilitation in 1998. His major research interests are molecular and cellular mechanisms of neuron-glia interactions in the CNS, development of transgenic mouse models to visualize neuronal and glial properties, development of transgenic mouse models to modulate glia function and imaging techniques to study neuronal and glial network activities in situ and in vivo.

Magdalena Gätz

Magdalena Götz is the Chair of Physiological Genomics and Director of the Institute of Stem Cell Research in Munich, Germany.
Her research topics are neural stem cells, mechanisms of adult neurogenesis; patterning, neuronal regeneration after injury; cellular and molecular biology or glial cell types; reaction of glial cells to injury.

Alexander Garthe

Alexander Garthe is a senior scientist in the group of Gerd Kempermann in the Center for Regenerative Therapies in Dresden, Germany. His main focus is the functional contribution of granular cells generated in adults in various hippocampal learning events. Second he examines the mechanism of recruiting in which because of a special activity condition new cells receive the survival signal. His goal is a standard model of coherence of the hippocampus and other brain areas.

Cédric Raoul

Cédric Raoul is the leader of the Avenir-Team « Experimental reiteration of motoneuron disease: from molecular insights to gene therapy approaches » in the Mediterranean Institute of Neurobiology Unit INSERM in Marseille, France.

Georg Kuhn

Georg Kuhn received his PhD from the University of Düsseldorf and his postdoctoral training at the Salk Institute in La Jolla. In 2007 he became Professor for Regenerative Neuroscience at the Center for Brain Repair and Rehabilitation, University of Gothenburg. He has studied basic regulatory mechanisms that control stem cell proliferation and survival in the postnatal and adult brain, including the role of growth factors and other trophic peptides. An important research focus is to define signals and conditions for neuroregeneration with the goal of achieving healthy brain aging and better rehabilitation following neurological diseases. Other aspects of his research include biomaterials for stem cell stimulation and the role of neural stem cells in brain tumor formation.

Paul Lingor

Paul Lingor is a senior scientist in the group of Mathias Baehr in the department of Neurology at the University of Goettingen. His main research interests are primary neuron culturing (mesencephalic and hippocampal), gene silencing in primary cell cultures and oxidative stress in neurodegenerative disorders.

Jens Minnerup

Jens Minnerup is a MD and Scientist in the Department of Neurology, University Muenster, Germany. His main research interests are cerebral ischemia and neuroprotection

Liliana Minichiello

Dr. Liliana Minichiello is a Group Leader at the EMBL, Mouse Biology Unit in Monterotondo, Italy. She has spent the last 15 years working on the biology of neurotrophin receptor tyrosine kinases (Trk receptors) first focusing on their role during the nervous system development then studying their involvement in synaptic plasticity in health and neurological disorders. Her group main aim is to identify the contribution of specific subtypes of neurons or networks to animal behavior by using combinatorial approaches and defined genetic mouse models.

Zaal Kokaia

Zaal Kokaia is the leader of the Stroke Department in RSE in the Lund Strategic Research Center for Stem Cell Biology and Cell Therapy in Lund, Sweden. His main scientific interests are neural stem cell biology, isolation and generation human neural stem cell lines, stem cell transplantation in stroke-damaged brain, post-stroke neurogenesis.

Dafin Muresano

Dafin F. Muresan is Professor of Neurology, Chairman of the Department of Neurology and Vice Dean at the Faculty of Medicine, University CFR Hospital at the University of Medicine and Pharmacy "Iuliu Hatieganu", Cluj-Napoca, Romania. His main research topics are neuroprotection and neuroplasticity after brain injuries.

Olivier Raineteau

Olivier Raineteau leads a Neuromorphology research group in the Brain Research Institute at the University of Zurich, Switzerland. His research interests are studying the pattern of expression and function of bHLH transcription factors in adult neurogenesis, studying the response of defined neural precursor cell populations to injuries/pathologies and the engineering of dominant forms of bHLH transcription factors in order to manipulate neural precursor cell differentiation outside adult neurogenic regions.

Marc van Zandvoort

Marc Zandvoort is the Associate Professor of Microscopic Imaging in the Cardiovascular Research Institute Maastricht (CARIM), Netherlands. His main job is the visualisation of (changes in) blood vessel wall structures during atherosclerosis and of interactions between endothelial cells of the vessel wall and blood cells, both in small and larger vessels. Interactions involve calcium or nitric oxide responses in blood cells and vascular cells. Besides the research within this field, he cooperates with several groups (UM and TUE) in other programs in order to explore and develop new possibilities of the two photon (lifetime) technique.

