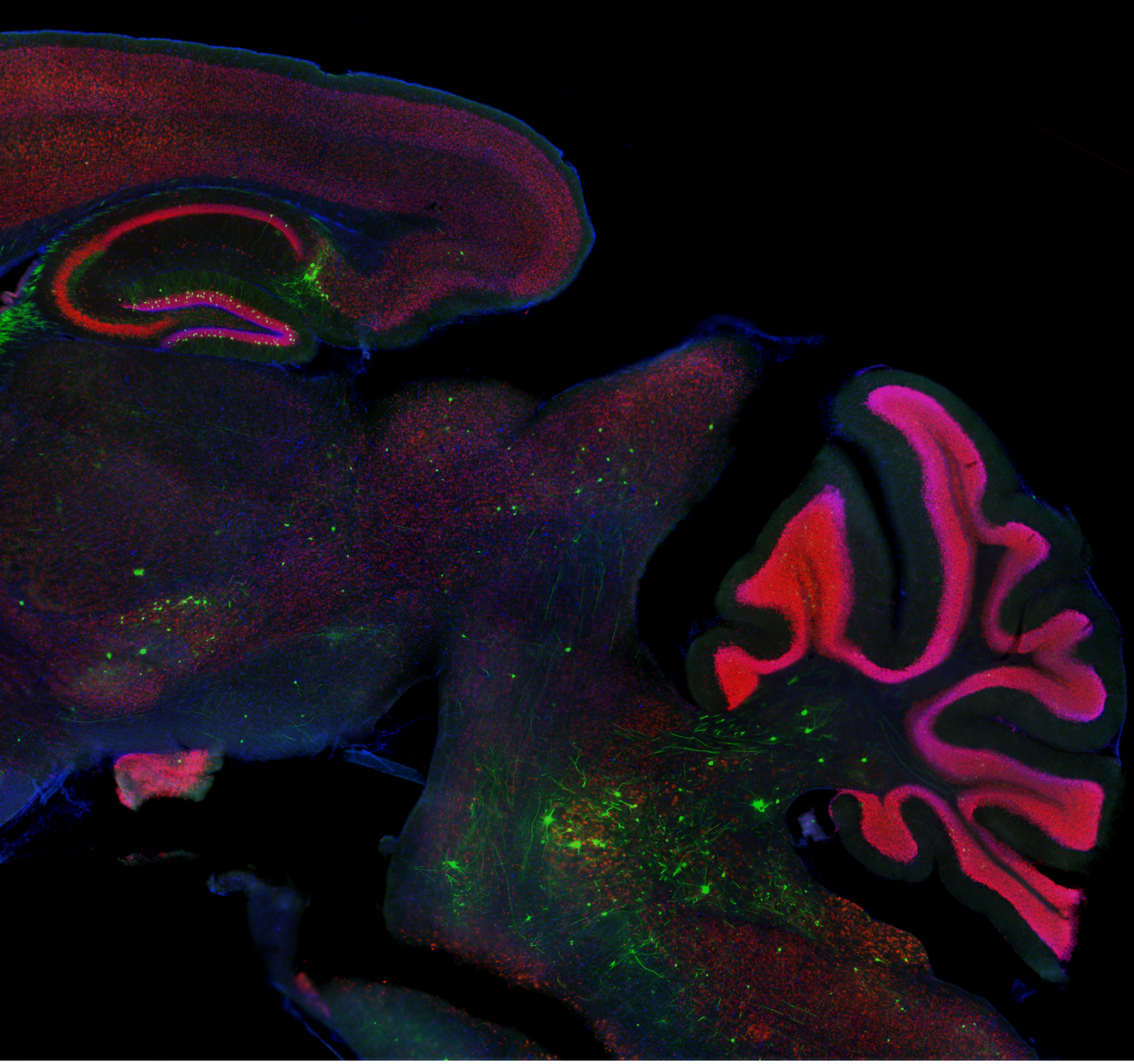

ZMNH

Center for
Molecular
Neurobiology
Hamburg

Research Report
2009 - 2014

Universitätsklinikum
Hamburg-Eppendorf

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Cover:
Sagittal section of the brain of a mouse mutant ($reln^{fl/fl}$ cre neg) expressing enhanced Green Fluorescent Protein (eGFP) under the Thy1 promotor. Section counterstained for NeuN (red) and DAPI (blue). This cre-negative mutant shows normal brain structure comparable to wild type, serving as a control for a new conditional Reelin knockout mouse.
Image from Jasmine Pahle, ZMNH Institute for Structural Neurobiology

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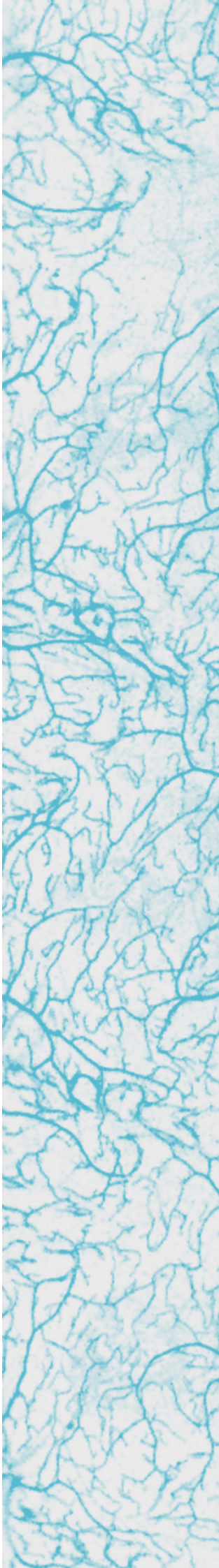

