UNIVERSITÄT OSNABRÜCK

GBM

8th Westerberger Herbsttagung
together with the
Meeting of the GBM study group "Molecular Neurobiology"

Perspectives of Molecular Neurobiology: From Single Molecules to Systems

September 22-24, 2016

Bohnenkamp-Haus,
Botanical Garden of the University of Osnabrück

Jörg-Walter Bartsch
(Marburg)

Mike Karl
(Dresden)

Hans-Georg Breitinger
(Cairo, Egypt)

Karl-Wilhelm Koch
(Oldenburg)

Benjamin Cooper
(Göttingen)

Dieter Langosch
(München)

Robert Fledrich
(Göttingen)

Hans Gerd Nothwang
(Oldenburg)

Johannes Hirrlinger
(Leipzig)

Marco Rust
(Marburg)

Jörg Isensee
(Köln)

Konstanze Winklhofer
(Bochum)

Christoph Kaether
(Jena)

Geraldine Zimmer
(Jena)

For further information and registration, visit https://www.wht-gbm2016-uni-osnabrueck.de/ *Contact: brandt@biologie.uni-osnabrueck.de*

Sponsored by:Gesellschaft für Biochemie und Molekularbiologie e.V., Sonderforschungsbereich 944, Osnabrücker Universitätsgesellschaft e.V., Nikon GmbH, Serva Electrophoresis GmbH, Diagonal GmbH & Co. KG, Carl Roth GmbH, Macherey-Nagel GmbH & Co. KG, Ewald Innovationstechnik GmbH, Eppendorf AG, Ewald Innovationstechnik GmbH, Altromin Spezialfutter GmbH & Co. KG, Fisher Scientific GmbH, Sarstedt AG & Co., Neurowissenschaftliche Gesellschaft

Welcome Letter

Osnabrück, September 2016

Dear Collegues:

It is our pleasure to welcome you at the **“8th Westerberg Herbsttagung”** on the Science Campus of the University of Osnabrück. For the second time in its history, the “Westerberger Herbsttagung” meeting is organized **together with the Study Group “Molecular Neurobiology”** of the GBM (Gesellschaft für Biochemie und Molekularbiologie). The Study Group was founded in 1977 as one of the first, has more than 500 members, and defines itself as a population of scientists with the aim to approach the function of the nervous system on a molecular level.

This year, the Meeting is entitled **"Perspectives of Molecular Neurobiology: From Single Molecules to Systems"** and the aim is to present new results as lectures, poster preview talks and posters, to facilitate contacts between established and young researchers, and to exchange information and material on all levels. A special focus of the Study Group as well as of the biyearly “Westerberger Herbsttagung” meetings is to promote young researchers. We hope to achieve this by inviting both, established researchers and young scientists, from all over Germany and neighboring countries. In addition, we are putting a special emphasis on poster presentations including attractive poster prize awards. In the tradition of our “Westerberger Herbsttagung” meetings we try our best to provide a familiar and informal atmosphere, which can be also witnessed from the booklets of the previous meetings (available at http://www.neurobiologie.uni-osnabrueck.de).

In the City of Peace, **Osnabrück**, the history is apparent on every corner, with the remains of the old city wall and its watchtowers, the castle dating from the 17th century and the town hall where the Peace of Westphalia was declared in 1648. The young **University of Osnabrück**, which was founded in 1973, has about 13,000 students with more than 1500 students on the Science Campus, which is located in the "Westerberg" area.

We are happy to welcome all of you in Osnabrück and look forward to an exciting meeting.

Roland Brandt
(speaker of the GBM study group “Molecular Neurobiology”,
on behalf of the organizing committee)

Program: “8. Westerberger Herbsttagung” together with the “Meeting of the GBM Study group ‘Molecular Neurobiology’”

“Perspectives of Molecular Neurobiology: From Single Molecules to Systems”

Thursday, September 22, 2016

From 14:00	Registration
14:30 – 15:00	Opening of the Meeting and welcome addresses (Roland Brandt, Department of Neurobiology, and Susanne Menzel, designated Vice-president for Research and Career Development, University of Osnabrück)
	Session I: Molecules (Chair: Lidia Bakota)
15:00 – 15:30	Lecture 1: Benjamin Cooper (Max-Planck-Institute of Experimental Medicine, Göttingen) „Molecular and morphological correlates of vesicle priming in neurosecretory cells”
15:30 – 16:00	Lecture 2: Hans-Georg Breitinger (German University in Cairo, Egypt) “Glucose and related drugs as positive modulators of neuronal ion channel receptors”
16:00 - 16:30	Coffee break
16:30 – 17:00	Lecture 3: Dieter Langosch (Technical University of Munich) „Model transmembrane peptides promote membrane fusion via lipid acyl chain protrusion”
17:00 – 17:30	Lecture 4: Jörg Isensee (University Medicine, Köln) „PKA-RIIbeta, an endogenous readout to study subgroup-specific GPCR signaling in nociceptive neurons“
17:30 – 17:45	Poster Preview 1: Dana Elbers, Alexander Scholten, Karl-Wilhelm Koch, “Cone-dominant visual system to investigate interaction of recoverin isoforms and G-protein-coupled receptor kinase”
17:45 – 18:00	Poster Preview 2: N. Helge Meyer, Tobias Madl, Klaus Zangger and Fabio Falsone, “MOAG-4/SERF: a direct modifier of amyloid assembly in neurodegenerative diseases”
18:00	Dinner Buffet
19:00	**Öffentlicher Vortrag** (Chair: Roland Brandt)
	Hans-Georg Breitinger (German University in Cairo, Egypt) „Impressionen von Forschung und Lehre in Ägypten“
20:00	Get together with drinks and live music ("Flaw and Order")

\cont.

Friday, September 23, 2016

	Session II: Networks part I (Chair: Jörg-Walter Bartsch)
09:00 - 09:30	Lecture 5: Christoph Kaether (Leibniz Institute on Aging, Jena) „Function of the sorting receptor Rer1 in purkinje cells”
09:30 - 10:00	Lecture 6: Konstanze Winklhofer (Ruhr-University Bochum) "Ubiquitin signaling in neurodegenerative diseases“
10:00 - 10:15	Poster Preview 3: Johannes F.W. Greiner, Janine Müller, Christian Kaltschmidt and Barbara Kaltschmidt, “Adult nasal stem cells – applicability for cell replacement therapy of neurodegenerative diseases”
10:15 – 10:45	Coffee break
10:45 – 11:15	Lecture 7: Marco Rust (Philipps University of Marburg) „Novel functions for ADF/cofilin in excitatory synapses - lessons from gene-targeted mice”
11:15 – 11:45	Lecture 8: Geraldine Zimmer (Jena University Hospital) “DNMT1 controls migratory shape and dynamics of immature cortical interneurons”
11:45 – 12:00	Poster Preview 4: Carsten Slotta, Peter Heimann, Patrick Lüningschrör, Barbara Kaltschmidt and Christian Kaltschmidt, “Loss of Schwann cell autophagy might contribute to a late onset motoneuron disease in Plekhg5 deficient mice”
12:00 – 16:00	Lunch buffet and Poster viewing (Poster presentation: 13-14:30 for even numbers; 14:30-16 for odd numbers)
	Session III: Networks part II (Chair: Gunnar Jeserich)
16:00 - 16:30	Lecture 9: Karl-Wilhelm Koch (University of Oldenburg) "Protein and signaling networks in vertebrate photoreceptor cells"
16:30 – 16:45	Poster Preview 5: Abdala M. Ussif, Roland Brandt, Lidia Bakota and Gunnar Jeserich, “Enhanced synaptic transmission in mice with homozygous tau deletion”
16:45 - 17:15	Coffee break
17:15 - 17:45	Lecture 10: Jörg-Walter Bartsch (Philipps University of Marburg) „Extracellular proteolysis shaping the brain microenvironment“
17:45 - 18:00	Award of Poster Prizes
18:00 – 18:30	Business Meeting
From 18:30	Dinner buffet and social program (night watch and city tours start at 20:30 at the old city hall)

\cont.

Saturday, September 24, 2016

Session IV: Systems (Chair: Roland Brandt)

09:00 - 09:30	Lecture 11: Johannes Hirrlinger (University of Leipzig) ”Brain energy metabolism assessed by genetically encoded sensors for metabolites”
09:30 - 10:00	Lecture 12: Mike Karl (German Center for Neurodegenerative Diseases, Dresden) „Deciphering limits of retinal regeneration – from mice to human”
10:00 - 10:30	Coffee break
10:30 - 11:00	Lecture 13: Hans Gerd Nothwang (University of Oldenburg) „miRNA-96 is required for normal development of the auditory hindbrain”
11:00 – 11:30	Lecture 14: Robert Fledrich (Max-Planck-Institute of Experimental Medicine, Göttingen) „The role of Neuregulin-1 in peripheral nervous system disorders”
11:30	Closing remarks and end of meeting

Abstracts: Lectures

Molecular and Morphological Correlates of Vesicle Priming in Neurosecretory Cells

Benjamin Cooper, PhD

Dept. Molecular Neurobiology, Max Planck Institute of Experimental Medicine, 37073 Göttingen

Excitation-secretion coupling is a sub-millisecond process that entails the transduction of an electrical stimulus into synaptic vesicle fusion and the release of neurotransmitter cargo into the synaptic cleft. Before fusion, synaptic vesicles are required to physically dock with the presynaptic active zone membrane and to undergo a functional priming step that renders them fusion-competent. Complex molecular interactions at the active zone provide tight spatial and temporal control of stimulus-evoked transmitter release and genetic mutants lacking key components of the presynaptic release machinery exhibit severe functional deficits. It has, however, proved experimentally challenging to dissect the molecular requirements for vesicle-membrane attachment and to relate the morphological nature of presynaptic vesicles with specific functional and dysfunctional synaptic states using conventional electron microscopy approaches.
To investigate the molecular mechanisms of synaptic vesicle docking in two morphologically and functionally distinct model synapses, namely hippocampal spine synapses and retinal ribbon synapses, we have exploited an experimental approach combining mouse genetics, rapid cryo-fixation, automated freeze-substitution, and 3D electron tomography to resolve the ultrastructural architecture and spatial organization of synaptic vesicles in knock-out mice lacking key presynaptic proteins. In hippocampal synapses, we have exposed previously indistinguishable, sequential steps in synaptic vesicle active zone recruitment (tethering) and membrane-attachment (docking), and found that vesicle docking requires Munc13/CAPS family priming proteins and all three neuronal SNAREs. Our data indicate that in conventional synapses membrane-attached vesicles comprise the readily-releasable pool of fusion-competent vesicles, and that synaptic vesicle docking, priming, and trans-SNARE complex assembly are the respective morphological, functional, and molecular manifestations of the same process, which operates downstream of vesicle tethering by active zone components. In contrast to hippocampal synapses, our ultrastructural analysis of photoreceptor ribbon synapses revealed that genetic deletion of Munc13 priming proteins has only subtle consequences on synaptic signaling in the mouse retina and does not prevent synaptic vesicle membrane-attachment at ribbon release sites. These data indicate that ribbon synapses likely rely on alternative molecular priming mechanisms to render vesicles fusion-competent and to support their unique mode of transmitter release.

Glucose and related drugs as positive modulators of neuronal ion channel receptors

Hans-Georg Breitinger, Ulrike Breitinger

Department of Biochemistry, German University in Cairo, New Cairo, Egypt

Ligand-gated ion channels are the principle mediators of fast synaptic transmission in the central and peripheral nervous system and at the neuromuscular junction. Upon binding of the agonist, an intrinsic ion channel opens, allowing the flux of ions across the cell membrane thus generating or abolishing electrical signals. The inhibitory glycine receptor is a major mediator of inhibitory synaptic transmission in the spinal cord, brainstem, and higher brain centres. Glycine receptors control muscle tone, reflexes and voluntary movement as well as higher neuronal processes in the human retina, cochlea and hippocampus.
We have identified glucose and related saccharides as positive modulators of glycinergic neurotransmission. In the presence of saccharides, the half-maximal concentration (EC_{50}) for receptor activation was reduced 4-5 – fold. Saccharides stabilize a high-activity state of the receptor. All saccharides were active in the physiological concentration range between 5 mM and 20 mM.
Glucose and related sugars were positive modulators of alpha1, alpha1beta, and alpha3 glycine receptors, i.e. those receptor species that are found in human spinal cord and brainstem. Since alpha3 glycine receptors participate in nociceptive transmission, part of the analgesic effects of glucose may be mediated by glycine receptor overactivation.
Kinetics of sugar modulation are consistent with those of protein glycation. A putative glycation site was identified from structure modeling and mutagenesis studies.
Our data suggest that glucose levels are a critical parameter in experimental design and modulation of neuronal transmission may be considered in the pathology of diabetes and other diseases where blood glucose levels escape control.