Karl Lenhard Rudolph

Karl Lenhard Rudolph is the head of the Institute for Molecular Medicine and Max-Planck research group in Stem cell Aging in Ulm, Germany. The main focus of our research is to analyze mechanisms of adult stem cell aging and its contribution to tissue aging at organismal level.

Abstracts

Functional relevance of adult hippocampal neurogenesis: on the influence of spatial learning on neurogenesis
Abrous N

The discovery of a continuous renewal of neurons in adult mammalian brains, in particular in the adult hippocampus, has been a breakthrough in Neuroscience. By virtue of the structure-function relationships, this adult hippocampal neurogenesis has been involved in learning and memory. Supporting this hypothesis, a reciprocal relationship between neurogenesis and memory has been evidenced. On one hand, the rate of neurogenesis determines learning and memory abilities. On the other hand, spatial learning sculpts memory networks by adding and removing new neurons in the DG. One of the requirements for the new neurons in order to process information from these memory networks is the development of extensive dendritic arbors capable of receiving and integrating complex spatio-temporal patterns of synaptic inputs. We will show that spatial learning influences the dendritic morphology of adult-born neurons, an effect dependant of the cognitive demand and NMDA receptors. In conclusion, similarly to the selective stabilization process, neo-networks are sculpted during learning by a tightly regulated selection of newly-born neurons.

Evaluation of therapeutic and diagnostic procedures using an ovine stroke model
Boltze J

Current pre-clinical stroke research has to face a significant problem. Although many therapeutic approaches for regenerative or neuroprotective therapies had been proven successfully in preclinical studies, the vast majority of subsequent clinical trials clearly failed. Although the exact reasons for this dilemma are still unclear, it is a common opinion that the large inter-species differences between rodents and man are at least partly responsible for unsuccessful translation therapeutic concepts. Consequently, leading experts recommend the use of large animal models to evaluate concepts in preclinical trials. As currently available large animal models in stroke research have numerous drawbacks, our group decided to develop a novel ovine model of stroke by middle cerebral artery occlusion (MCAO) which allows: (i) long term observation of treated subjects, (ii) implementation of sophisticated imaging protocols and (iii) the possibility of autologous cell therapies. The talk will describe the development of the model and line out special features, drawbacks and advantageous. It will also give examples for preclinical therapy evaluation for therapeutic concept (bone marrow cell therapy) and a diagnostic procedure (early discrimination between hemorrhage and stroke by transmission ultrasound).

Transplantation of stem cells after experimental stroke in rats
Holger Braun

Transplantation of stem cells has been investigated in the last years as an option for the treatment of stroke.
The outcome of this therapeutic approach is mainly influenced by the fate of grafted cells which includes the survival, migration and functional differentiation. There is a complex interaction between grafted cells and host tissue. Critical parameter for this interaction are the time point of transplantation, the route of delivery, the site of deposition, the nature of grafted cells and the immunological relationship between cells and recipient. We have demonstrated that embryonic stem (ES-) cells can differentiate into functional neurons and astrocytes after transplantation into ischemic rats. ES-cells provide important information about side effects like tumour formation or graft rejection. For clinical purposes, however, they will be substituted by induced pluripotent stem (iPS-)cells, which can be derived from cells of the patient. Mesenchymal stem cells (MSC) represent a further easily accessible source of stem cells for autologous transplantation. Many studies revealed that MSC after transplantation protect ischemic tissue and promote repair processes by secretion of trophic factors. Interestingly, MSC contain sub-populations of cells displaying features common to pluripotent and embryonic stem cells.

Post-stroke depression in a mouse model
Endres M

Post-stroke depression (PSD) is the most frequent neuro-psychiatric complication of stroke, affecting up to 50% of stroke survivors. Moreover, PSD has severe adverse effects on functional recovery and on longer-term survival. Despite its great clinical and therapeutic relevance, PSD remains underresearched. This may be partly due to the fact that suitable animal models are lacking and existing models are poorly characterized. Here, we set out to validate our well-defined stroke paradigm of 30 min middle cerebral artery occlusion (MCAo) in the mouse as a potential model to study pathogenetic mechanisms underlying the development of PSD and how these are impacted by psychopharmacotherapy.