Welcome Address of the Dean and the Director of the University Medical Center Hamburg-Eppendorf

Since its inception in 1987 the ZMNH has rapidly developed into a focal point of excellence in basic biomedical neuroscience research. Today, the institute is internationally regarded as world-class institution in the field of neurobiology and is considered as one of the premier university-affiliated research centers in Germany. The ZMNH has been the catalyst of a multitude of interdisciplinary projects and has substantially advanced neuroscience at the highest level. The combination of rich output of seminal scientific work published in the most renowned international peer reviewed journals, and the numerous scientific awards bestowed upon the researchers of the ZMNH attest to the institute's international reputation. The impressive performance of the

ZMNH is a reflection of exemplary cooperation between basic and clinical aims. Its research concerns fundamental questions of molecular neurobiology with a special emphasis on understanding the molecular mechanisms of synaptic transmission and plasticity in health and disease. In many cases, research results at the ZMNH are swiftly applied to diagnostic and therapeutic problems in medicine and human genetics. This process is greatly facilitated by the generation and analysis of transgenic and *"knock-out"* mouse lines as indispensable models for the study of the molecular and cell biological basis of the diseases of the nervous system. The study of mutant mouse strains generated at the ZMNH has led to identification of novel disease genes and has greatly helped in understanding and elucidating the pathophysiology of human nervous system disorders. As such, the ZMNH has significantly contributed on various levels to improvements in diagnosis and therapy of human disease.

In the last five years the ZMNH successfully underwent a phase of important recruitments. This process was initiated by imminent changes in leadership. The 'guard' at the ZMNH consists of five preeminent scientists directing the Institutes of Molecular and Cellular Cognition (Dr. Kuhl), Molecular Neurogenetics (Dr. Kneussel), Structural Neurobiology (Dr. Frotscher), Synaptic Physiology (Dr. Oertner), and Neuroimmunology and Multiple Sclerosis (Dr. Friese). In addition several independent research groups were recruited to the ZMNH. The strategic hiring not only of the ZMNH but of the entire UKE in this area of neurobiological research over the last several years has allowed us to gather an impressive number of basic and clinical scientists who are working on different aspects of this endeavor, spanning from systems analysis to molecular neurobiology.

We take pride in fostering basic discovery research at the ZMNH of our University Hospital. The ZMNH served over the years as model that has been copied at other places in Germany. This success is also owed to an external scientific advisory board which has the important function of evaluating the performance of the ZMNH at regular intervals and to advise the Dean of the Faculty of Medicine as well as the Head of the University Medical Center Hamburg-Eppendorf (UKE) on matters of strategic importance. As a result, the UKE is fully committed to conserve the model character of the ZMNH. We are aware that success comes at a cost and will further strengthen the ZMNH as highly supportive research environment, with minimal administrative burden and teaching obligations and endowed with generous personnel and materiel support. We are convinced of our concept and wish the ZMNH success in our common endeavour to understand and fight the debilitating diseases of the brain.

Uwe Koch-Gromus, M.D., Ph.D., Dean UKE
Burkhard Göke, M.D., Director UKE

ZMNH Director's Message

The ZMNH is a research center of the Faculty of Medicine at the University Medical Center Hamburg-Eppendorf (UKE). The mission of the ZMNH is to conduct basic research into the molecular mechanisms of synaptic transmission of the brain in health and disease. To understand the brain both as the organ of mental function and as a target of disease we will need to understand fundamental brain mechanisms in molecular and cellular detail. Such an understanding is a prerequisite for the development for new therapeutics to combat the neurological and mental illnesses that ever-increasingly affect both our young and aged population. The ZMNH has a strong foundation of basic discovery research which always has been the engine that drives the development of new and better therapies of debilitating diseases of the nervous system. In addition to research, the ZMNH teaches advanced courses in Neurobiology, engages in graduate training, and carries out a two-year graduate course program that has been widely appreciated and used across the different faculties of the university and the institutes of the UKE to train students in Molecular Biology.

As a step towards achieving this mission, I am delighted to report that the ZMNH has attracted world-renowned neuroscientists. The ZMNH has undergone a generational turnover which allows its current investigators to decisively shape the scientific, conceptual and organizational directions for the next decade. The Center today comprises five institutes which are headed by full professors. In addition, the Center provides space and infrastructure for twelve internally and externally funded independent research groups. Although working in different animal models and using a wide range of different techniques, all these scientific groups focus on understanding fundamental mechanisms that control brain functions. My Institute for Molecular and Cellular Cognition (Dietmar Kuhl) is taking an integrative approach to the studies of learning and memory building on expertise in genetics, biochemistry, molecular and cellular physiology, and behavioral analysis. The Institute for Molecular Neurogenetics (Matthias Kneussel) aims to understand cellular processes of synaptic plasticity by studying intracellular cytoskeleton-based transport, synaptic turnover and anchoring of neurotransmitter receptors. The Institute for Structural Neurobiology (Michael Frotscher) studies the mechanisms that are responsible for the maintenance of cortical architecture and the correct positioning of neurons and their processes. The Institute for Synaptic Physiology (Thomas Oertner) uses optogenetic methods to understand the rules and molecular mechanisms that govern the ability to learn and to remember. The Institute for Neuroimmunology and Multiple Sclerosis (Manuel Friese) is interested in pathomechanisms of neuroimmunological disorders, in particular multiple sclerosis, and tries to implement the results in novel therapies for this disease.