References:
[1] Breitinger U, Raafat KM, Breitinger HG (2015) Glucose is a positive modulator for the activation of human recombinant glycine receptors. J. Neurochem. 134, 1055-1066.
[2] Breitinger U, Breitinger HG (2016) Augmentation of glycine receptor alpha3 currents suggests a mechanism for glucose-mediated analgesia. Neuroscience Letters 612, 110-115.
[3] Breitinger U, Sticht H, Breitinger HG (2016) Modulation of Recombinant Human alpha1 Glycine Receptors by Mono- and Disaccharides: A Kinetic Study. ACS Chem Neurosci. 7, 1077-1087.

Corresponding author: ulrike.breitinger@guc.edu.eg

Model transmembrane peptides promote membrane fusion via lipid acyl chain protrusion

Dieter Langosch

Technische Universität München, Lehrstuhl Chemie der Biopolymere, Weihenstephaner Berg 3, 85354 Freising, Germany

We have previously designed a series of model transmembrane helices that mimic SNARE transmembrane domains in that they drive liposome fusion depending on their conformational backbone flexibility. A critical question is how flexibility affects the peptide/lipid interactions promoting bilayer fusion. Recent computational studies in the literature suggest that natural fusogenic proteins initiate membrane fusion by inducing lipid acyl chain exposure at the site of membrane contact. Here, we provide experimental support of this hypothesis by relating the fusogenic activity of our model transmembrane helices to their ability to induce lipid acyl chain exposure. To this end, we have developed a novel assay where the exposure of lipid acyl chains to the aqueous phase is determined by mass spectrometry. The results suggest that the backbone flexibility of a transmembrane helix is connected to its fusogenicity by its ability to facilitate lipid acyl chain exposure.

PKA-RIIβ, an endogenous readout to study subgroup-specific GPCR signaling in nociceptive neurons

Jörg Isensee

Uniklinink Köln, Experimental Anesthesiology and Pain Research (Prof. Tim Hucho), Robert Koch Str. 10, 50931 Cologne, Germany

Nociceptive sensory neurons detect noxious stimuli in the periphery and transmit signals to the dorsal horn of the spinal cord. Upon tissue injury, they respond to various inflammatory mediators reducing their activation threshold (pro-nociceptive sensitization). Long-term exposure to these mediators, however, induces endogenous anti-nociceptive mechanisms such as the release of endomorphins to dampen pro-nociceptive signaling.
We recently established a High content screening microscopy approach to analyze sensitization signaling in nociceptive subgroups with single cell resolution. This method revealed the regulatory RIIβ subunit of protein kinase A type II (PKA-II) as a first integrative marker expressed in all nociceptive subgroups, which allowed to quantify endogenous PKA-II activity using a novel assay based on antibodies detecting a phospho-epitope of RII inhibitory sites [1 2].
This talk will focus on the balance of pro- and antinociceptive GPCR signaling in a mouse model of congenital pain insensitivity (CIP) due to loss of the voltage-gated sodium channel $Na_v1.7$. Recent findings demonstrate that CIP involves the upregulation of endogenous opioids in mice and humans [3], but the impact on cellular sensitization signaling remained unknown. Contrary to expected opioid receptor desensitization and upregulation of counterbalancing pro-nociceptive signaling, we show that loss of $Na_v1.7$ rather decreases the the pro-nociceptive serotonergic 5-HT_4 receptor and its intracellular mediator, PKA-RIIβ. Simultaneously, the efficacy of anti-nociceptive opioid signaling was increased also leading to more efficient inhibition of tetrodotoxin resistant currents. Thus $Na_v1.7$ controls the intracellular homeostatic interplay of pro- and anti-nociceptive signaling in a synergistic and long-lasting manner contributing to lifelong endogenous analgesia.

References

1 Isensee, J. *et al.* Pain modulators regulate the dynamics of PKA-RII phosphorylation in subgroups of sensory neurons. *J Cell Sci* **127**, 216-229, doi:10.1242/jcs.136580 (2014).
2 Isensee, J. *et al.* Subgroup-Elimination Transcriptomics Identifies Signaling Proteins that Define Subclasses of TRPV1-Positive Neurons and a Novel Paracrine Circuit. *PLoS One* **9**, e115731, doi:10.1371/journal.pone.0115731 (2014).
3 Minett, M. S. *et al.* Endogenous opioids contribute to insensitivity to pain in humans and mice lacking sodium channel Nav1.7. *Nat Commun* **6**, 8967, doi:10.1038/ncomms9967 (2015).

Function of the sorting receptor Rer1 in Purkinje cells

Christina Valkova[1], Lutz Liebmann[2], Andreas Krämer[1], Christian A. Hübner[2] and Christoph Kaether[1#]

[1]Leibniz Institut für Alternsforschung-Fritz Lipmann Institut, 07743 Jena, Germany,
[2]Institut für Humangenetik, Universitätsklinikum Jena, Friedrich-Schiller-Universität Jena, Germany

Rer1 is a sorting receptor in the early secretory pathway that controls the assembly and the cell surface transport of selected multimeric membrane protein complexes. Mice with a Purkinje cell (PC) specific deletion of Rer1 showed normal polarization and differentiation of PCs and normal development of the cerebellum. However, PC-specific loss of Rer1 led to age-dependent motor deficits in beam walk, ladder climbing and gait. Analysis of brain sections revealed a specific degeneration of PCs in the anterior cerebellar lobe in old animals. Electrophysiological recordings demonstrated strongly reduced capacities of PCs to generate the constant firing rates essential for normal function. Measurements of resurgent currents indicated decreased surface densities of voltage-gated sodium channels (Na_v), but not changes in individual channels. Western Blot of mice with a CNS-specific Rer1-deletion demonstrated a strong down-regulation of the mature forms of $Na_v1.6$ and 1.1 in the absence of Rer1, whereas protein levels of the related $Ca_v2.1$ channel were not affected. The data suggest that in PCs Rer1 controls the trafficking of $Na_v1.1$ and 1.6, the principal sodium channels responsible for the neuronal excitability.

Ubiquitin Signaling in Neurodegenerative Diseases

Konstanze F. Winklhofer

Ruhr-University Bochum

A common feature of neurodegenerative diseases is the prominent role of aging in the diseases pathogenesis. Aging cells are characterized by a decrease in the efficiency of cellular quality control and stress reponse systems. Indeed, there is increasing evidence that the fidelity of cellular machineries implicated in the removal of damaged and dysfunctional proteins, such as the ubiquitin/proteasome or the autophagosomal/lysosomal system, are compromised in aged individuals. Moreover, quality control systems like the chaperone network, which prevents the generation and accumulation of misfolded protein species, are not adequately up-regulated during aging. As a consequence, there is an increase in proteotoxic stress, which seems to be particularly detrimental to postmitotic neurons.
We are interested in the role of ubiquitination as a highly versatile posttranslational modification in regulating cellular quality control and stress response pathways. Ubiquitin can be attached to substrate proteins as a single moiety or as polymeric chain. Depending on the type of ubiquitin linkage, polyubiquitin chains adopt various conformations and thereby mediate different cellular functions. Degradative as well as non degradative functions of ubiquitination in models of neurodegenerative diseases will be discussed.

Novel functions for ADF/cofilin in excitatory synapses - lessons from gene-targeted mice

Marco Rust

Philipps University of Marburg

Actin filaments (F-actin) are the major structural component of excitatory synapses. In excitatory synapses, F-actin is enriched in presynaptic terminals and in postsynaptic dendritic spines, and actin dynamics – the spatiotemporally controlled assembly and disassembly of F-actin – have been implicated in pre- and postsynaptic physiology, additionally to their function in synapse morphology. Hence, actin binding proteins that control actin dynamics have moved into the focus as regulators of synapse morphology and physiology. Actin depolymerizing proteins of the ADF/cofilin family are important regulators of actin dynamics, and several recent studies highlighted the relevance of cofilin 1 for dendritic spine morphology, trafficking of postsynaptic glutamate receptors, and synaptic plasticity. Conversely, almost nothing was known about the synaptic function of ADF, a second ADF/cofilin family member present at excitatory synapses, and it remained unknown whether ADF/cofilin is relevant for presynaptic physiology. To comprehensively characterize the synaptic function of ADF/cofilin we made use of mutant mice lacking either ADF or cofilin 1 or both proteins. Our analysis revealed presynaptic defects (altered distribution and enhanced exocytosis of synaptic vesicles) and behavioral abnormalities reminiscent of attention deficit-hyperactivity disorder in double mutants that were not present in single mutants. Hence, by exploiting gene-targeted mice, we demonstrated the relevance of ADF for excitatory synapses, and we unraveled novel functions for ADF/cofilin in presynaptic physiology and behavior.

DNMT1 controls migratory shape and dynamics of immature cortical interneurons

Geraldine Zimmer

Jena University Hospital

Cortical interneuron development requires tight regulation to ensure correct interneuron numbers in the mature cerebral cortex for proper cortical information processing. The migration from sites of origin within the subpallium to the cortical targets, accomplished by the adoption and maintenance of a particular migratory morphology, is a critical step of the post-mitotic maturation. To identify factors orchestrating this process, we performed single-cell transcriptome analysis and detected *Dnmt1* expression in murine migratory GABAergic cells. Deletion of DNA methyltransferase 1 (DNMT1) in post-mitotic immature interneurons of the preoptic area (POA) caused defective migration, resulting in severely diminished numbers of cortical interneurons in adults. We provide evidence that DNMT1 preserves the migratory shape of post-mitotic GABAergic interneurons in part through negative regulation of *Pak6* independent of its DNA-methylating action, which stimulates neuritogenesis at post-migratory stages. Our data underline the importance of DNMT1 for the post-mitotic maturation of cortical GABAergic interneuron precursors.

Protein and signaling networks in vertebrate photoreceptor cells

Karl-Wilhelm Koch

Department of Neuroscience, Biochemistry Group, University of Oldenburg, Carl-von-Ossietzky-Strasse 9-11, D-26129 Oldenburg, Germany

Vertebrate photoreceptor cells are exquisite light detectors operating under very dim and bright illumination. The photoexcitation and adaptation machinery in photoreceptor cells consists of protein complexes that can form highly ordered supramolecular structures and control the homeostasis and mutual dependence of the secondary messengers cGMP and Ca^{2+}. The visual pigment in rod photoreceptors, the G protein-coupled receptor rhodopsin is operating in a dynamic scaffolding process for activation of the G protein transducin. Illuminated rhodopsin is turned off by phosphorylation catalyzed by rhodopsin kinase GRK1 under control of Ca^{2+}-recoverin. The GRK1 protein complex partly assembles in lipid raft structures, where shutting off rhodopsin seems to be more effective. Re-synthesis of cGMP is another crucial step in the recovery of the photoresponse after illumination. It is catalyzed by membrane bound sensory guanylate cyclases and is regulated by specific neuronal Ca^{2+}-sensor proteins called GCAPs. Photoreceptor specific guanylate cyclase 1 (ROS-GC1 or GC-E) is part of a multiprotein complex involving *retinal degeneration protein 3* (RD3), Ca^{2+}-sensor proteins and others having strong interactions with the cytoskeleton and being controlled in a multimodal Ca^{2+}-dependent fashion. While RD3 inhibits photoreceptor GC1, it increases the activity of guanylate kinase thus being a critical regulatory step in the recycling of the GC substrate GTP.
Numerous mutations in photoreceptor proteins correlate with different forms of retinal diseases leading in affected patients to blindness or severe visual impairments. For example, dysfunction of cGMP signaling often results in a strong disturbance of the calcium-cGMP homeostasis. Parameters describing dynamic changes of cyclic GMP levels in a photoreceptor cell can be incorporated into a comprehensive computational kinetic model of phototransduction allowing a quantitative description and prediction of cellular responses.