Qualitative changes in learning after differential regulation of adult hippocampal neurogenesis
Garthe A

Despite considerable progress in the last few years the function of new granule cells that are born in the adult hippocampus is still not clear. Picking up predicitions from a theoretical model we found a specific functional relevance of adult neurogenesis for the quality of hippocampal learning.
In the reference memory version of the water maze task suppression of adult neurogenesis caused highly specific deficits. Both the integration of highly similiar spatial configurations as well as relearning after switching the task's specific goal conditions were impaired or improved after reducing or increasing the number of new neurons, respectively. New neurons in the dentate gyrus thus do not seem to be necessary for learning the task in general but for adding flexibility to some “hippocampal” qualitative parameters of learning. It also shows how a careful quantitative analysis of the qualitative aspects of learning reveals even subtle contributions of the relevant brain regions involved.
The differential effects of modulating the numbers of newborn granule cells in the dentate gyrus provide an example on how cellular plasticity can influence higher levels of information processing in the brain.

Neuron-glia interactions – imaging dynamics after CNS injuries
Kirchhoff F

Acute CNS injuries induce fast neuronal and glial cell damage. Secondary injury processes involve activation of different cell types like astroglia, oligodendrocytes and microglial cells. A complex and yet not understood sequence of cellular responses initiate functional recovery after the neurodegeneration process.
We have generated two types of transgenic mouse models which enable us (1) to visualize and follow cellular reactions during de-and regeneration and (2) to perform fate mapping of injury-activated glial cells.
To visualize axons and glial cells in the dorsal columns of the lumbar spinal cord, we used triple-transgenic mice (TgN(Thy1-EYFP)xTgN(GFAP-ECFP)xTgH(CX3CR1-EGFP)) in which axons, astrocytes and microglial cells are labelled by yellow, cyan and green fluorescent proteins, respectively. The same mice were imaged before and after lesioning at the day of injury and at subsequent days for up to three months. The combination of multi-cellular labeling with multiple-time-point imaging allowed for the first time to explore unambiguously the spatio-temporal relationship between the cellular responses in spinal cord injury.
To study the differentiation fate of activated glial cells, we generated transgenic mice with functional complementation of split Cre DNA fragments as detectors of coincident gene activities observed after injury. In these mice N- and C-terminal Cre fragments (NCre and CCre) are targeted by the GFAP and PLP promoter. We could demonstrate that after acute brain trauma oligodendrocyte lineage cells can differentiate into protoplasmic astrocytes. Combination of transgenesis and in vivo imaging is a powerful approach to study brain function in health and disease.

Stem cell transplantation vs. Post-stroke neurogenesis
Kokaia Z

Stroke is a common neurodegenerative disorder and one of the leading causes of death and disability in adult humans. Treatments to support efficient functional recovery in stroke patients are lacking. Cells from different sources have been tested for their ability to reconstruct the forebrain and improve function after transplantation in animals subjected to stroke. The transplanted cells can survive and partly reverse some behavioural deficits. However, the underlying mechanisms are unclear and there is little evidence for neuronal replacement. Recent findings in rodents that stroke leads to increased, long-term generation of neurons from neural stem cells (NSCs) in the subventricular zone, suggest an alternative approach to cell therapy in stroke based on self-repair. The newly formed immature neurons migrate into the damaged area, where they express markers of those mature neurons which died due to ischemic insult. For the development of stem cell therapy for stroke, the immediate goal is to learn much more how to control stem cell proliferation and differentiation into specific phenotypes, induce their integration into existing neural and synaptic circuits, and optimize the functional recovery in animal models closely resembling the human disease.

Adult neurogenesis after postnatal injuries
Kuhn G

New neurons are continually generated in discrete regions of the adult mammalian brain. In order to study the usefulness of this mechanism of brain repair, we applied several lesion paradigms to alter the postnatal brain (i.e. irradiation, hypoxia and hypothyroidism) and study the longterm consequences for the adult brain. This allows us to compare responses at distinct ages as well as responses of the different neurogenesis regions to various pathologies. Moreover, we study cellular and functional improvements in these models using physical exercise.