A major change that has been instituted was the integration of a larger number of junior research group leaders into the ZMNH. We have enticed exceptional young scientists to strengthen the Center as independent Research Group leaders. These smaller research groups enjoy the acces-

sibility to all developed expertise and infrastructure and bring in turn new themes and techniques. The Research Group for Development and Maintenance of the Nervous System (Edgar Kramer) is interested in the function of cell surface receptor signaling in the nervous system during development and aging. The major goal of the Research Group for Neuronal Translational Control (Kent Duncan) is to understand how translational control contributes to neuronal function. The Research Group Neuronal Patterning and Connectivity (Peter Soba) aims to understand patterning mechanisms at the molecular level that allow dendrites and axons to innervate appropriate targets and form functional circuits. The Research Group Neuronal Development (Froylan Calderon de Anda) is particularly interested in understanding how neurons develop axons and dendrites in vivo, in order to gain insight into the cellular and molecular events that may underlie neuropsychiatric diseases. The group Behavioral Biology (Fabio Morellini) is specialized in the analysis of animal behavior and focusses on cognitive function and coping strategies in mice. Work of the Research Group for Neuronal Networks in Developing Brain (Ileana L. Hanganu-Opatz) centers on the mechanisms of cortical "wiring" during early development by analyzing the role of electrical activity in brain maturation; besides being part of the ZMNH, the group is also affiliated with the Department of Anatomy of the UKE. The research group of Experimental Neuropediatrics is affiliated with the Department of Pediatrics at the UKE and hosted by the ZMNH to foster translational research in the field of developmental neurobiology; major research interests include pathophysiological processes in ion channel disorders (e.g. epilepsy) and creatine deficiency syndromes. The Biomarker and Translational Research Group (Ole Pless) offers research services for Drug Discovery and is operated by the European ScreeningPort but is situated in the ZMNH. Most recently two additional Research Group leaders were recruited to the ZMNH. The group Neuronal and Cellular Signal Transduction (Meliha Karsak) studies neural membrane receptor function and molecular interactions with special interest of pathologically associated protein variants. The Emmy Noether Group Neuronal Protein Transport (Marina Mikhaylova) is interested in understanding the molecular mechanism underlying synaptic clustering, specifically the group explores how transport of synaptic proteins and dendritic secretory organelles may contribute to functional compartmentalization of dendritic segments. Finally, our center has become home of a Guest Scientist group and two Emeritus groups. Research of the Guest Scientist group (Jürgen Schwarz) is concerned with the role of voltage-dependent ion channels, especially erg K channels, in the excitability of neurons. Dietmar Richter, founding director of the ZMNH, heads the Emeritus Group Cell Biochemistry and Clinical Neurobiology and Melitta Schachner Carmartin the former director of the Institute for Biosynthesis of Neural Structures continues her research on the function of neural recognition molecules in the developing and adult brain at the ZMNH.

Two former directors of the ZMNH left in 2011. Olaf Pongs, former head of the Institute for Neural Signal Transduction, retired and Roland Martin, former head of the Institute for Neuroimmunology

and Multiple Sclerosis Research, relocated his department to the University of Zurich. I am pleased to report that the research group leader Hans-Christian Kornau secured an independent position at the Charité in Berlin and Dirk Isbrandt who directed the research group Experimental Neuropediatrics as Heisenberg Professor at the ZMNH was appointed to a prestigious professorship at the University of Bonn and the DZNE.

Research at the ZMNH is supported by central scientific service units for Bioanalytics (Sabine Hoffmeister-Ullerich), Morphology and Electronmicroscopy (Michaela Schweizer), Systems Biology (Christian Schulze), and by Transgenic Mouse Facility (Irm Hermans-Borgmeyer). These facilities are led by highly competent and experienced scientists, who are administratively associated with individual institutes but provide services to the entire Center. Also available is an in-house Scientific Workshop (Torsten Renz, Fritz Kutschera) that has proven indispensable for the development and maintenance of scientific instrumentation, a library (Heiko Pump), and an in-house IT Service and Development unit (Hans-Martin Ziethen) which autonomously manages the entire data transfer and storage needs of the ZMNH. Furthermore, a largely independent administration led by Katja Husen ensures efficient and flexible administrative support. In many decisive steps I could rely on her advice and judgement. For future strategic planning we will continue to draw on the expertise of our external scientific advisory board.