References

Dell'Orco, D., Schmidt., H, Mariani, S., Fanelli, F. (2009) *Mol. Biosyst*. 5, 1232-1246.
Invergo , B. I., Dell'Orco, D., Montanucci, L., Koch,. K.-W., Bertrandpetit, J. (2014) *Mol. Biosyst.* 10, 1481-1489.
Koch, K.-W., Dell'Orco, D. (2013) *ACS Chem Neurosci*. 4, 909-917.
Koch, K.-W., Dell'Orco, D. (2015) *Front. Mol. Neurosci.* Vol.8, Article 67

Extracellular proteolysis shaping the brain microenvironment

Jörg-Walter Bartsch

Philipps University of Marburg

In my talk, I will present two pathological conditions that require extracellular proteolysis to modulate disease progression. Extracellular proteolysis is accomplished by the presence of proteases amongst which are zinc-dependent proteases, either secreted or membrane-bound proteins, termed MMP (matrix metalloproteases) or ADAM (A Disintegrin and Metalloprotease) proteases. Under neurodegenerative conditions, these molecules are instrumental in the processing of APP (Amyloid-Precursor Protein) or in mediating a pro-inflammatory response, i.e. by shedding of TNF-alpha or TNF receptors. In a mouse model for motoneuron disease, we have demonstrated that TNF- alpha leads to activation of ADAM proteases which in turn causes neuroprotection, as breeding of these mouse models into an ADAM-deficient background caused enhanced neurodegeneration mainly by lack of neuronal TNF receptor shedding. Whilst beneficial under neurodegenerative conditions, ADAM proteases are detrimental under neoplasias. Glioma cells expressing MMPs and ADAM proteases can infiltrate the brain and contribute to glioma progression with bad patient prognosis. In gliomas, the main function of MMPs and ADAM proteases is the proteolytic processing of factors that are chemoattractive for tumor-associated cells such as macrophages (TAMs) and for endothelial cells resulting in enhanced angiogenesis. Macrophages respond to proteolytic signals by a distinct differentiation that determines their role in the tumor context, as M1 macrophages are pro-inflammatory and anti-tumorigenic macrophages while M2 macrophages are mainly pro-tumorigenic. MMPs and ADAM proteases contribute to the particular role of macrophages by enhancing the release of SDF-1 (CXCL-12) and MCP-1 (Macrophage chemoattractant protein 1). In addition, the role of metalloproteases in glioma angiogenesis is mediated by regulating the release of osteopontin (SPP1), a factor with essential functions in angiogenesis. Thus, under malignant conditions, extracellular proteases are excellent target molecules for therapeutic approaches and examples for their therapeutic value will be presented.

Brain energy metabolism assessed by genetically encoded sensors for metabolites

Johannes Hirrlinger

Carl-Ludwig-Institute for Physiology, Leipzig, Germany and
Department of Neurogenetics, Max-Planck-Institute for Experimental Medicine, Göttingen, Germany

To provide proper maintenance of brain function appropriate supply of energy is essential. Deficiency of energy delivery as e.g. during stroke or other injuries in the central nervous system will very quickly severely impair brain activity. Also during normal brain function, brain energy metabolism involves complex interactions of different types of brain cells. This metabolic cooperation between different types of brain cells has been a major topic of research in brain energy metabolism for many years focussing mainly on astrocytes and neurons for a long time and only recently also oligodendrocytes have entered the stage. To address the dynamics of metabolites within cells at an appropriate high spatial and temporal resolution we employed genetically encoded fluorescent sensors for metabolites like ATP, glucose, lactate as well as the NAD^+/NADH-redox state to follow the concentration of these metabolic parameters in real time in specific cell types both in vitro as well in tissue preparations. For example, using a novel transgenic mouse line expressing a sensor for ATP in neurons and an experimental setup allowing electrophysiology and confocal imaging of excised optic nerves simultaneously, we obtained novel insight into axon-glia interactions. The ATP content of myelinated axons and their conduction properties showed similar, but not identical dynamics when confronted with different types of energy deprivation. Moreover, in the presence of glucose as the nerve's energy substrate, lactate metabolism is still required to maintain axonal ATP levels. Finally, in a mouse model of spastic paraplegia type-2 (SPG2) we demonstrated that the energy metabolism of well myelinated axons is perturbed months before the onset of clinical symptoms or pathological changes. Furthermore, we now investigate the dynamics of several parameters of astrocyte metabolism. In summary, genetically encoded sensors for metabolites are powerful tools for an in depth analysis of metabolism and its regulation.

Deciphering limits of retinal regeneration – from mice to human

Mike O. Karl

German Center for Neurodegenerative Diseases, Dresden

Vision loss due to retinal degenerative disease, specifically age-related macula degeneration (AMD), are a major health burden without efficient therapies available. Notably, some animal species, like fish and chick, have the capacity to restore sight by regenerating lost neurons endogenously from an adult retinal stem cell, the Müller glia (MG). In contrast, MG exist in mammalian retina and respond upon retinal pathologies, called reactive gliosis, but naturally do not regenerate the retina. Reactive gliosis is incompletely understood and may have beneficial and detrimental consequence, like proliferative disorders and scarring. Of note, AMD is characterized by retinal scar formation. Therefore, using mouse and human retina model systems we want (i) to find out if the mammalian glia response is a failed regenerative program, (ii) to prevent scar formation and (iii) to decipher and overcome the regeneration barrier. Various evidences showed that a very limited number of MG–derived neurons could be stimulated in the damaged mouse retina in vivo. We recently discovered that the MG regenerative response could be more efficiently stimulated and studied in juvenile mouse retina organotypic culture ex vivo. Our data suggests that regulated mechanisms might restrict regenerative competence animal age-dependently, which is the basis for our mouse retina regeneration assay. Using this ex vivo approach we began to investigate the neuronal damage dependent MG reactivation, proliferation and stemness responses. We found that neuronal cell death, possibly either by apoptotic or non-apoptotic mechanisms, is required to prime MG to gain proliferation competence. The very low number of MG recruited into the cell cycle is a major limitation of the mouse retina regeneration response. Thus, we sought and found efficient means to induce MG proliferation by extrinsic or intrinsic manipulation – some of which also resulted in additional pathologic changes suggesting a potential model of gliotic scar formation. To facilitate our studies we established methods to reliably isolate and purify MG, which improve studies on MG genomic responses. In parallel, we developed mouse and human pluripotent stem cell derived retina organoid systems to translate our findings and to study neuronal degeneration and regeneration in the human retina in the future.

miRNA-96 is required for normal development of the auditory hindbrain

Tina Schlüter[1], Christina Berger[2], Elena Rosengauer[1], Felix Felmy[2], Hans Gerd Nothwang[1]

[1]Neurogenetics group, Center of Excellence Hearing4All, Carl von Ossietzky University Oldenburg, 26111 Oldenburg, Germany
[2]Division of Neurobiology, Ludwig-Maximilians University Munich, 82152 Martinsried, Germany

microRNAs are a class of short single-stranded RNAs that are important players in RNA interference-mediated posttranscriptional gene regulation. Their canonical role is to bind the 3' untranslated region of target messenger RNAs via a complementary nucleotide seed sequence to reduce mRNA stability. microRNAs represents an indispensable layer in gene regulatory networks that control developmental processes and adult function in many animal and plants species.
In the auditory system, miRNA-96 plays a pivotal role. Point mutations in its seed region result in hearing loss in man and mice by arresting inner hair cell development. miR-96 is also expressed in central auditory circuits. To investigate whether it plays a role in the auditory system beyond the cochlea, we characterized homozygous *Dmdo/Dmdo* mice with a point mutation in miR-96. Anatomical analysis demonstrated a significant decrease in volume of auditory nuclei in *Dmdo/Dmdo* mice (range 23-36%). This decrease resulted from reduced cell number and decreased cell size. In contrast, non-auditory structures in the brainstem of *Dmdo/Dmdo* mice or auditory nuclei of the congenital deaf *Cldn14*$^{-/-}$ mice showed a much milder phenotype. Microscopic analysis revealed altered organization in the giant calyx of Held, as the mature morphology with synaptic vesicle donuts was largely absent. Electrophysiological analysis revealed that postsynaptic MNTB neurons fired action potentials predominantly with a multiple pattern upon depolarization (65%), in contrast to the single firing pattern prevalent in controls and *Cldn14*$^{-/-}$ mice (~38%). Furthermore, these neurons displayed larger synaptic short-term depression and slower decay kinetics for both the AMPA and NMDA components of glutamatergic transmission. Again, these synaptic changes were not present in *Cldn14*$^{-/-}$ mice. Immunohistochemistry identified significantly reduced expression of $K_v1.6$ and the BK channels, two predicted targets of the mutated miR-96. This might contribute to the electrophysiological phenotype. These data propose an on-site role of miR-96 in the auditory system beyond the cochlea. The apparent requirement for postnatal maturation of auditory neurons closely mimics its role in hair cells of the inner ear. Finally, our data underline the functional diversity in central auditory circuits by mutations in deafness genes.

The role of Neuregulin-1 in peripheral nervous system disorders

Robert Fledrich[1], Michael W. Sereda[1,2], Klaus-Armin Nave[1] and Ruth M. Stassart[1,3]

[1]Max-Planck-Institute of Experimental Medicine, Department of Neurogenetics, Göttingen, Germany
[2]University Medical Center Göttingen, Department of Clinical Neurophysiology, Göttingen, Germany
[3]University Medical Center Göttingen, Department of Neuropathology, Göttingen, Germany

The peripheral nervous system (PNS) displays an exceptional plasticity after injury. In response to an acute nerve trauma, nerve fibers degenerate and resident glia, the Schwann cells, demyelinate and undergo dedifferentiation. Schwann cells then facilitate axonal regrowth and eventually redifferentiate and remyelinate newly regenerated axons. However, Schwann cell myelination and efficient axonal regeneration is compromised in various chronic PNS disorders. Charcot Marie Tooth disease 1A (CMT1A) is the most common inherited neuropathy. Affected humans display perturbed myelination, slowly progressive demyelination, secondary axonal loss and subsequent muscular atrophy. No therapy is available.
PNS myelination is regulated by the growth factor neuregulin-1, expressed on the axonal surface. We have shown, that in response to nerve injury, neuregulin-1 expression transiently switches to Schwann cells and promotes redifferentiation and remyelination. In contrast, neuregulin-1 is persistently expressed by Schwann cells in CMT1A disease and its influence on the disease pathogenesis is subject of ongoing research. However, therapeutic treatment of transgenic rodent models of CMT1A with recombinant soluble neuregulin-1 modulates impaired developmental myelination and improves the clinical phenotype. Targeting neuregulin-1 signaling may thus render a therapeutic strategy for PNS disorders where myelination is perturbed.

Abstracts: Poster

Posters can be displayed throughout the entire meeting at the poster boards in the winter garden.

The presenting authors are asked to be present at their poster during the poster viewing (Friday, 13-14:30 for even numbers; 14:30-16 for odd numbers)

Glial Neuregulin-1 regulates Schwann cell pathology in Charcot-Marie-Tooth disease 1A (CMT1A)

[1)]Akkermann D., [1)]Fledrich R., [1)]Abdelaal T., [1)]Schütza V., [1)]Unternbarnscheid T., [1)]Soto-Bernardini C., [1)]Kusch K., [1)]Mott A., [1)]Möbius W., [1)]Maack C., [1)]Schwab M., [1,2)]Sereda M.W., [3)]Brück W., [1)]Nave K.-A., [1,3)]Stassart R.M.

[1)]Department of Neurogenetics, Max-Planck-Institute of Experimental Medicine, Göttingen, Germany; [2)]Department of Clinical Neurophysiology, University Medical Center Göttingen, Göttingen, Germany; [3)]Institute of Neuropathology, Medical Center Göttingen, Göttingen, Germany.