Axonal de- and regeneration in the CNS
Lingor P

Axonal degeneration, apoptotic cell death as well as an insufficient regenerative potential contribute to dysfunction and disease progression in traumatic and degenerative CNS disorders. A successful restorative approach will therefore have to simultaneously target all of the above mentioned mechanisms. The retino-tectal system is an ideal model for the study of traumatic CNS lesions and we have evaluated therapeutic options addressing different disease-relevant mechanisms using small molecule drugs and viral vectors in vitro and in vivo.
Starting with studies on apoptotic cell death and inhibitory signaling in a singular manner, this talk will demonstrate combinatorial approaches to address both mechanisms. In the optic nerve lesion model this could be achieved by the use of growth factors, pharmacological inhibitors of myelin signaling and AAV vectors expressing pro-regenerative genes.
The second part will elaborate on studies on acute axonal degeneration following traumatic lesion. Using a novel imaging setup, we could visualize the dynamics of axonal degeneration in the living animal and get insight into relevant pathophysiological mechanisms. Calcium influx and autophagy are identified as major therapeutical targets in acute axonal degeneration induced by traumatic lesion.

Molecular basis of Neurodegeneration
Minichiello L

Most of the slowly progressive neurodegenerative disorders are characterized by similar events such as accumulation of aberrant or misfolded proteins, synaptic failure, failure of axonal and dendritic transport etc., which result in deterioration of neurons that affect the normal life of humans. One major problem encountered when studying the molecular basis underlying the pathogenesis of neurodegenerative diseases is distinguishing primary from secondary events. We have concentrated our effort on understanding some molecular basis of neurodegeneration in diseases like Alzheimer' (AD) by generating more precise mouse models. In particular, nerve growth factor (NGF), the founder neurotrophin, has generated great interest as a potential target for the treatment of ageing related neurodegenerative diseases like AD. Nonetheless, the molecular mechanisms by which NGF would regulate such functions are not well understood. We have started to reveal some of these mechanisms, which will be discussed at the meeting.

From Animal Studies to Clinical Trials - Problems and Solutions in Translational Stroke Research
Minnerup J, Wersching H, Ringelstein EB, Schäbitz WR

As widely discussed efficacy of candidate neuroprotectants in animal experiments does not reliably predict efficacy in stroke patients. One reason therefore is the overall low quality of animal experimental stroke studies. It was shown that neglecting quality characteristics in animal studies, such as a random allocation of treatment or a blinded outcome assessment, leads to an overestimation of the efficacy of candidate stroke drugs. This raises the question about the motivation for stroke scientists to include or not to include quality aspects in their experiments. Since publishing of research results in high impact journals is an important incentive for scientists, we analyzed whether study quality is relevant for high impact publishing. Animal experimental stroke studies of drugs recently investigated in clinical phase II/III trials were included in our analysis. We found neither study quality as measured by a quality scale derived from the STAIR recommendations nor particular quality characteristics to be relevant for publication in high impact journals. We therefore propose that important quality characteristics should be indispensably considered in animal stroke research and have to be reported in publications of preclinical stroke studies. In addition, using the example of G-CSF and EPO, we present meta-analyses of experimental stroke studies as a tool to estimate the impact of the study quality on a drugs efficacy. Moreover, we demonstrate that meta-regression analysis is a tool to estimate the therapeutical time-window and the dose-response relationship when singular studies that investigate these important issues are lacking.

Becoming a new neuron in the adult brain - insights from live imaging
Mizrahi A

As widely discussed efficacy of candidate neuroprotectants in animal experiments does not reliably predict efficacy in stroke patients. One reason therefore is the overall low quality of animal experimental stroke studies. It was shown that neglecting quality characteristics in animal studies, such as a random allocation of treatment or a blinded outcome assessment, leads to an overestimation of the efficacy of candidate stroke drugs. This raises the question about the motivation for stroke scientists to include or not to include quality aspects in their experiments. Since publishing of research results in high impact journals is an important incentive for scientists, we analyzed whether study quality is relevant for high impact publishing. Animal experimental stroke studies of drugs recently investigated in clinical phase II/III trials were included in our analysis. We found neither study quality as measured by a quality scale derived from the STAIR recommendations nor particular quality characteristics to be relevant for publication in high impact journals. We therefore propose that important quality characteristics should be indispensably considered in animal stroke research and have to be reported in publications of preclinical stroke studies. In addition, using the example of G-CSF and EPO, we present meta-analyses of experimental stroke studies as a tool to estimate the impact of the study quality on a drugs efficacy. Moreover, we demonstrate that meta-regression analysis is a tool to estimate the therapeutical time-window and the dose-response relationship when singular studies that investigate these important issues are lacking.