I could not be more pleased that at the Center I found colleagues that share my interest in bridging the gap between molecules and mind, and trying to understand the brain in health and disease at many levels utilizing multidisciplinary approaches and new ways of integrating insights from many areas of technical expertise. I feel privileged to work with such a distinguished group of researchers and have complete faith that the ZMNH will act as a research accelerator and a focal point for innovation at the University Medical Center. I am more optimistic than ever that research at the ZMNH, in collaboration with our colleagues on the University Hospital campus, significantly advances our understanding of the brain and helps to insightfully and effectively treat the avalanche of neurological and mental ill-health disorders that account for almost half of the disease burden of our community. I invite you to peruse this booklet and share our pride in our accomplishments and our optimism for the future.

Dietmar Kuhl, Ph.D., Director, Center for Molecular Neurobiology (ZMNH) University Medical Center Hamburg-Eppendorf (UKE)

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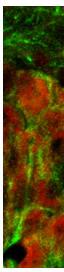

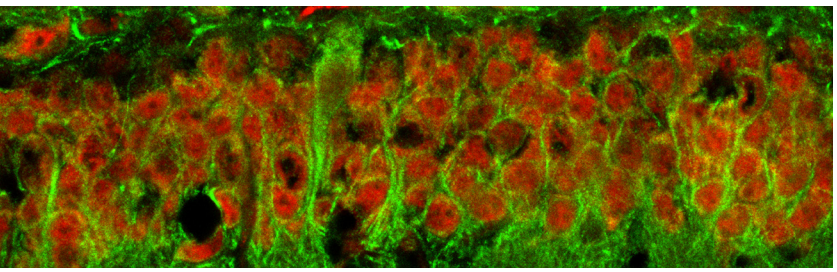

Research Reports of the ZMNH Institutes

Institute of Neuroimmunology and Multiple Sclerosis (INIMS)[1]

Manuel A. Friese

After the first three constitutive years since its foundation in 2006 the Institute for Neuroimmunology and Clinical Multiple Sclerosis Research (INIMS) has undergone a profound developmental process implementing excellent infrastructural and operative conditions for the conduction of state-of-the art translational research in multiple sclerosis (MS). Committed to the mission to better understand the etiology and pathogenesis of MS and develop efficacious and well-tolerated treatments for all courses and stages of MS, the INIMS also constantly provides excellent patient care. In order to achieve these goals it was essential to interlock basic research with clinical activities ensuring access to MS patients as well as setting up operative platforms for conducting clinical studies. With the financial support of the Hertie-Foundation and the German Federal Ministry of Education and Research, INIMS became the central academic partner of the research consortium NEU^2 (www.neu-quadrat.de) in 2009.

This development greatly facilitated the creation of a translational institute for MS research with a unique profile consisting of three operational units: INIMS integrates (i) a basic science institute located at the Centre for Molecular Neurobiology Hamburg (ZMNH) with (ii) a clinical research platform located at the dedicated day hospital for patients with MS and other neuroimmunological diseases (outpatient clinic) affiliated with the Department of Neurology; and operates (iii) a section for MS imaging (SeMSi) dedicated to MRI studies in collaboration with the Department of Neuroradiology. The INIMS basic science institute is equipped with state-of-the-art cell and molecular biology laboratories as well as *in-vivo* facilities focussing on immunology and neurobiology research. The INIMS closely interacts with the Department of Neurology to assure continuity in inpatient and outpatient care of neuroimmunological patients, biomaterial collection (MS biobanking with samples of more than 2,000 patients) and continuous medical education as well as teaching of students. The imaging section is equipped with a 3T Siemens Skyra MRI scanner and a fully established infrastructure destined predominantly to MS diagnostics and research. Moreover, the European ScreeningPort, which became a designated Fraunhofer Institute (IME SP) in 2014, operates a Biomarker and Discovery Biology platform located at the INIMS. The IME SP closely collaborates with the INIMS in biomarker development for MS as well as treatment trials in several projects, which are mainly associated with the consortium NEU^2 .

Under the leadership of Roland Martin, who headed the institute from 2006 to 2011, and Christoph Heesen (head of the MS day hospital and outpatient clinic since 2006) the INIMS extended its basic, translational and clinical research program and further improved MS patient care. In 2011 Roland Martin was appointed as professor at the University of Zurich and left the INIMS. From 2011 until 2014 the INIMS was provisionally headed by Dietmar Kuhl/ZMNH. In 2014 Manuel Friese was appointed as director of the institute.

As leaders of associated research groups, two junior scientists were hosted by the INIMS, Manuel Friese (Neuroimmunology), supported by the Emmy Noether programme of the DFG (German Research Foundation) and Stefan Gold

[1] Renamed in 2014

(Neuropsychiatry in MS) supported by a Marie Curie International Reintegration Grant from the EU as well as a Heisenberg fellowship from the DFG. Manuel Friese was appointed as Professor of Neuroimmunology in 2013 and has been heading the INIMS since 2014. Stefan Gold accepted an appointment as associate professor at Charité Universitätsmedizin Berlin in 2014, but maintains an affiliation with the INIMS.

Embedded into the excellent, open and stimulating ZMNH environment the INIMS has profited in many aspects from collaborations and services, but has also advanced fruitful interactions and specific projects with research groups at the UKE as well as within the consortium NEU^2 and beyond. Related to the translational profile of the INIMS the following report will be structured in a basic and clinical research section and the respective groups operating in these sections.