Charcot-Marie-Tooth disease 1A (CMT1A) is the most common inherited neuropathy, caused by a duplication of the gene encoding for the peripheral myelin protein of 22 kDa (PMP22). *PMP22* overexpression results in perturbed peripheral nerve myelination with secondary axonal loss, slowly progressive muscle atrophy and sensory impairment. *Pmp22*^{tg} mice resemble human CMT1A disease and recapitulate histopathological hallmarks like supernumerary Schwann cells, hypermyelination of small caliber axons, demyelination and onion bulb formations. The nature of these disease hallmarks remains largely unknown. We here demonstrate that the expression of the growth factor Neuregulin-1 (Nrg-1) type I is induced in Schwann cells upon *Pmp22* overexpression. Nrg1 type I is not produced by intact Schwann cells, and we previously reported a transient expression of Schwann cell Nrg-1 type I after acute nerve injury, which supports regeneration and remyelination of injured nerve fibers. In contrast, a persistent expression in chronic nerve injury (as in CMT1A) drives disease progression and ablation of the *Nrg-1* gene from Schwann cells of *Pmp22*^{tg} mice strongly ameliorates histopathology as well as the clinical phenotype. In turn, ectopic overexpression of Nrg-1 type I in Schwann cells triggers a peripheral neuropathy in healthy mice. Production of Nrg-1 type I by Schwann cells therefore is beneficial after acute nerve injury, but turns into a detrimental response when persistently expressed in chronic CMT1A disease.

Corresponding authors: akkermann@em.mpg.de, fledrich@em.mpg.de

catFISH for analysis of memory-related gene expression

Florian Drews[1], Christian Kaltschmidt[2], Barbara Kaltschmidt[1]

[1]Molecular Neurobiology, Universität Bielefeld, Germany
[2]Cell Biology, Universität Bielefeld, Germany

The dentate gyrus has an important role regarding different aspects in the formation of new memories and is known as one of the few regions of the adult brain with a high rate of neurogenesis. The expression of immediate early genes (IEG) is of particular interest in this part of the brain. Although IEG-expression is not limited to neuronal cells, it represents a marker for neuronal activity in the brain. During this work, the cellular compartment analysis of temporal activity by fluorescence in situ hybridization (catFISH) was established for analysing the expression of the NF-κB target genes (IEGs) c-fos, Egr1 and Egr2. A superrepressor IκB/tTa mouse-line was used as a model organism. The results of this work form the basis for future behavioural experiments with Novel Object Recognition tests stimulating neuronal activity. In this regard, new insights into IEG-expression within the dentate gyrus can be of use in understanding neurodegenerative diseases like Parkinson or Alzheimer.

Corresponding author: fdrews@uni-bielefeld.de

Cone-dominant visual system to investigate interaction of recoverin isoforms and G-protein-coupled receptor kinase

Dana Elbers, Alexander Scholten, Karl-Wilhelm Koch

Department of Neuroscience, Biochemistry Group, University Oldenburg, 26111 Oldenburg, Germany

Purpose: Phototransduction in cones is less well understood than in rods. The faster light responses of cones, their lower sensitivity and wider operation range under changing background illumination intensities likely originate from specific features of the visual transduction machinery. Since zebrafish (*Danio rerio*) cones harbor cone pigments that allow the animals to detect the full range of visible light and even wavelengths of the near UV, zebrafish became a widely used model organism in vision research. Many photoreceptor proteins are duplicated in the zebrafish genome. For example, two paralogs of G-protein coupled receptor kinase 1 (GRK1), namely 1-A & 1-B and of GRK7, namely 7-A & 7-B (Rinner *et al.* 2005) are expressed in rods and cones. Mammalian GRK1 is under Ca^{2+}-dependent control of recoverin and thereby plays a key role among different Ca^{2+}-dependent feedback mechanisms. A similar operation mode of zebrafish rod and cone GRKs can be hypothesized, but is not proven so far. In fact, the physiological meaning of four different recoverin isoforms (zRec1a, zRec2a, zRec1b, zRec2b) (Zang *et al.* 2015) in the zebrafish retina is unclear. Our aim is to investigate protein-protein interaction of recoverin and GRK isoforms as well as the specific Ca^{2+}-sensing properties of the different recoverin isoforms.
Methods: The interaction of recoverin and GRK isoforms was investigated with Surface Plasmon Resonance Spectroscopy (SPR). SPR enables investigations of protein-protein-interactions in real time by an immobilization of one protein followed by a titration of a second protein. Additionally, an enzyme-linked immunosorbent assay (ELISA) was performed to verify a protein-protein interaction by an enzyme-coupled antibody reaction. To investigate different Ca^{2+}-sensitivities of the recoverin isoforms a fluorescence resonance energy transfer (FRET) assay was performed by taking advantage of Ca^{2+}-triggered conformational changes leading to an increase or decrease of FRET signals.
Results: Four recoverin isoforms were expressed in *E.coli* and purified by a Hydrophobic-Interaction-Chromatography except of zRec1b, which is purified by an Ammonium-Sulfate-Precipitation followed by a Size-Exclusion-Chromatography. The GRK paralogs were also expressed in *E.coli* followed by an Immobilized-Metal-Ion-Chromatography Purification. Previous experiments showed that based on Ca^{2+}-binding all recoverin isoforms are functional after the purification procedure. The interaction of all recoverin isoforms with the GRK7-A and GRK7-B was tested by ELISA and indicated an operative range of recoverin at low [Ca^{2+}]. Additionally, the FRET experiments suggested different Ca^{2+}-sensitivities between the recoverin isoforms. The SPR interaction studies indicated heterogeneous binding modes of recoverin isoforms and GRK targets.
Conclusion: The Ca^{2+}-sensitivities of recoverin forms indicate a differential mode of target binding and regulation. Ongoing experiments are designed to identify which pair of recoverin and GRK is operating in which rod or cone cell and whether different Ca^{2+}-binding modes reflect a step-by-step activation/inhibition of the target GRKs.

References:
Zang, J., Keim, J., Kastenhuber, E., Gesemann, M. & Neuhauss, S. (2015). Recoverin depletion accelerates cone photoresponse recovery. *Open Biol*., **5**, 1-8
Rinner, O., Makhankov, Y.V., Biehlmaier, O. & Neuhauss, S.C.F. (2005). Knockdown of cone-specific kinase GRK7 in larval zebrafish leads to impaired cone response recovery and delayed dark adaptation, *Neuron*, **47**, 231-242

Corresponding author: dana.fabienne.elbers@uni-oldenburg.de

Adult nasal stem cells – applicability for cell replacement therapy of neurodegenerative diseases

Johannes F.W. Greiner[1*], Janine Müller[2], Christian Kaltschmidt[1] and Barbara Kaltschmidt[2]

[1] Cell Biology, University of Bielefeld
[2] Molecular Neurobiology, University of Bielefeld

[*]Presenting author

Treatment of neurodegenerative diseases represents a major challenge in regenerative medicine. Allowing autologous cell transplantation, the application of adult stem cells is highly promising for cell replacement therapies. Here, we investigated the potential of neural crest-derived stem cells from the adult human nasal cavity to regenerate a Parkinsonian rat model and established a bag cultivation system for their clinical-grade expansion prior to transplantation.
Demonstrating the broad plasticity of inferior turbinate stem cells (ITSCs), we observed their successful *in vitro*-differentiation into functional neurons as well as into vGlut2^{+} forebrain neurons after integration into organotypic hippocampal slice cultures *ex vivo*. Chemically defined differentiation conditions resulted in highly efficient differentiation of ITSCs into TH+ DA neurons. Tranplantation of ITSCs into a unilaterally lesioned 6-OHDA Parkinsonian rat model resulted in recovery of rotational behavior. We further observed a significant restoration of DA neurons within the *Substantia nigra* after transplantation of ITSCs. Optimizing *in vitro* expansion steps of ITSCs prior to transplantation into the patient in terms of contamination risks, we also established a cost-reducing and animal-serum free bag cultivation system. Application of a human blood plasma(BP)-based 3D fibrin matrix led to significantly increased proliferation of ITSCs compared to standard culture conditions. Expansion of ITSCs in the BP-matrix within cGMP-grade Afc-FEP bags did not affect their expression profile, telomerase activity, genetic stability and differentiation into mesodermal and ectodermal cell types.
In summary, the broad plasticity of ITSCs to generate cell types of the nervous system combined with the here established culture bag system has a great potential for future medical applications in terms of treating neurodegenerative diseases.

Calcium channel surface dynamic influences synaptic transmission

Jennifer Heck[1], Pierre Parutto[2], Romy Freund[1], Anna Ciuraszkiewicz[1], Arthur Bikbaev[1], Maria Andres-Alonso, David Holcman[2], Martin Heine[1]

[1]Molecular Physiology Group, Leibniz-Institute of Neurobiology, Magdeburg, Germany; [2]Theoretical Modelling of Cellular Physiology, École Normale Supérieure, Paris, France; [3]FG Praesynaptische Plastizitaet, Leibniz-Institute of Neurobiology, Magdeburg, Germany

The localization of voltage gated calcium channels (VGCCs) and vesicles at the presynaptic active zone is critical for the release probability of neurotransmitters. Using single particle tracking photoactivation localization microscopy (sptPALM) we show that the majority of synaptic VGCC is confined but mobile within the presynaptic membrane. Several molecular interactions between VGCCs and presynaptic scaffold proteins in mammalian synapses as RIM, RBP and Bassoon have been reported to influence the localization of VGCCs as well as the recruitment of synaptic vesicles and have a major impact on synaptic transmission. Described binding motives for channel scaffold interactions are located at the distal C-terminus of VGCCs. In order to probe whether interactions between VGCCs and scaffold proteins manipulate channel localization, we used two C-terminal splice variants of VGCCs. Here, alternative splicing of exon 47 results in the expression of a shorter C-terminus (delta47) lacking a variety of protein-protein interactions.
Both splice variants, $Ca_V2.1_{delta47}$ and $Ca_V2.1_{+47}$ accumulated into the presynaptic terminals and co-localized with presynaptic proteins as Bassoon, RIM and Munc13 and the vesicular protein synapsin. Within ~50 % of synapses, the endogenous $Ca_V2.1$ population was similarly replaced by both tagged $Ca_V2.1$ C-terminal splice variants. Despite the differences in the C-terminus, the $Ca_V2.1_{delta47}$ splice variant promotes a stronger accumulation of scaffold proteins. However, the shorter $Ca_V2.1_{delta47}$ was significantly more mobile compared to $Ca_V2.1_{+47}$ but had similar confinement and dwell time within small energy domains. Synaptic calcium signals in $Ca_V2.1_{+47}$ or $Ca_V2.1_{delta47}$ dominated synapses were similar. Using light induced channel aggregation via fusing of cryptochrome2olig to the N-terminus of VGCCs lead to altered kinetics of vesicle release.
Our data suggest that recruitment of calcium channels is independent of the C-terminal interacting domains to scaffold proteins. Further, we hypothesize that aggregation and immobilization of VGCCs at the presynapse favors multi vesicular release and thus modulates the variability of presynaptic release properties.

Corresponding author: Jennifer.Heck@lin-magdeburg.de

Gender- and genotype-dependent modulation of synaptic connectivity in a presymptomatic mouse model for Alzheimer's disease

Mariya Hrynchak, Roland Brandt, Lidia Bakota

Department of Neurobiology, University of Osnabrück, Osnabrück, Germany

Synaptic failure is an immediate cause of cognitive decline and memory dysfunction in Alzheimer's disease (AD). Dendritic spines are specialized structures on pyramidal neurons, each of which receives input typically from one excitatory synapse. Their shape determines the stability, strength, and function of excitatory synaptic connections. Spine loss, spine length reduction and shift in spine shape represent the consequence of elevated amyloid beta peptide. Therefore, spine-related changes might compromise learning, memory and contribute to neurodegeneration during AD [1].

The key goal of this project was to evaluate changes in synaptic connectivity during chronical presence of elevated soluble amyloid beta species in two different cortical regions of APP_{SDL} mice in comparison to B6 controls. Twenty-four months old mice of both genders were analyzed. In order to obtain structural information, mice were crossed with the GFP M line, which harbours expression of EGFP in spares amounts of pyramidal cells within the cortical areas. Fixed brain sections were imaged using laser scanning confocal microscope. High-resolution images were obtained from sensory (SCTX) and associative cortices (ACTX). Images of apical dendrites of the pyramidal cell were subjected to 3D blind deconvolution and algorithm-based recognition of spine density and morphology. Statistical analysis was carried out with SPPS.