Focus on blood vessels: imaging of vascular structure and function
van Zandvoort MAMJ

Two-Photon Microscopy (TPM) combines optical sectioning, penetration depth, subcellular resolution, and reduced photodamage. This enables imaging deep into intact and living tissues that normally forbid proper imaging. We use TPM mostly to study structure and function of blood vessels in various disease processes. During this presentation I will discuss the two-photon technique and give ample examples of its application. I will demonstrate that it enables imaging of vascular details (see figure 1). I will give examples of its application in imaging atherosclerosis in carotid arteries (see figure 2) and plaques and of microvasculature in tumor angiogenesis. This will also demonstrate how it can be applied as a bimodular technique for confirmation of low-resolution non-invasive techniques such as MRI and Ultrasound. Finally, I will give examples of its application in vivo in mice, even in complex systems as fast moving large arteries.

bHLH proteins and cellular differentiation in the adult central nervous system
Raineteau O

Cellular differentiation is a complex multi-steps process involved in the development of the central nervous (CNS), but also in the maintenance of its cellular homeostasis during postnatal life. Adult CNS regions however show striking differences in their capacity for cellular replacement. Whereas this process is very pronounced in some restricted brain regions, i.e. the germinal zones, also called neurogenic regions, it is more limited outside these regions. Identifying the molecular cues explaining these pronounced differences remains a key challenge of regenerative neurosciences.
We are interested in studying the role of a family of transcription factors, the basic-helix-loop-helix (bHLH) proteins, in the control of adult CNS cellular differentiation. I will present our most recent work aiming at understanding the function of these proteins in cellular replacement in and outside adult CNS germinal zones.

Telomeres and stem cell aging: possible roles in neurodegeneration,
Rudolph KL

There is emerging evidence that the function of adult stem cells declines during aging. Telomere shortening represent a cell intrinsic mechanism that can contribute to the accumulation of DNA damage in aging cells. In previous work we have shown that telomere dysfunction induces cell intrinsic checkpoints (Exo1, p21) and environmental alterations that impair the function of adult hematopoietic stem cells. The contribution of DNA damage and telomere dysfunction to neurodegenerative disease remains to be defined. In recent studies, we have seen that telomere dysfunction impairs dentate gyrus neurogenesis and leads to loss of hippocampus CA1 neurons and short-term memory deficits. In contrast, telomere shortening had protective effects in a mouse mode of Alzheimer disease (AD). In APP23 transgenic mice, telomere shortening limited Amyloid-β-plaque formation and the evolution of memory defects. Studies on humans showed a significant increase in DNA damage markers in liquor of AD patients compared to non-AD patients and the number of γH2AX-DNA-damage-foci was increased in neuronal cells of the olfactory bulb of AD patients. However, this increase in DNA damage did not associate with telomere shortening. Together, these data indicate that neuronal accumulation of non-telomeric DNA damage associates with the evolution of AD in humans. The studies in mice indicate that telomere shortening has diverse effects on neurodegeneration impairing adult neurogenesis but protecting from Aβ-plaque pathology and AD progression.

TGF-beta in neurodegeneration and neurogenesis
Aigner L

Chronic neurodegenerative diseases are often associated with disruptions in the reparative potential provided by stem cells in the adult brain. In animal models of Huntingon's Disease (HD), we noticed a significant reduction in hippocampal stem / progenitor cell proliferation. Reduced proliferation was associated with an induction of Smad2 phosphorylation in Sox2 / GFAP positive subgranular zone cells, the presumed neural stem cell population. The presence of phospho-Smad2 corelated with the quiesence of this cell population. Experimental elevation of TGF-beta levels similarly induced Smad2 phosphorylation and caused a cell cylce exit of neural stem / progenitor cells in vitro and in vivo. Our current goal is to block TGF-beta signaling in the neural stem cell niche of the diseased brain with aim to re-enter quiescent neural stem cells into the cell cycle to promote cellular repair in neurodegenerative diseases.