1. Basic Research

FRIESE GROUP

1.1 Characterising CD8$^+$T cells in multiple sclerosis *(Friese, Piedavent, Steinbach, Ufer, Willing)*

T lymphocytes can be divided into CD4$^+$ and CD8$^+$ T cells, of which CD8$^+$ T cells predominate in MS lesions. However, the precise role of CD8+ T cells in the disease aetiology and pathogenesis is still not understood. Especially it is unknown what conventional CD8$^+$ T cells infiltrating the brain recognise with their diverse T cell receptors (TCR) and whether they contribute to CNS tissue damage. Furthermore, mechanisms leading to their dysregulation and brain infiltration remain to be defined.

MS has long been considered to be a CD4$^+$ T-cell-mediated disease, amongst others, attributed to the fact that the best-established genetic associations are located within the HLA class-II region. Additional and independent associations with the HLA class-I region, including a protection by the HLA-A*0201 allele and a predisposition by HLA-A*0301, indicate an involvement of CD8$^+$ T-cells in the pathogenesis, with controversial data in the past. However, several recent genetic association studies reconfirmed the protective effect of HLA-A*0201 (Fugger et al., 2009; Willing and Friese, 2012). We provided the first functional evidence based on a humanized mouse model of MS, which is double-transgenic for HLA-A*0301 and an HLA-A*0301-restricted, myelin-recognizing TCR from an MS patient. This murine model spontaneously develops optic neuritis and other MS-like disease symptoms initiated by infiltrating CD8$^+$ T-cells. Corresponding to the studies on human genetics, addition of transgenic HLA-A*0201 in this model has a protective effect by reducing the number of autoreactive CD8$^+$ T-cells, possibly through enhanced negative selection in the thymus, which would imply a cross-reactivity of HLA-A*0301-restricted autoreactive TCRs with HLA-A*0201. A high similarity of the TCR binding surface of HLA-A*0301 and HLA-A*0201 supports this hypothesis (McMahon et al., 2011).

Although the phenotype and specificity of CNS-infiltrating CD8$^+$ T cells remains largely unknown, interleukin (IL)-17-producing CD8$^+$ T cells are enriched in active MS lesions, implicating a central role for this specific population

in MS pathogenesis. In human peripheral blood, IL-17 production by $CD8^+$ T cells is restricted to a subset that belongs to the mucosal-associated invariant T (MAIT) cells. MAIT cells resemble a unique innate-like T-cell population that is restricted to the major histocompatibility complex (MHC)-related protein 1 (MR1) and is activated by bacteria and yeast but not virus-infected cells. Metabolites of riboflavin biosynthesis pathways in bacteria and yeast complex with MR-1 and specifically activate MAIT cells. Since the role of $CD8^+$ MAIT cells in MS is controversial, we recently explored their frequency, their ability to infiltrate the CNS and mechanisms that might influence their CNS infiltration in MS patients. We were able to show a reduction of $CD8^+$ MAIT cell frequencies in the peripheral blood of MS patients. Furthermore, $CD8^+$ MAIT cell frequencies inversely correlated with IL-18 serum levels in MS patients. Therefore, a reduction in peripheral blood frequencies might be explained by an IL-18-mediated activation, promoting the infiltration of $CD8^+$ MAIT cells into CNS lesions of MS patients that we indeed detected by immunohistochemistry. However, $CD8^+$ MAIT cells do not enrich in the CSF of MS patients implicating that they might preferentially use other routes for entry to the perivascular space and parenchyma, as for example directly via parenchymal vessels (Willing et al., 2014).

Apart from IL-17 MAIT cells and $CD4^+$ Th-17 produce other cytokines that might contribute to the MS pathogenesis. They include interleukin-21 (IL-21). We investigated the expression of IL-21 and its receptor IL-21R on mRNA and protein level in acute, chronic, and inactive MS lesions. We were able to show expression of IL-21 by the majority of $CD4^+$ T cells and of IL-21R by the majority of T cells, including $CD4^+$ and $CD8^+$ T cells, but also by B cells in acute and chronic MS lesions. This suggests a possible role of IL-21 in MS pathogenesis. We also detected expression of IL-21 and IL-21R in neurons in the cortical gray matter, which may implicate IL-21 in modulating neuronal responses to inflammation and neuronal injury (Tzartos et al., 2011).

Publications

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1.2 Instrumental role of dendritic cells in initiating and amplifying a CNS-specific autoimmune response *(Friese, Schattling, Steinbach, Ufer)*

Dendritic cells (DC) coordinate the innate and adaptive immune response. Therefore, they are involved in the initiation of an autoimmune response. However, many fundamental questions are still unanswered and the mechanisms how they induce and amplify an autoimmune response is ill defined.