The results indicate a gender-specific differences in spine density in both cortical subdomains, and differences in the spine morphology only in associative cortical region. Genotype-specific differences seem also to be restricted to ACTX.

Considering all data together, spine parameter alterations are specific to each subcortical area and there are clear differences in males *vs* females. More and more, the sex differences become an important factor in assessing the AD progression in different aspects and, consequently, it might be important to provide a therapy for each gender separately.

References:

1. Herms, J. and M.M. Dorostkar, *Dendritic Spine Pathology in Neurodegenerative Diseases.* Annu Rev Pathol, 2016. **11**: p. 221-50.

Corresponding author: hrynchak@biologie.uni-osnabrueck.de

Unravelling novel physiological functions of the actin-binding protein CAP2 by using a systemic knockout mouse model

Kepser L, Rust MB

Molecular Neurobiology Group, Biochemical-Pharmacological Center (BPC), University of Marburg, Germany

Dynamic reorganization of actin filaments (F-actin) plays a major role in many biological processes such as cell motility and morphology or membrane trafficking. There is a variety of known actin-binding proteins that control actin dynamics by modulating polymerization and depolymerization of F-actin through the so-called actin treadmilling mechanism [1]. One important family of actin-binding proteins are the cyclase associated proteins (CAPs). While CAP1 is widely expressed, CAP2 is predominantly expressed in the brain, heart, skeletal muscle, testis and skin [2]. Recent studies on systemic mutants linked CAP2 to heart physiology [3], but the function of CAP2 in skeletal muscles has not been investigated yet. In this study we examine the effects of CAP2 inactivation on skeletal muscle histology and function in mice. Already during the early postnatal days CAP2-KO mice show significant delays in motoric functions that are persistent through adulthood and manifest in muscle strength deficits and defective motor coordination. On the histological level, we see several structural changes in skeletal muscle cells such as centralized nuclei, ring fibers or an altered mitochondrial distribution. These changes are characteristic for human myopathies like myotonic dystrophies or centronuclear myopathies. Overall, our study for the first time unravelled an important role for CAP2 in skeletal muscle ultrastructure and function in mammals.

References:

1. Baum, J., et al., *Regulation of apicomplexan actin-based motility.* Nat Rev Microbiol, 2006. **4**(8): p. 621-8.
2. Peche, V., et al., *CAP2, cyclase-associated protein 2, is a dual compartment protein.* Cell Mol Life Sci, 2007. **64**(19-20): p. 2702-15.
3. Peche, V.S., et al., *Ablation of cyclase-associated protein 2 (CAP2) leads to cardiomyopathy.* Cell Mol Life Sci, 2013. **70**(3): p. 527-43.

Corresponding author: lara-jane.kepser@staff.uni-marburg.de

MCP1 results in an increased proliferation of human neural crest-derived neural progenitor cells

M. Merten[1], F. Wandhöfer[1], J. F.W. Greiner[1], B. Kaltschmidt[2], C. Kaltschmidt[1]

[1]Cell Biology, Universität Bielefeld, Germany
[2]Molecular Neurobiology, Universität Bielefeld, Germany

Ageing results in a decline in the amount of adult neural progenitor cells and neurogenesis, leading to impairments in cognitive functions. Previous studies showed that the exchange of blood (parabiosis) between old and young mice led to an improved health state of the old animals. In this regard, the use of blood plasma from healthy young donors holds great promise to treat neurodegenerative diseases.
Here, we investigated the influence of human blood plasma on adult neural crest-derived stem cells isolated from the inferior turbinate (ITSCs) of the human nose. We observed that human blood plasma has a beneficial effect on ITSC proliferation, independent of sex and age of the donor. Cultivation of ITSCs in human blood plasma did not affect their ability to undergo neuronal differentiation. Determining our observations in more detail, we treated ITSCs with the systemic factors Growth differentiation factor 11 (GDF11), Eotaxin 1 and Monocyte chemotactic protein 1 (MCP1), which are endogenously present in human blood plasma. We initially validated the biological activity of Eotaxin1 and MCP1 by performing a cell migration assay with THP-1 human acute monocytic leukemia cells. The biological activity of GDF11 was showed by induction of hemoglobin formation in K562 human chronic myelogenous leukemia cells visualized by benzidine staining. In contrast to GDF11 and Eotaxin, treatment of ITSCs with MCP1 resulted in an induced proliferation rate.
In summary our data show beneficial effects of human blood plasma on ITSC proliferation, which are strongly suggested to be based on the presence of the systemic factor MCP1. Based on these promising findings, future studies will particularly focus on potential effects of systemic factors on neuronal differentiation of ITSCs.

Corresponding author: madlen.merten@uni-bielefeld.de

MOAG-4/SERF: a direct modifier of amyloid assembly in neurodegenerative diseases

N. Helge Meyer[1], Tobias Madl[2], Klaus Zangger[3], Fabio Falsone[4]

[1] Department of Neuroscience, Biochemistry, University Oldenburg
[2] Institute of Biochemistry and Molecular Biology, Medical University Graz
[3] Institute of Chemistry, University Graz
[4] Institute of Pharmaceutical Sciences, University Graz

Protein misfolding into a toxic conformation and the extra- or intracellular accumulation of misfolded protein in large oligomeric structures - termed amyloid fibrils - coincides with the onset of numerous age-related neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. In spite of being structurally and functionally unrelated, amylogenic proteins can generally be converted into insoluble fibers with a distinct cross beta-sheet structure. Understanding the structural and dynamical principles underlying the pathways of amyloid formation can thus point to novel strategies in the clinical treatment of neurodegenerative diseases. Recently, the evolutionary conserved class of proteins - MOAG-4 (modifier of aggregation-4)/SERF (small ERDK rich factor) - was identified to affect amyloid formation in vivo and it was thus proposed that MOAG-4/SERF provides a previously unexplored mechanism to regulate age-related proteotoxicity. Therefore, we initiated a study to reveal the molecular mechanisms underlying the interaction of SERF1a with the amylogenic protein alpha synuclein. Here, we show that both proteins remain entirely disordered and no secondary structural content is formed in the transient protein complex. Notably, we could pinpoint the interaction to three critical lysine side chains of SERF1a within the interaction surface. A combination of small angle X-ray scattering (SAXS) and nuclear magnetic resonance (NMR) experiments revealed that SERF predisposes alpha synuclein into a conformation prone to amyloidogenesis. Our results provide evidence that hSERF1a can promote a highly ordered structural process such as amyloid polymerisation without the explicit requirement of stable structure.

Corresponding author: helge.meyer@uni-oldenburg.de

RNA binding proteins in neuronal stress granules studied by single-molecule tracking

Benedikt Niewidok[1], Maxim Igaev[1], Abel Pereira da Graça[1], Michael Peters[1], André Strassner[1], Christian Richter[2], Jacob Piehler[2] and Roland Brandt[1]

[1] University of Osnabrück, School of Biology/Chemistry, Department of Neurobiology
[2] University of Osnabrück, School of Biology/Chemistry, Department of Biophysics

Maintenance of cellular polarity as well as fast response upon extracellular cues requires fast and tightly regulated expression of proteins, especially in morphologically complex cells like neurons. Ribonucleoprotein (RNP) granules contribute to the regulation of gene expression via posttranscriptional coordination of mRNA translation, localization and degradation. These self-assembling structures lack a membrane and can be considered as dynamic microcompartments.
The Ras GTPase activating protein SH3 domain binding protein 1 (G3BP1) and the Insulin like growth factor II mRNA binding protein 1 (IMP1) are present in stress granules (SGs), *i.e.*, RNP granules that are induced upon cellular stress. Our previous studies based on confocal laser scanning microscopy (cLSM) have shown that these two proteins colocalize in SGs and that overexpression of either of them is sufficient to induce the SG formation (Moschner et al., 2014). Furthermore, fluorescence decay after photoactivation (FDAP) analysis demonstrated that IMP1 exhibits rather slow SG-cytosol exchange with SGs being its preferred location, whereas G3BP1 readily fluctuates between the SG and cytosolic phase. Induction of stress by sodium-arsenite treatment increased the fraction of G3BP1 in SGs. Nevertheless, the dynamic organisation of SGs and their components at the super-resolution level and, hence, their behaviour remain unclear. Currently, there exist two concepts trying to explain the behaviour of mRNPs, the liquid droplet model and the scaffolding assembly. In the former model, the SGs are formed via liquid-liquid phase separation (LLPS), remain amorphous and are held together by surface tension. In the latter model, the SGs grow upon binding of cytosolic proteins to a relatively robust scaffold presumably made up of proteins of the same type.
In order to shed light on the internal arrangement of G3BP1 and IMP1 inside SGs, we monitored the mobility of Halo-tagged G3BP1 and IMP1 constructs within granules induced upon sodium-arsenite treatment in neuronally differentiated PC12 cells using total internal reflection microscopy (TIRF) followed by single-molecule tracking (SMT) analysis. Our data indicate significant differences in the binding times of G3BP1 and IMP1 depending on whether both or only one of the two proteins is expressed, suggesting an interaction of those proteins inside SGs, which might favour the scaffold assembly model. On the contrary, 2D cluster analysis revealed only a weak overlap between the binding hotspots of G3BP1 and IMP1, suggesting a widespread distribution in an amorphous phase. Currently, we are analyzing the mobility of G3BP1 and IMP1 to gain insight into the diffusion properties of these proteins in SGs.

Reference:
Moschner K*, Sündermann F*, Meyer H, Pereira da Graca A, Appel N, Paululat A, Bakota L, and Brandt R (2014) RNA-protein granules modulate tau isoform expression and induce neuronal sprouting. (*joint first authors) J. Biol. Chem. 289:16814-16825

Study of hippocampal dendritic spine parameters in an old presymptomatic mouse model of amyloidosis

Marina Rierola, Roland Brandt, Lidia Bakota

Department of Neurobiology, University of Osnabrück, Osnabrück, Germany

Alzheimer's disease is an age-dependent disorder, characterized by an irreversible and progressive neurodegeneration that leads to a loss of cognitive functions. It is mainly sporadic, although in few percent of cases mutations in amyloid precursor protein (APP), presenilin 1 and 2 were reported.
Our main goal was to explore whether genotype or gender differences are present on a presymptomatic mouse model of amyloidosis regarding dendritic spines in different subregions of the hippocampus after the reproductive age. Dendritic spines are dynamic sub-organellar microcompartments, which represent the postsynaptic entities of excitatory inputs, serving as platforms for molecular changes [1].
For structural analysis mice were crossed with mice expressing EGFP in subsets of pyramidal cells within the hippocampus (GFP-M line). Apical dendritic spine parameters in 24 month-old APP_{SDL} mice of both genders were analyzed. Mice were transcardially perfused and the mouse brains were cut using a vibratome. High-resolution images were obtained from pyramidal cells of CA1 and CA3 subfields of dorsal hippocampus with confocal laser-scanning microscope. Micrographs were subjected to 3D blind deconvolution and to algorithm-based recognition of spine density and morphology. SPSS software was used for statistics and graphs.
Our preliminary results suggest that there are differences in spine density on cortical pyramidal neurons of both CA1 and CA3 subregions, resulting in significantly higher spine density in control males compared to female mice. Surprisingly, genotype-specific reduction of dendritic spine density was only observed in male APP_{SLD} mice compared to control animals. Morphological alterations between the two genotypes were restricted to the CA3 subregion but were present in both genders.
Taken together our results show that aged APP_{SDL} mice do not display severe spine alterations that were obvious in the same mice at young age.

1. Tackenberg C, and Brandt R (2009) Divergent Pathways mediate spine alterations and cell death induced by Amyloid-beta, wild-type tau, and R406W tau. J Neurosci **46**:14439-14450.

Corresponding author: rierola@biologie.uni-osnabrueck.de

NF-kB dependent cell fate determination in the specification of human stem cells into glutamatergic neurons

Lucia Ruiz-Perera[1], Christian Kaltschmidt[2], Barbara Kaltschmidt[1]

[1]Molecular Neurobiology, University of Bielefeld, Bielefeld, Germany.
[2]Cell Biology, University of Bielefeld, Bielefeld, Germany.