Glial cells generate neurons, Mechanisms of neurogenesis and new approaches to repair
Götz M

Our discovery that radial glial cells are not only support cells for migrating neurons during development, but rather act as progenitor and stem cells themselves, have prompted us to take this approach to the adult brain. In the mammalian brain, neurogenesis comes to a permanent end in most regions and radial glial cells disappear in most brain regions. Therefore there is virtually no replacement of neurons lost by acute injury or in neurodegenerative diseases.
To overcome this problem, we examine on the one hand glial cell types and their molecular specification in the two regions where adult neurogenesis continues even in the mammalian brain. On the other hand we examine how glial cells in the normal adult brain parenchyma that fail to generate neurons actually differ from those that can generate neurons during development or in adulthood with the aim to understand and overcome the reasons for failure of neurogenesis after neuronal loss.
Towards this aim we developed a method to prospectively isolate adult neural stem cells in order to determine their identity and expression profile in comparison to radial glial cells during development and other non-neurogenic glial cells in the adult brain. This led us to the discovery of novel mechanisms that regulate neurogenesis and neuronal subtype specification in regions of adult neurogenesis.
Examination of glial cells outside the neurogenic regions in the adult brain revealed a striking dedifferentiation of astroglial cells reacting to injury, including their reacquisition of stem cell properties. However, in vivo they are inhibited in regard to neurogenesis and driven towards the generation of glial cells. This bias towards glial fate can be overcome by forced expression of neurogenic fate determinants that is sufficient to drive even differentiated or non-dividing glial cells, also of adult human origin, towards the generation of fully functional neurons. These exciting new data will be discussed within the general concept of understanding neurogenesis and utilizing these mechanisms for reinstructing neurogenesis when it is needed.

Motoneuron pathology: death receptor signalling and therapeutic perspectives
Raoul C

Amyotrophic lateral sclerosis (ALS) is a fatal paralytic disorder that primarily affects upper and lower motoneurons. Dominant mutation in Sod1 gene is the most prominent cause of inherited ALS. Accumulating evidence suggests that mutant SOD1 damages non-neuronal cells to release factors selectively toxic for motoneurons. The precise mechanisms responsible for the selective vulnerability of motoneurons remain largely unknown, impeding therefore the development of pertinent therapies.
Death pathways restricted to specific classes of neurons might explain the selectivity of neuronal loss in neurodegenerative diseases, such as ALS. We previously unravelled a motoneuron-restricted death pathway triggered by the Fas death receptor. Involvement of Fas death signalling has been documented in ALS mice and signs of activation of the pathway have also been reported in sporadic patients. However, Fas death pathway may not be responsible for the loss of all motoneurons, suggesting that other death pathways might be implicated. Recently, we discovered a novel motoneuron-restricted pathway triggered by the activation of lymphotoxin-β receptor (LT-βR) by LIGHT. We show that LIGHT can act in concert with proinflammatory cytokines to trigger death of motoneurons following an unconventional signalling cascade. Interestingly, signs of activation of these pathways have been documented in ALS mice and sporadic patients. We proposed that motoneuron-selective death pathways synergised by inflammatory cytokine might be implicated in non-cell-autonomous neurotoxic effects of mutant SOD1 and represent therefore potential therapeutic targets.
Delivery of therapeutic instruction to both upper and lower motoneurons remains the most challenging issue of therapies for ALS. Viral-based gene therapy, by allowing long-lasting delivery of therapeutic information, fits to the chronic aspect of the disease. We and others have validated the proof-of-concept of gene therapy intervention as a promising therapeutic approach for ALS. Our goal is to use gene therapy, or alternative approaches such as continuous delivery of molecules into the cerebrospinalfluid, to evaluate the therapeutic relevance of potential candidates that emerge from our research.

Poster Abstracts

Long–term hypothermia reduces the ANXA1 levels in aged rat brains after cerebral ischemia,
Buga AM, Joseph C, Balseanu A, Popa-Wagner A

In aged humans, stroke is a major cause of disability for which no neuroprotective measures are available. A major goal of the stroke therapy is to reduce inflammation but treatments aimed at reducing inflammation using anti-inflammatory drugs have been met with limited success. A viable alternative to conventional drug-based neuroprotective therapies is brain/body cooling, or hypothermia. In animal studies of focal ischemia, short-term hypothermia consistently reduces infarct size. Nevertheless, efficient neuroprotection requires long-term, regulated lowering of whole body temperature. Previously we have reported that post-stroke exposure to hydrogen sulfide is an efficacious method to lower whole body temperature and confers neuroprotection in aged animals. In the present study using DNA macroarrays and western blotting we report for the first time, that annexin A1 (ANXA1; 346 aa long; 37kDa protein) was among the downregulated proteins in the post-ischemic aged rat brain after long-term hypothermia. The results were confirmed by semi quantitative real-time PCR. Double immunostaining with microglia/macrophagic markers show that ANXA1 co-localized with the macrophagic marker, ED1. Since annexin 1 is produced by microglia/macrophages we conclude that long-term gaseous hypothermia is an efficient method to reduce neuroinflammation which is thought to be a detrimental factor in a range of neurological disorders.