The development of an encephalitogenic T cell response in the CNS is a multi-step process, which depends on the encounter of cognate DCs with CNS-infiltrating T cells. However, it is incompletely understood how a pro-inflammatory environment that facilitates reactivation of autoreactive T cells is generated in the CNS. We recently investigated the role of neutrophils in

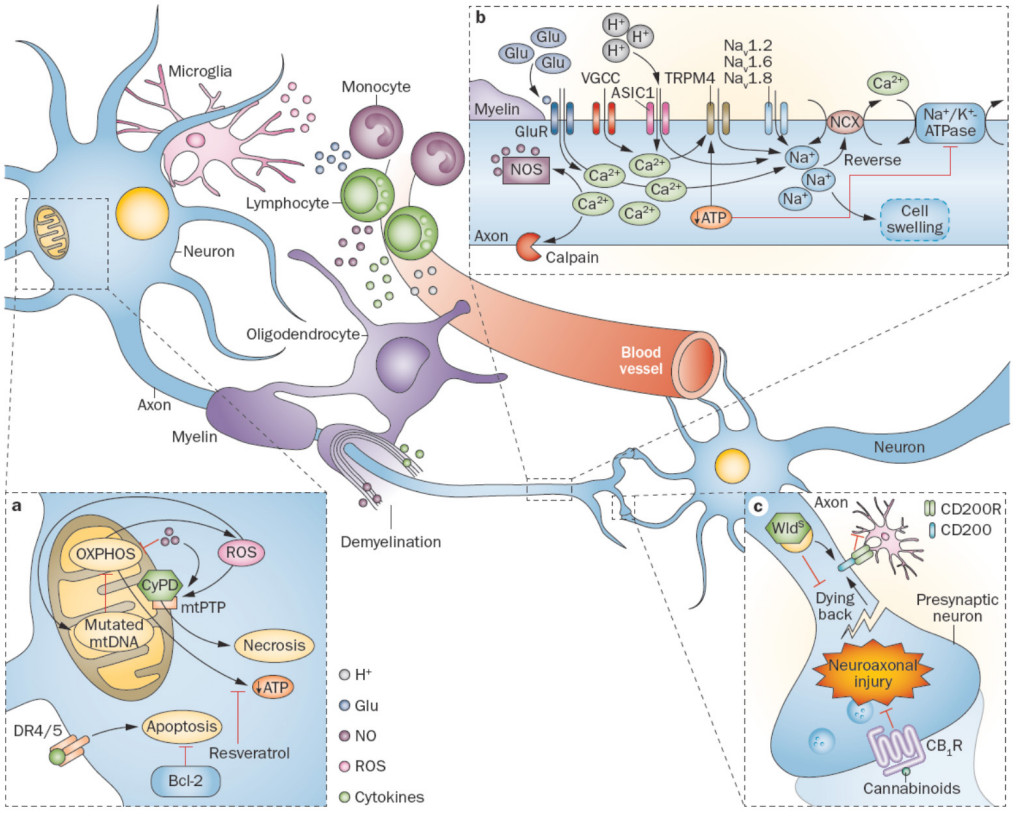

Figure 1. Neuronal injury and counteracting pathways in chronic CNS inflammation (Friese et al., 2014).

the initiation of a chronic CNS inflammation and were able to demonstrate an important contribution of neutrophils in setting up early, preclinical CNS-inflammation in EAE. CNS-infiltrating neutrophils produce several pro-inflammatory molecules and are able to mature bone marrow-derived dendritic cells *in vitro*, thereby enhancing their capacity to re-stimulate myelin-specific T cells. In the absence of CNS-infiltrating neutrophils *in vivo*, the maturation of microglia and infiltrating monocytes is significantly decreased, resulting in a strong impairment of leukocyte recruitment to the CNS and amelioration of clinical disease. Overall, this shows that inside the CNS neutrophils provide local cofactors that are required for the maturation of myeloid cells into DCs representing an essential step for the local amplification of myelin-specific T cells and the development of autoimmune disease (Steinbach et al., 2013).

Tissue injury in the CNS is characterized by oxidative stress (e.g. hydrogen peroxide; H_2O_2) and the release of a manifold of stress mediators, among them adenosine-based mediators. Since these factors modulate the open-probability of the calcium-permeable transient receptor potential melastatin-2 (TRPM2) cation channel, this channel has been implicated in CNS injury. While TRPM2 did not contribute to EAE pathogenesis (unpublished data), we recently explored its contribution to stroke pathophysiology. We were able to show that TRPM2 detrimentally contributes to ischemic brain injury following stroke, which primarily depends on its role in activating peripheral immune cells. Although Trpm2-deficient neurons are protected against hypoxic stimuli *in vitro*, TRPM2 regulates neutrophil and macrophage infiltration *in vivo* that primarily determines its injurious role in stroke, while Trpm2 deficiency in CNS-resident cells does not contribute to stroke outcome (Gelderblom et al., 2014).

Publications

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1.3 Investigating neuronal ion channels in determining neurodegeneration in multiple sclerosis *(Friese, Schattling, Steinbach, Ufer)*

Inflammatory insults lead to progressive degeneration of axons and neurons that is key for the development of permanent neurological disability in chronic inflammatory diseases such as MS. Our neurobiological studies focus on the molecular mechanisms of this inflammation-induced neuronal degeneration. Stress response pathways can either determine neuronal injury, but hormetic stress also stimulates signalling pathways that enhance the abilities of neurons to resist inflammatory stressors.