Adult human neural crest-derived stem cells (NCSCs) are promising candidates for the use in regenerative medicine, due to their wide differentiation potential and their persistence into adulthood. A particularly interesting population of NCSCs has been found within the respiratory epithelium in the inferior turbinate of human nose. Inferior turbinate stem cells (ITSCs) of glial origin, are able to differentiate into a great variety of cell types from mesodermal and neuro-ectodermal lineages, like chondrocytes, osteocytes, adipocytes, and glutamatergic and dopaminergic neurons.
Due to their capability to efficiently differentiate into functional mature neurons in vitro, ITSCs harbor great potential as a model for the treatment of neurodegenerative diseases and other cell based therapies. However, little is known about the molecular mechanisms regulating their properties during differentiation, especially into the neuronal fate.
NF-kappaB is an ubiquitously expressed, inducible transcription factor that regulates the expression of a broad number of genes and is involved in different cellular processes such as cell survival, proliferation, stress, immune and inflammatory processes. In the nervous system NF-kappaB is also involved in neuroprotection/degeneration, in neurite growth, in dendritic spine formation and functionality, in axonal outgrowth and synaptic plasticity. For this reason, we wanted to study the role of NF-kappaB in the fate specification of ITSCs during neuronal differentiation into the glutamatergic phenotype.
In this work we analyze the expression pattern of different NF-kappa B subunits in early stages of glutamatergic differentiation. Here we show an increase in c-Rel expression after 2 days of differentiation, which is gradually reduced afterwards. This increase is followed by a similar behavior of IkappaB-alpha, while RelB has an opposite effect, being decreased during the same period of time, and suddenly increased for a short period later. In contrast p65 and p50 are very lowly expressed having little variation. These data suggests a differential NF-kappaB subunit composition pattern during early stages of neuronal differentiation, where the increase of IkappaB-alpha might be involved in the regulation of c-Rel and RelB, whose modulation could directly lead the specification of ITSCs towards the glutamatergic neuronal fate.

Corresponding author: lucia.ruiz@uni-bielefeld.de

Establishment of human nasal tissue and cell cultures as model systems for pharmacological research

Johanna Schäfermann[1,2], Johannes F.W. Greiner[1], Matthias Schürmann[2], Viktoria Brotzmann[2], Holger Sudhoff[2], Barbara Kaltschmidt[1,3] and Christian Kaltschmidt[1]

[1]Department of Cell Biology, University of Bielefeld, Bielefeld, Germany; [2]Department of Otolaryngology, Head and Neck Surgery, Klinikum Bielefeld, Bielefeld, Germany; [3]AG Molecular Neurobiology, University of Bielefeld, Bielefeld, Germany

1,8-Cineole is the active ingredient of the drug Soledum, which is therapeutically applied for inflammatory diseases. However, 1,8-Cineole was described to have an protective effect in an *in vitro* model of Alzheimer's disease, suggesting a beneficial use in therapy of neurodegenerative diseases. This study establishes model systems of inflammatory diseases, including human nasal tissue, inferior turbinate stem cells (ITSCs) and epithelial cells obtained from inferior turbinates or nasal polyps. Pure epithelial cell cultures were achieved by differential trypsinisation and preplating. Ciliation was received by differentiation using air-liquid interface (ALI) conditions and retinoic acid. Characterisation of the cells was done by immunofluorescence, Alcian blue staining, SEM and PCR. The established model systems were tested to inflammatory stimuli like lipopolysaccharide (LPS) and/ or Polyinosinic:polycytidylic acid (Poly(I:C)), simulating inflammatory diseases, and were tested to their response to 1,8-cineole. This study demonstrates for the first time that 1,8-cineole potentiates a Poly(I:C)-induced increase of nuclear antiviral transcription factor interferon regulatory factor 3 (IRF3) in *ex vivo* cultivated human nasal turbinate tissue. Simultaneously, 1,8-cineole leads to a reduction in nuclear localized proinflammatory nuclear factor (NF)-kappaB after Poly(I:C)-dependent stimulation. In addition, 1,8-cineole potentiates significantly elevated expression levels of the IRF3 target gene RANTES in a model of bacterial superinfection. Taken together this study establishes model systems of human nasal tissue and primary cells, which represent promising tools for future pharmacological research and cellular engineering.

Corresponding author: j.schaefermann@uni-bielefeld.de

Genome editing of NF-KB family member c-Rel using mCRISPR/Cas9n for future applications in the nervous system

Thomas Schlüter[1], Angela Kralemann-Köhler[1], Carsten Slotta[1], Barbara Kaltschmidt[2], Christian Kaltschmidt[1]

[1]Department for Cell Biology, University Bielefeld, Bielefeld Germany
[2] Molecular Neurobiology, University Bielefeld, Bielefeld Germany

NF-kappaB is one of the most important transcription factors in the nervous system and involved in learning, memory, neuroprotection, neuronal survival and synaptic plasticity. Accordingly, NF-kappaB is associated with many neuronal diseases like Alzheimer's disease, Parkinson's disease, and Huntington's disease. Here, we used the recently established genome editing method CRISPR/Cas9n in a multiplex way to obtain a knockout of the NF-kappaB subunit c-Rel. Four single-guide RNAs were designed and cloned in just one vector containing the Cas9n enzyme. We successfully generated heterozygous as well as homozygous deletion in exon 2 of the REL gene on chromosomes 2 in HeLa cells. For characterizing further analysis including Western blotting, immunostaining, native PAGE and qPCR were done. Based on these promising findings, the here cloned vectors will be used to study the role of NF-kappaB in the development of the nervous system and in stem cell differentiation.

Corresponding authors: thomas.schlueter@uni-bielefeld.de

Impaired Ca^{2+}-signaling of the neuronal Ca^{2+}-sensor GCAP1 associated with retinal dystrophies cause aberrant regulation of retinal guanylate cyclase

Valerio Marino[b], Alexander Scholten[a], Karl-Wilhelm Koch[a] and Daniele Dell'Orco[b]

[a] Dept. of Neurosciences, Biochemistry Group, University of Oldenburg, 26111 Oldenburg, Germany; [b] Dept. of Neurosciences, Biomedicine and Movement Sciences, Sect. of Biological Chemistry, University of Verona, 37134 Verona, Italy

Guanylate cyclase-activating proteins (GCAPs) are retina specific neuronal Ca^{2+} sensor proteins (NCS proteins) that regulate the activity of sensory membrane bound guanylate cyclases (GCs). GCAPs switch conformation and function upon binding of divalent cations: from GC-inhibitor (Ca^{2+} bound) to GC-activator (Mg^{2+} bound).
Strict control of GC-activity is crucial for the interplay between Ca^{2+} and cGMP homeostasis in photoreceptor cells. In healthy cells this interplay is important for shaping the kinetics of photoresponse and for light adaptation. Point mutations in GUCA1A, the gene encoding GCAP1, cause inherited retinal degenerative diseases due to an imbalance of second messenger homeostasis in photoreceptor cells.
Most GCAP1 mutations lead to autosomal dominant cone (COD) or cone-rod (CORD) dystrophies. Here we investigated two GCAP1 mutants (L84F and I107T), which exhibit additional symptoms of macular dystrophies. We therefore investigated biochemical and biophysical properties of the two mutants to see, whether they share common molecular features with other retinal dystrophy variants of GCAP1.
Similar to other GCAP1-mutants described before GC-activity assays revealed a shift in Ca^{2+}-sensitivity towards higher Ca^{2+}-concentrations for both mutants, resulting in constitutive active GCs in affected photoreceptor cells. Interestingly, when tested with a Ca^{2+}-chelating reagent, only I107T exhibited a decreased Ca^{2+}-affinity, whereas L84F binds Ca^{2+} with similar constants as wildtype-GCAP1.
When we compared structural aspects of both mutants with wildtype-GCAP1, employing circular dichroism spectroscopy and Ca^{2+}-titration monitored by tryptophan fluorescence, I107T showed high similarities with wildtype-GCAP1, whereas L84F exhibited greater differences, specifically in the tertiary structure.
Our results suggest that these two novel GCAP1-mutants affect GC-regulation via different processes.

Corresponding author: alexander.scholten@uni-oldenburg.de

Loss of Schwann cell autophagy might contribute to a late onset motoneuron disease in Plekhg5 deficient mice

Carsten Slotta[1], Peter Heimann[1], Patrick Lüningschrör[1,2], Barbara Kaltschmidt[1,3], Christian Kaltschmidt[1]

[1]Department of Cell Biology, University of Bielefeld, Bielefeld, Germany; [2]Institute of Clinical Neurobiology, University of Wuerzburg, Wuerzburg, Germany; [3]Molecular Neurobiology, University of Bielefeld, Bielefeld, Germany

Mutations in the *PLEKHG5* gene are associated with distal spinal muscular atrophy type IV (DSMA-IV) and an intermediate form of Charcot-Marie-Tooth (CMT) disease. In order to study the contribution of Plekhg5 to the disease mechanisms, we generated Plekhg5 deficient mice. These mice developed a motoneuron disease with late onset. Histopathological analysis of the spinal cord revealed a progressive loss of motoneurons and axonal swellings. This pathology is associated with a reduced neuronal Nuclear Factor kappa B signaling.
In peripheral nerves we detected an altered myelination of the axons, mostly characterized by myelin infoldings, which progressed with age. In addition, we observed a loss of large caliber axons, as well as an altered g-ratio. The total number of Schwann cells within the sciatic nerve is increased in Plekhg5 deficient mice.
With Plekhg5 being expressed not only in neurons but also in Schwann cells, we cultivated primary Schwann cells to search for cell autonomous effects contributing to the disease phenotype. We detected reduced amounts of autophagosomes indicating impaired autophagy in Schwann cells lacking Plekhg5. This might contribute to the observed myelin alterations with recent publications showing the ability of Schwann cells to break down their myelin sheaths by a specific form of autophagy (myelinophagy) in response to axonal stress[1].

[1]Gomez-Sanchez, J. A., L. Carty, et al. (2015). "Schwann cell autophagy, myelinophagy, initiates myelin clearance from injured nerves." J Cell Biol **210**(1): 153-168

Corresponding author: carsten.slotta@uni-bielefeld.de

Enhanced synaptic transmission in mice with homozygous tau deletion

Abdala M. Ussif, Roland Brandt, Lidia Bakota, Gunnar Jeserich

Department of Neurobiology, University of Osnabrueck

The microtubule-associated protein tau (MAPT), owing to the fact of its association with axonal microtubules and demonstrated ability to polymerize tubulin, has long been held to be essential for the dynamics, and perhaps mechanics, of microtubules. However, it is becoming increasingly clear that MAPT plays additional, and perhaps, direct roles in neuronal and synaptic function outside this traditional function. Much of this understanding has emerged from studies of animal models with homozygous deletion of the tau gene. It has been previously reported that mice with homozygous tau deletion performed better than age-matched wild-type controls in certain spatial memory tasks, although no comprehensive underpinning electrophysiological differences in long-term potentiation (LTP), a neural correlate of memory, has ever been reported.

In the present study, we employ a multielectrode array system and acute hippocampal sections to examine the effect of homozygous tau deletion on synaptic transmission, including long-term potentiation, in CA1 hippocampal subfield of 1-year old mice. We show by means of strict separation of responses in CA1 dendritic and cell layers that MAPT$^{-/-}$ mice exhibit greater potentiation in CA1 cell layer than age-matched controls after 100 Hz LTP induction, and this is true for both gender. We also show that paired pulse facilitation, a test of presynaptic calcium behavior, in CA1 dendritic layer of MAPT-deficient mice is significantly higher than in control slices.

The results establish an electrophysiological basis for higher spatial memory in MAPT-deficient mice and provide, perhaps, a microtubule-independent role of tau in synaptic transmission.