Effects of Granulocyte-Colony Stimulating Factor after stroke in aged rats,
Popa-Wagner A, Stöcker K, Balseanu A, Diederich K, Minnerup J, Schäbitz WR

Background and purpose: In aged humans, stroke is a major cause of disability for which no neuroprotective measures are available. G-CSF, a member of the cytokine family of growth factors, promotes brain neurogenesis and improves functional outcome after stroke in the young animal. Here, we test the hypothesis that G-CSF provides restorative therapeutic benefit to the aged animal.
Methods: Focal cerebral ischemia was produced by reversible occlusion of the right middle cerebral artery in 19-20 month-old male Sprague Dawley rats. One hour after stroke, the aged rats were treated daily with 15μg/kg G-CSF and for 15 days in total. Rats were behaviourally tested and the brains analyzed after 28 days post-stroke.
Results: G-CSF treatment had a beneficial effect on survival rate, functional recovery of motor function (rotating pole, inclined plane) and working memory (radial maze). Except the rotating pole where the treatment was beneficial during the 4-week testing period, the beneficial effects of treatment in other tests was generally limited to the first 12 days post-stroke. At cellular level, the G-CSF treatment increased the number of proliferating cells in the SVZ and the dentate gyrus and increased the number of new born neurons in the SVZ, ipsilateral to the lesion.
Conclusions: These results suggests that the G-CSF treatment in aged rats has primarily a survival enhancing capacity and a beneficial effect on functional outcome most likely via supportive cellular processes such as neurogenesis. Further studies are required to optimize G-CSF treatment schedule in aged subjects.

Long-term hypothermia using H2S greatly reduces infarct volume in aged rats after focal ischemia,
Joseph C, Vintilescu RE, Buga AM, Kessler C and Popa-Wagner A

In aged humans, stroke is a major cause of disability for which no neuroprotective measures are available. A viable alternative to conventional drug-based neuroprotective therapies is brain/body cooling, or hypothermia. In animal studies of focal ischemia, short-term hypothermia consistently reduces infarct size. Nevertheless, efficient neuroprotection requires long-term, regulated lowering of whole body temperature.
Focal cerebral ischemia was produced by reversible occlusion of the right middle cerebral artery in 17 month-old male Sprague Dawley rats. After stroke, the aged rats were exposed for 2 days to a mixture of air and a mild inhibitor of oxidative phosphorylation, hydrogen sulfide (H2S), which resulted in sustained, deep hypothermia (30.8 ± 0.7°C). Long-term hypothermia led to a 50% reduction in infarct size with a concomitant reduction in the number of phagocytic cells. At the transcription level, hypothermia caused a reduction in the mRNA coding for caspase 12, NF-kappa B and grp78 in the peri-infarcted region, suggesting an overall decrease in the transcriptional activity related to inflammation and apoptosis. By proteomics we identified Annexin 1 whose expression was increased in the infarcted area of hypothermic rats. Behaviorally, hypothermia was associated with better performance on tests that require complex sensorimotor skills, in the absence of obvious neurological deficits or physiological side-effects, in aged rats.
Conclusions: Prolonged, H2S-induced hypothermia is a simple and efficacious method to limit damage inflicted by stroke in aged rats.