A growing body of evidence has suggested that the inflammatory insults in MS determine neurodegeneration at any stage of the disease by causing axonal and neuronal mitochondrial dysfunction, energy failure and alterations of ion exchange mechanisms (Friese et al., 2014; Schattling et al., 2014). However, only few neuronal receptors/ion channels have been identified, which sense the inflammatory environment and thereby contribute to inflammation-induced neurodegeneration. We recently identified two previously unrecognised ion channels, which crucially contribute to maladaptive cation handling under inflammatory conditions. First, we discovered that inflammation lowers the pH from 7.4 to approximately 6.6 in the CNS, which activates Na^+- and Ca^{2+}-permeable acid sensing ion channel-1 (ASIC1) that is expressed in neurons and axons and thereby contributes to neurodegeneration. Subsequently, we identified a licensed drug (amiloride), which was able to attenuate neurodegeneration in the mouse model of MS and is now taken into a clinical trial in MS (Vergo et al., 2011). Second, we recently discovered the ion channel transient receptor potential melastatin 4 (TRPM4) to be functionally expressed in CNS neurons. This channel is pathologically activated by a rise in intracellular calcium and a lowering in neuronal ATP, resulting in the conduction of monovalent but not divalent cations. Pathological conditions in which ATP reduction occur together with a rise in intracellular calcium, lead to TRPM4 channel activity resulting in neurodegeneration as seen in CNS inflammation. We were able to show that uncontrolled activity of TRPM4 does not only depolarize the cell but also results in osmotic stress and cell death *in vitro* (Schattling et al., 2012).

Non-invasively quantifying neuronal injury remains a challenge in neurological diseases. One potential candidate as blood biomarker of neuronal damage is the neuron-specific enolase (NSE), an isoenzyme of the glycolytic enzyme enolase, which is exclusively expressed in neurons and cells of neuroendocrine origin. We investigated whether the plasma concentration of NSE can be used to quantify the extent of neuronal injury in animal models of MS, experimental autoimmune encephalomyelitis (EAE) and stroke. Plasma NSE levels correlated significantly with stroke size, EAE score and histopathological damage in EAE. Investigations into the dynamics of neuronal loss over time correlated well with the dynamics of NSE levels. NSE even predicted the onset of EAE, before clinical signs were recordable. Therefore, plasma NSE is a valid and simple experimental biomarker that allows quantifying the degree of neuronal injury in a non-invasive approach (Gelderblom et al., 2013).

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J., Glatzel, M., Gerloff, C., Friese, M.A., et al. (2013). Plasma levels of neuron specific enolase quantify the extent of neuronal injury in murine models of ischemic stroke and multiple sclerosis. Neurobiol Dis 59, 177-182.

Schattling, B., Eggert, B., and Friese, M.A. (2014). Acquired channelopathies as contributors to development and progression of multiple sclerosis. Exp Neurol 262 Pt A, 28-36.

Schattling, B., Steinbach, K., Thies, E., Kruse, M., Menigoz, A., Ufer, F., Flockerzi, V., Bruck, W., Pongs, O., Vennekens, R., et al. (2012). TRPM4 cation channel mediates axonal and neuronal degeneration in experimental autoimmune encephalomyelitis and multiple sclerosis. Nat Med 18, 1805-1811.

Vergo, S., Craner, M.J., Etzensperger, R., Attfield, K., Friese, M.A., Newcombe, J., Esiri, M., and Fugger, L. (2011). Acid-sensing ion channel 1 is involved in both axonal injury and demyelination in multiple sclerosis and its animal model. Brain 134, 571-584.

GOLD GROUP

1.4 Sex-related factors in the pathobiology of autoimmune disorders *(Engler, Friese, Gold, Heesen, Patas)*

Several clinical observations strongly support the role of sex-related factors in the pathogenesis, activity, and progression of autoimmune disorders (Voskuhl & Gold, 2012): Many autoimmune disorders including MS affect women more frequently than men. Moreover, in female MS patients, pregnancy is associated with a substantial decrease in relapse rate during the third trimester. However, a rebounding increase is observed during the postpartum period. The biological mechanisms underlying these clinical phenomena are incompletely understood but suggest that the study of sex differences (Sasidhar et al., 2012) and pregnancy hormones (Gold et al., 2009) in autoimmunity can provide unique insight into the pathobiology and highlight novel targets for therapy.

In order to better understand the immunological mechanisms underlying the protective effects of pregnancy, we have launched the Hamburg MS pregnancy cohort in 2010 with the support of a Marie Curie Grant from the EU. Here, we longitudinally investigate immune function in MS patients and healthy women across pregnancy and postpartum. Our preliminary results indicate phenotypical changes within the Natural Killer cell population consistent with increasing immunoregulation and declining cytotoxicity during pregnancy. In addition, we have first preliminary data suggesting that pregnancy may modulate T cell function in a highly specific fashion, as evidenced by shifts in the $CD8^+$ T cell receptor repertoire during pregnancy and after delivery. These findings may account, either alone or synergistically, for pregnancy-related suppression of MS disease activity.

This project is now part of a larger research initiative at the UKE investigating the implications of feto-maternal immune cross talk for health and disease in the mother and her offspring. The consortium was initially funded by a start-up grant (2011–2013) from the Forschungs- und Wissenschaftsstiftung Hamburg (speaker: Prof. Petra Arck). It has since resulted in the joint application for a DFG Clinical Research Unit (Klinische Forschergruppe KFO 296 “Feto-maternal immune cross talk: Consequences for maternal and offspring’s health”). Here, Manuel Friese and Stefan Gold jointly head a translational project on pregnancy protection in EAE and MS. A final decision on this application is expected in March 2015.