Protein-protein interaction of the putative magnetoreceptor cryptochrome 4 expressed in the avian retina

Haijia Wu[1], Alexander Scholten[1], Anja Günther[2], Dana Elbers[1], Henrik Mouritsen[2] and Karl-Wilhelm Koch[1]

[1]Department of Neuroscience, Biochemistry group, University of Oldenburg, D-26111 Oldenburg, Germany; [2]Department of Biology and Environmental Sciences, Neurosensorics/Animal Navigation, University of Oldenburg, D-26111 Oldenburg, Germany

Migratory birds can sense the Earth's magnetic field and use it for orientation tasks. A light-dependent radical-pair mechanism, which is associated with the visual system, is currently discussed as the underlying mechanism of the magnetic compass.
The blue light receptor cryptochrome (Cry) has been considered as a potential primary sensor that detects the geomagnetic field. Moreover, cryptochrome and its co-factor FAD are assumed to be the molecular components performing photo-chemical reactions leading to radical-pair intermediates. Four different cryptochromes are localized in the avian retina (Cry1a, Cry1b, Cry2 and Cry4), but their precise function is not known so far. In the present study we suggest Cry4 as a putative candidate for the magnetoreceptor in the avian retina. Therefore, we try to find putative interaction partners that could be part of a downstream signaling cascade.
Here we used the yeast-two-hybrid system to screen avian cDNA libraries for possible interaction partners of Cry4 in chicken and European Robin. We were able to uncover a Cry4 interaction network offering us clues about intracellular trafficking, function of Cry4 and down-stream targets in a signaling cascade of light-dependent magnetoreception. Furthermore, we tested directly the interaction of Cry4 with the ubiquitous iron-sulfur protein IscA1, that was suggested as Cry4 interaction partner by Qin et al. (2015, Nature Materials). Finally, by comparing the differences of the interactome of the cryptochromes in different species, we will enhance our understanding about their mediated signal pathways between migratory birds and non-migratory birds and further gain insight into the species evolution of this sort of conserved molecules.

Reference:
The radical-pair mechanism of magnetoreception. P.J. Hore and H. Mouritsen, 2016, ***Annu.Rev. Biophys***.A magnetic protein biocompass. Qin *et al*, 2015, ***Nature Materials***

Corresponding author: Haijia Wu@uni-oldenburg.de

Lecithin Long Term Therapy Ameliorate Disease Progression in a Charcot Marie Tooth Disease 1A Rat Model

Abdelaal T[1], Rasch L[1], Prukop T[1], Stassart RM[1], Nave KA[1], Sereda MW[1,2] Fledrich R[1]

[1]Max-Planck-Institute of Experimental Medicine, Department of Neurogenetics, Göttingen, Germany
[2]University Medical Center Göttingen, Department of Clinical Neurophysiology, Göttingen, Germany

Demyelination is a characteristic of peripheral neuropathies, such as the incurable Charcot Marie Tooth disease type 1A (CMT1A), which is caused by a duplication of the gene encoding the peripheral myelin protein 22kDa (PMP22). Even though most affected patients only seek medical advice in young adulthood, a moderate walking disability and electrophysiological abnormalities are usually already present in childhood. That CMT1A renders an early-onset disease is also supported by a Pmp22 transgenic rat model (CMT rat) in which the number of myelinated fibers per peripheral nerve never reaches a wildtype level through development. In line, Schwann cells display a pronounced downregulation of genes involved in lipid biosynthesis, which is also reflected by reduced lipid content in peripheral nerve. We hypothesize that Schwann cells in CMT1A have a compromised endogenous ability to synthesize lipids required for myelination and that a substitution of exogenous lipids could help to overcome that deficit. Hence we fed CMT rats with a chow enriched in lecithin, a major constituent of the myelin sheath. We found that treatment from postnatal day 2 to adulthood markedly ameliorated disease progression on the histological, electrophysiological and behavioral levels in CMT rats. Supplying patients with extra lipids may thus constitute a promising therapeutic approach for CMT1A disease.

Corresponding author: Abdelaal@em.mpg.de &Fledrich@em.mpg.de

Sponsors

We would like to thank the following sponsors for their generous support, which helped to make the conference possible:

- Gesellschaft für Biochemie und Molekularbiologie e.V.
- Sonderforschungsbereich 944
- Osnabrücker Universitätsgesellschaft e.V.
- Nikon GmbH
- Serva Electrophoresis
- Diagonal GmbH & Co. KG
- Carl Roth GmbH
- Macherey-Nagel GmbH & Co. KG
- Ewald Innovationstechnik GmbH
- Altromin Spezialfutter GmbH&Co. KG
- Eppendorf AG
- Fisher Scientific GmbH
- Sarstedt
- Neurowissenschaftliche Gesellschaft

Pressemeldung der Universität Osnabrück (Nr. 197 / 2016; 13.09.2016)

Einblick in die Forschung zur Molekularen Neurobiologie aus erster Hand: Uni lädt zur 8. Westerberger Herbsttagung ein

Die »Westerberger Herbsttagung« ist inzwischen gute Tradition: Bereits zum achten Mal veranstaltet die Universität Osnabrück, diesmal zusammen mit der Studiengruppe »Molekulare Neurobiologie« der Gesellschaft für Biochemie und Molekularbiologie (GBM), von Donnerstag, 22. bis Samstag, 24. September, ein Symposium zu den Perspektiven der molekularen Neurobiologie.

Im Rahmen der Tagung hält am Donnerstagabend Prof. Dr. Hans-Georg Breitinger, Leiter der Abteilung Biochemie und Prodekan für Studium und Lehre der „German University in Cairo“ (Ägypten) einen Vortrag zum Thema „Impressionen von Forschung und Lehre in Ägypten“. Der öffentliche Vortrag beginnt um 19 Uhr im Helikonien-Saal des Bohnenkamp-Hauses im Botanischen Garten der Universität Osnabrück, Albrechtstraße 29.

Unter dem Titel »Perspectives of Molecular Neurobiology: From Single Molecules to Systems« werden während der Herbsttagung neue Resultate der Forschung in Form von Vorträgen und Postern präsentiert. Dabei liegt der Fokus auch in der Förderung junger Forscher und deren Austausch mit etablierten Wissenschaftlern. Die besten Poster werden mit Posterpreisen ausgezeichnet.

Seit 2002 findet die Tagung alle zwei Jahre in der Biologie auf dem Westerberg statt. Im Vordergrund steht das Ziel, das breite Spektrum und die neuen Möglichkeiten durch die aktuellen Entwicklungen in der neurobiologischen Forschung zu präsentieren, wie sie auch bei der Behandlung von Störungen des Nervensystems wichtig sind. »Dabei sind vor allem in den letzten Jahren durch neuartige Methoden, die es ermöglichen, das Schicksal einzelner Moleküle zu beobachten, grundlegende Fortschritte erzielt worden, um die molekularen Mechanismen der Entstehung neurodegenerativer Erkrankungen zu untersuchen. Hierin sehen wir auch eine Chance, neue Ansätze für grundlegende therapeutische Interventionen zu entwickeln« so der Tagungsleiter Prof. Dr. Roland Brandt von der Universität Osnabrück, dessen Arbeitsgruppe über die Mechanismen der Alzheimerschen Erkrankung forscht.

Unter anderem referieren Prof. Dr. Jörg-Walter Bartsch (Marburg), Dr. Benjamin Cooper (Göttingen), Prof. Dr. Johannes Hirrlinger (Leipzig), Dr. Mike Karl (Dresden), Prof. Dr. Dieter Langosch (München), Prof. Dr. Konstanze Winklhofer (Bochum), und Dr. Geraldine Zimmer (Jena). Zu der Tagung sind alle Interessierten herzlich eingeladen.

Erneut beteiligt sich in diesem Jahr wieder die GBM an der Westerberger Herbsttagung. Die GBM e. V. ist die größte biowissenschaftliche Fachgesellschaft in Deutschland. Ihr gehören rund 5300 Mitglieder aus Hochschulen, Forschungsinstituten und der Industrie an. Ziel der Vereinigung ist die Förderung von Forschung und Lehre der Biochemie und molekularen Biowissenschaften, die Umsetzung wissenschaftlicher Erkenntnisse in Biotechnologie und Medizin und deren Verbreitung in der Öffentlichkeit. Neben der GBM wird die Tagung durch den lokalen Sonderforschungsbereich, die Universitätsgesellschaft Osnabrück e.V., die Neurowissenschaftliche Gesellschaft (NWG) und verschiedene Firmen unterstützt.

Meeting Site:

Bohnenkamp House in the Botanical Garden of the University of Osnabrück, Albrechtstraße 33, 49076 Osnabrück

Index of Abstracts

- Lectures

Lecture 11	Brain energy metabolism assessed by genetically encoded sensors for metabolites	Johannes Hirrlinger	16
Lecture 12	Deciphering limits of retinal regeneration – from mice to human	Mike O. Karl	17
Lecture 13	miRNA-96 is required for normal development of the auditory hindbrain	Hans Gerd Nothwang	18
Lecture 14	The role of Neuregulin-1 in peripheral nervous system disorders	Robert Fledrich	19

Index of Abstracts

- Poster

	tracking		
Poster 11	Study of hippocampal dendritic spine parameters in an old presymptomatic mouse model of amyloidosis	Marina Rierola	31
Poster 12	NF-kB dependent cell fate determination in the specification of human stem cells into glutamatergic neurons	Lucia Ruiz-Perera	32
Poster 13	Establishment of human nasal tissue and cell cultures as model systems for pharmacological research	Johanna Schäfermann	33
Poster 14	Genome editing of NF-KB family member c-Rel using mCRISPR/Cas9n for future applications in the nervous system	Thomas Schlüter	34
Poster 15	Impaired Ca^{2+}-signaling of the neuronal Ca^{2+}-sensor GCAP1 associated with retinal dystrophies cause aberrant regulation of retinal guanylate cyclase	Valerio Marino	35
Poster 16	Loss of Schwann cell autophagy might contribute to a late onset motoneuron disease in Plekhg5 deficient mice	Carsten Slotta	36
Poster 17	Enhanced synaptic transmission in mice with homozygous tau deletion	Abdala M. Ussif	37
Poster 18	Protein-protein interaction of the putative magnetoreceptor cryptochrome 4 expressed in the avian retina	Haijia Wu	38
Poster 19	Lecithin Long Term Therapy Ameliorate Disease Progression in a Charcot Marie Tooth Disease 1A Rat Model	T. Abdelaal	39

Contact:

Prof. Dr. Roland Brandt, Universität Osnabrück
Fachbereich Biologie/Chemie, Abteilung Neurobiologie
Barbarastraße 11, D-49076 Osnabrück
Tel.: +49 541969 2338, Fax:+49 541969 2354
Email: brandt@biologie.uni-osnabrueck.de
Web: www.neurobiologie.uni-osnabrueck.de

Advisory Board of the Study Group:

Prof. Dr. Jörg-Walter Bartsch (Marburg)
Prof. Dr. Hans-Georg Breitinger (Kairo)
Prof. Dr. Eckart Gundelfinger (Magedeburg)
Prof. Dr. Rolf Heumann (Bochum)
Prof. Dr. Tim Hucho (Köln)
Prof. Dr. Barbara Kaltschmidt (Bielefeld)
Prof. Dr. Christian Kaltschmidt (Bielefeld)
Prof. Dr. Matthias Kneussel (Hamburg)
Prof. Dr. Karl-Wilhelm Koch (Oldenburh)
Prof. Dr. Stefan Lichtenthaler (München)
Prof. Dr. Hans Gerd Nothwang (Oldenburg)

Local Organizers:

Dr. Lidia Bakota, Henning Borgstädde, Bettina Flenker, Christian Gach, Susanne Grosse-Kettler, Dr. Wilfried Hamann, Vanessa Herkenhoff, Mariya Hrynchak, Dr. Maxim Igaev, apl. Prof. Gunnar Jeserich Benedikt Niewidok, Marina Rierola-Carrera, Abdala Ussif, Daniel Villar-Romero, with the help of local students

Opening of the Meeting and Welcome Addresses:
Roland Brandt (Department of Neurobiology) and Susanne Menzel (designated Vice President for Research and Career Development, University of Osnabrück)

Session I: Molecules (Chair: Lidia Bakota)

Lecture 1: Benjamin Cooper (Max-Planck-Institute of Experimental Medicine, Göttingen)

Lecture 2: Hans-Georg Breitinger (German University in Cairo, Egypt)

Lecture 3: Dieter Langosch (Technical University of Munich)

Lecture 4: Jörg Isensee (University Medicine, Köln)

Poster Preview 1: Dana Elbers

Poster Preview 2: N. Helge Meyer

Öffentlicher Vortrag: Hans-Georg Breitinger (German University in Cairo, Egypt)