Improved Functional Recovery after Stroke through Enhancement of the Endogenous Neurogenesis in Aged Rats, Pöhlke C, Mostertz J, Kaiser J, Buga AM, Balseanu A, Anklam J, Homuth G, Popa-Wagner A

Background: In adult rats the endogenous neurogenesis is maintained in the subventricular zone and the dentate gyrus of the hippocampus and could be used to improve post-stroke outcome. Here we explored the hypothesis that stimulations of endogenous neurogenesis before or after stroke in aged rats, which are known to be more severely affected by stroke than young rats, may improve recuperation after stroke.
Methods: Stroke was induced by middle cerebral artery occlusion (MCAO) in aged rats and neurogenesis was stimulated at different time points using neurogenesis enhancer pentylentetrazole. After MCAO, rats were behaviourally tested for 7 weeks. After 7 weeks, global gene expression analyses of the periinfarcted region was done.
Results and conclusion: Behavioural testing by T-Maze (labyrinth) and inclined plane tests showed improved rehabilitation in rats with a stimulated neurogenesis after stroke. Immunohistochemical stainings for doublecortin, a marker of neurogenesis, showed increased expression in rats stimulated after, and to a lesser extent before stroke. Global gene expression analysis revealed a significant change of genes involved inflammation and neurogenesis in aged rats. Our results indicate that stimulation of neurogenesis at 4 wks before stroke does not improve post-stroke outcome. In contrast, stimulation of post-stroke neurogenesis is beneficial for behavioural recovery of aged rats.

Three-dimensional assessment of cerebral microvasculature and gliosis in a rat model of ischemic stroke
Pirici D, Mogoanta L, Margaritescu O, Tudorica V, Pop OT

Reactive astrocytes occur as a general response of the brain tissue to a variety of conditions. Particularly for ischemic strokes, this proliferation has been deemed responsible for both the isolation of the necrotic tissue and the formation of a glial scar that interferes with the migration of newly formed neurons attempting to re-colonize the lesional site. Although on rat models with medial cerebral artery occlusion (MCAO) it has been showed that glial scar formation increases in aged animals, the actual interactions between the newly formed astrocytes and the rest of the neuropil are not yet completely explored.
On a rat model of MCAO, and utilizing triple immunohistochemistry to detect astrocytes (GFAP), proliferating cell nuclei (ki-67) and vascular endothelium (von Willebrand factor) on large series of serial sections, we performed here high resolution three-dimensional reconstructions for complete infarct, peri-infarct and contralateral areas on rats of different ages, and at different time points after the ischemic event.
Three-dimensional stacks showed that the highest GFAP immunoreactive astrocytes surrounded vessels with decreased volumetric ratios compared to penumbra and contralateral regions. This effect was even more obvious in aged animals, and was found to be modulated also by the time elapsed from the ischemic event itself. Although this reduction was most intense in the vicinity of necrotic areas, the brains of the MCAO rats showed brain-wide decreased astrocytic-vascular indexes compared to control animals.
The present study demonstrates that impaired vascular perfusion induces an early increase in GFAP immunoreactivity, and that reactive astrocytes may contribute later on to a further reduction of the local cerebral blood flow. Also, the present three-dimensional quantitative imaging analysis based on serial sections (with optimized processing algorithms) offers better tissue coverage compared to confocal methods for high resolution brain-wide analysis on MCAO models.

A case report of intracerebral hemorrhage with prominent T lymphocyte infiltration
Mogoanta L, Pirici I, Tudorica V, Coconu M, Pop OT

Intracerebral hemorrhage represents an aggressive form of stroke that leads to extensive disabilities and also a form for which there is only very limited treatment available. While for ischemic stroke animal models are available to mimic the pathogenic mechanisms that underlie this type of lesion, currently there are only a few current models for the hemorrhagic variant.
In the present study we aimed to asses the immunohistochemical profile of cerebral tissue obtained from a 61 years old male patient, known with hypertension, obliterant arteriopathies of the lower extremities and who was admitted with an intracerebral hemorrhage of the deep right temporal lobe. The patient died 12 hours later.
For this study we used markers for astrocytes (GFAP), for macrophages (CD68), for vascular endothelium (CD31 and FVIII), and markers of inflammation (CD20cy and CD3 for B and T lymphocyte populations).
Together with the classically injury- and age –related changes as foamy macrophages, ischemic neurons, astrogliosis, microgliosis and microglial iron deposition, we identified a strong autoimmune response constituted mostly of T lymphocytes and present only around a morphologically apparent intact blood brain barrier.
Around the hemorrhagic core there are thus important immune-mediated changes in the vascular endothelium and in the glial compartment, changes that can modulate the further development of cerebral edema around hemorrhagic sites, thus contributing to the progression of the cerebral lesions.
We consider that such systematic studies can be useful in both understanding some of the pathogenic mechanisms of the disease and in the implementation of new therapeutic strategies.

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