Get Together with Drinks and Live Music

Session II: Networks part I (Chair: Jörg-Walter Bartsch)

Lecture 5: Christoph Kaether (Leibniz Institute on Aging, Jena)

Lecture 6: Konstanze Winklhofer (Ruhr-University Bochum)

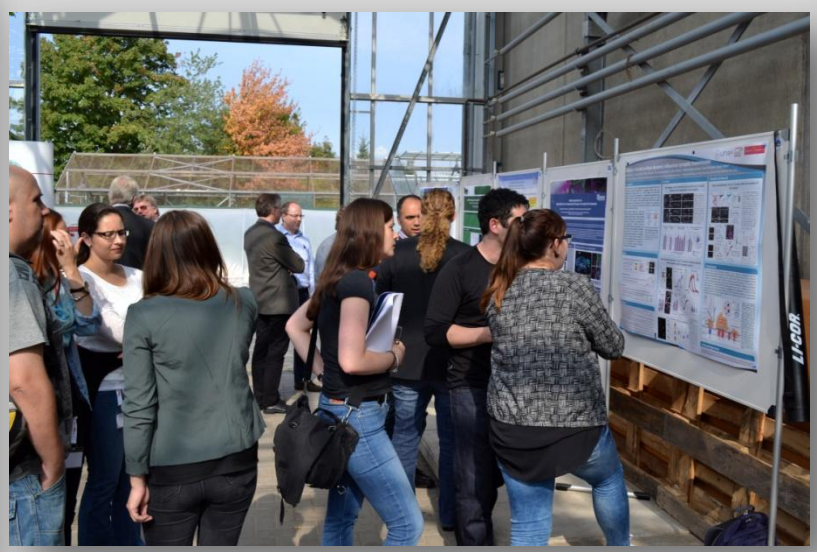
Poster Preview 3: Johannes F.W. Greiner

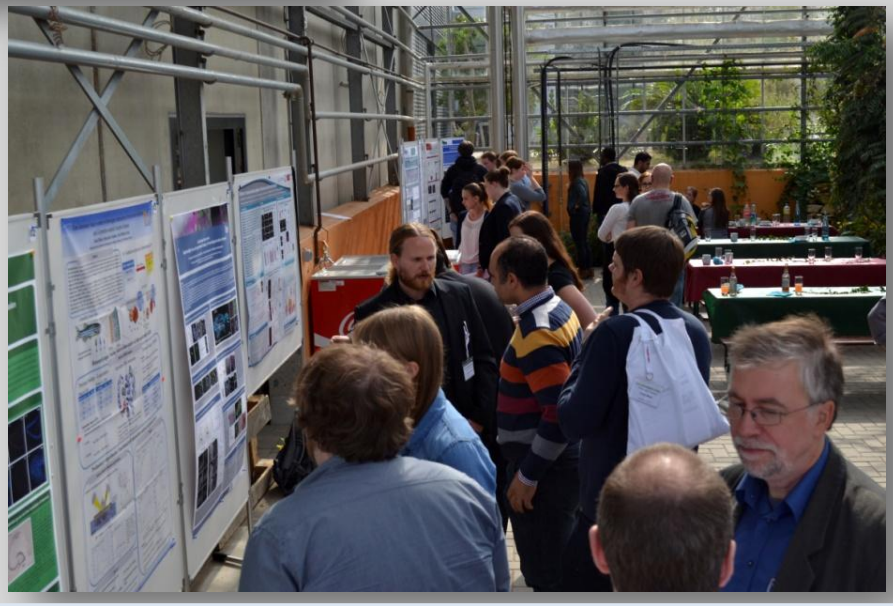
Lecture 7: Marco Rust (Philipps University of Marburg)

Lecture 8: Geraldine Zimmer (Jena University Hospital)

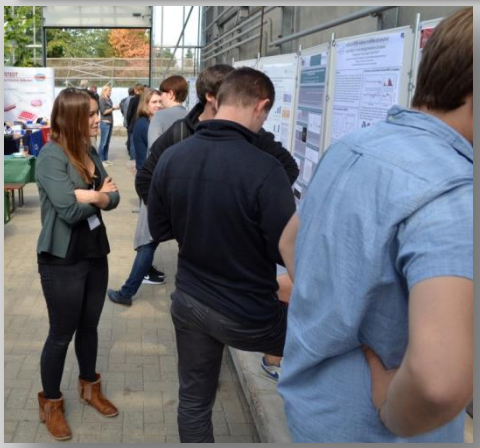
Poster Preview 4: Carsten Slotta

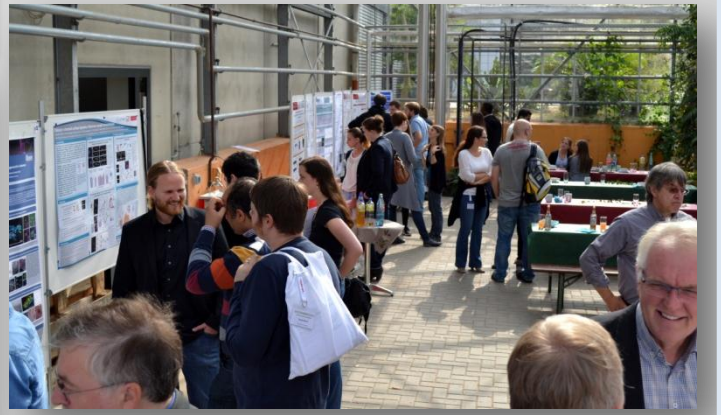
Poster Viewing

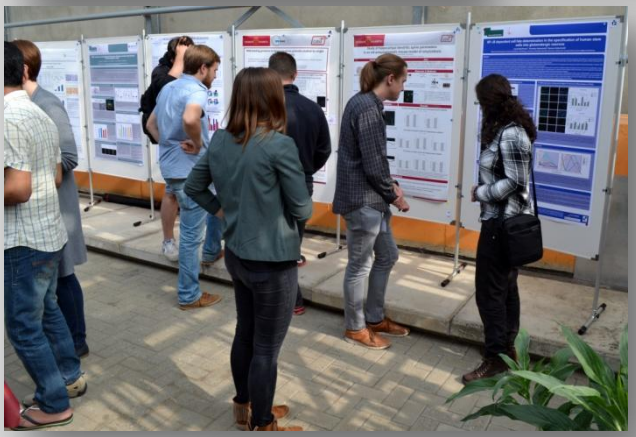


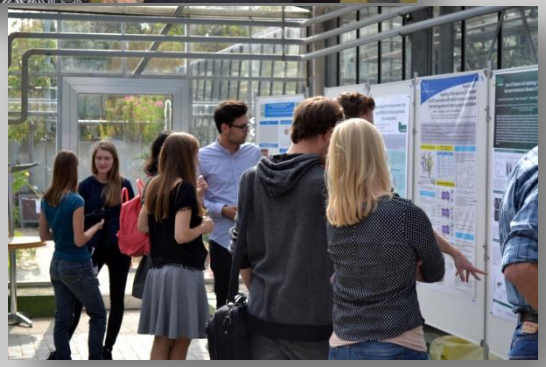


Poster Viewing and Company Exhibition





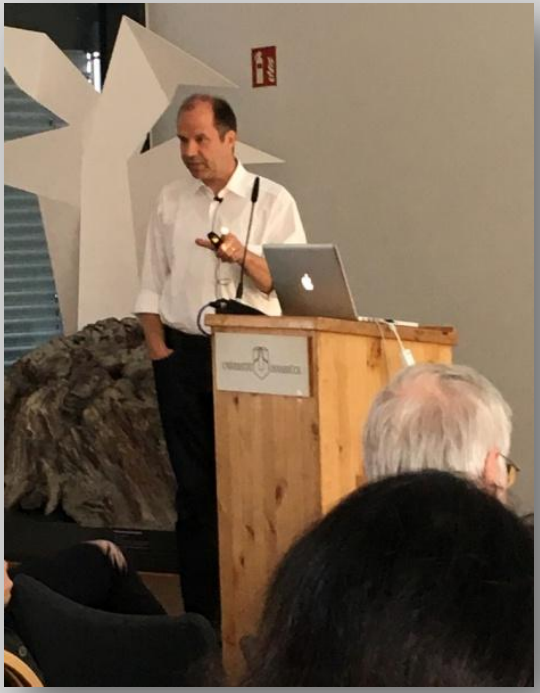




Session III: Networks part I (Chair: Gunnar Jeserich)

Lecture 9: Karl-Wilhelm Koch (University of Oldenburg)

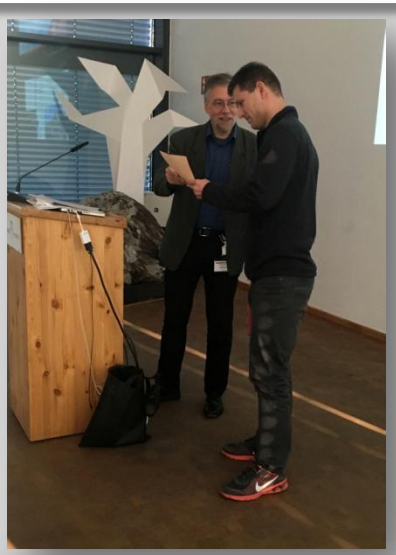
Lecture 10: Jörg-Walter Bartsch (Philipps University of Marburg)



Poster Preview 5: Abdala M. Ussif

Award of Poster Prizes

1. Prize: Jennifer Heck, Leibniz-Institute Magdeburg
2. Prize: Benedikt Niewidok, University of Osnabrück
3. Prize: Tamer Abdelaal, Max-Planck-Institute Göttingen



Session IV: Systems (Chair: Roland Brandt)

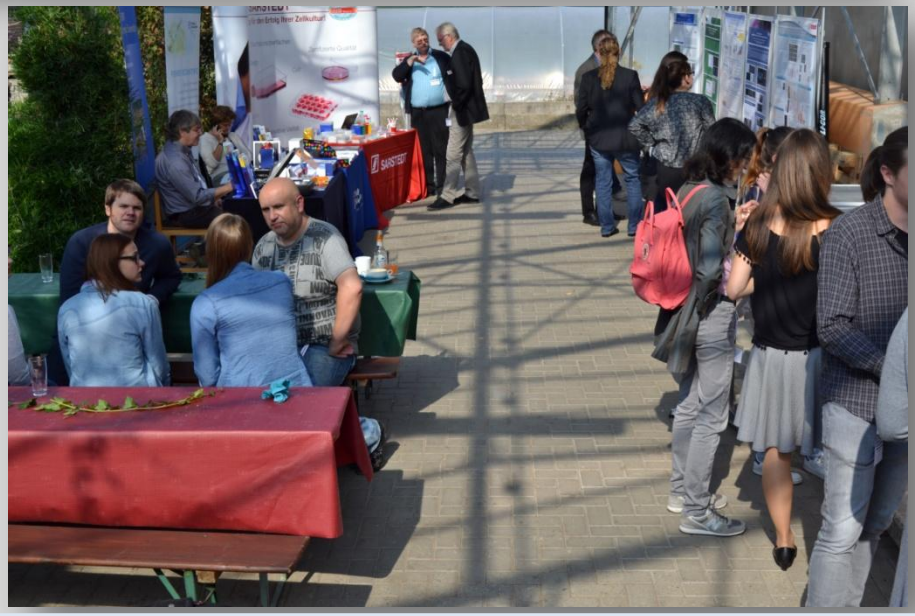
Lecture 11: Johannes Hirrlinger (University of Leipzig)

Lecture 12: Mike Karl (German Center for Neurodegenerative Diseases, Dresden)

Lecture 13: Hans Gerd Nothwang (University of Oldenburg)

Lecture 14: Robert Fledrich (Max-Planck-Institute of Experimental Medicine, Göttingen)

Discussions during Buffet and Coffee



Discussions during Buffet and Coffee

Discussions during Buffet and Coffee

The Organization Crew in the Background

8th Westerberger Herbsttagung
together with the
Meeting of the GBM study group "Molecular Neurobiology"

Perspectives of Molecular Neurobiology: From Single Molecules to Systems

September 22-24, 2016

Bohnenkamp-Haus,
Botanical Garden of the University of Osnabrück