Publications

Gold, S.M., Sasidhar, M.V., Morales, L.B., Du, S., Sicotte, N.L., Tiwari-Woodruff, S.K., andVoskuhl, R.R. (2009). Estrogen treatment decreases matrix metalloproteinase (MMP)-9 in autoimmune demyelinating disease through estrogen receptor alpha (ERalpha). Laboratory investigation; a journal of technical methods and pathology 89, 1076-1083.

Patas, K., Engler, J.B., Friese, M.A., and Gold, S.M. (2013). Pregnancy and multiple sclerosis: feto-maternal immune cross talk and its implica-

tions for disease activity. J Reprod Immunol 97, 140-146.

Sasidhar, M.V., Itoh, N., Gold, S.M., Lawson, G.W., and Voskuhl, R.R. (2012). The XX sex chromosome complement in mice is associated with increased spontaneous lupus compared with XY. Annals of the rheumatic diseases 71, 1418-1422.

Voskuhl, R.R., and Gold, S.M. (2012). Sex-related factors in multiple sclerosis susceptibility and progression. Nature reviews Neurology 8, 255-263.

1.5 Biological substrates of neuropsychiatric symptoms in MS and other CNS disorders

(Fischer, Gold, Heesen, Patas, Ramien)

Psychiatric disorders such as depression are very common in MS and often have a major impact on patients' quality of life, ability to work, and psychosocial well-being. Neuropsychiatric symptoms of MS, such as depression, fatigue and cognitive impairments, are at least partially mediated by biological processes including inflammation, neuroendocrine dysfunction (e.g. stress mediated) or regional brain damage. In order to better treat these symptoms we need to unravel their underlying pathogenetic mechanisms.

Our studies have provided first evidence that depressive symptoms in MS are associated with atrophy in hippocampal subfields (Gold et al., 2010; Gold et al., 2014). In an international collaboration with the Netherlands Brain Bank in Amsterdam, we were able to identify synaptic abnormalities and complement deposition in hippocampal subfields as potential pathological correlates of hippocampal atrophy in MS.

In addition to MS-related CNS damage, our work also suggests that neuroendocrine and inflammatory mechanisms can contribute to the high incidence of depression in this patient population. We have found hypersecretion of the stress hormone cortisol in depressed MS patients compared to MS patients without depression and healthy controls (Gold et al., 2010; Gold et al., 2011). Moreover, we could demonstrate that T

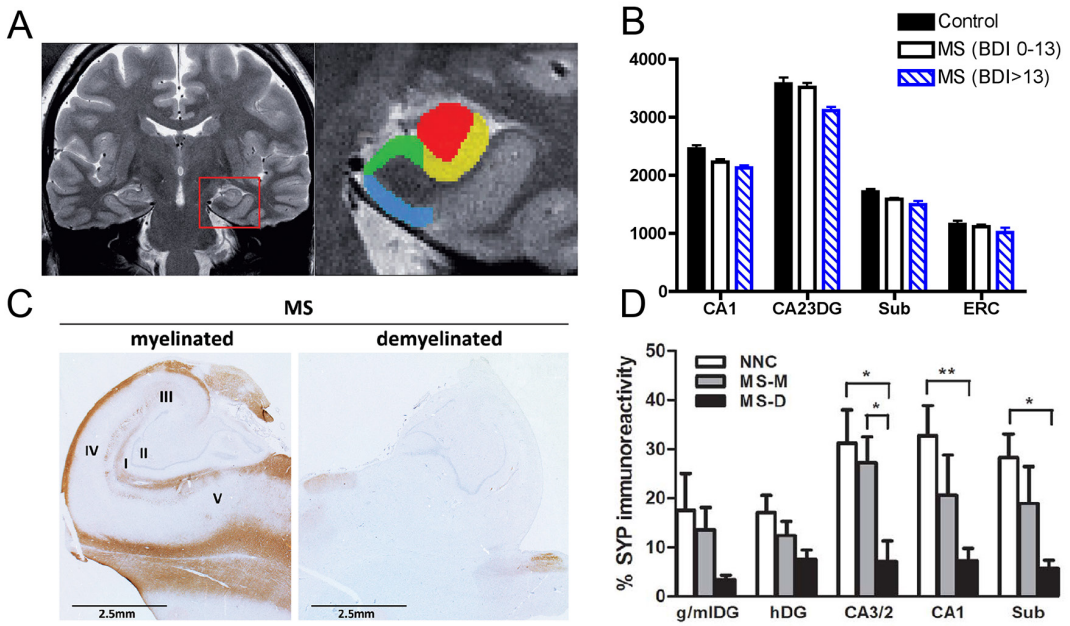

Figure 2. Hippocampal pathology in MS. (A-B) High resolution MRI revealed subregional hippocampal atrophy in MS. A specific association was observed between volume reductions in CA23/DG subfields and depressive symptoms (Gold et al., 2010). (C-D) In a human post mortem study, complement (C1q-C3)-mediated synaptic loss in these subfields was identified as a mechanism of hippocampal atrophy in MS (Michailidou et al., 2015).

lymphocytes of depressive MS patients produce more TNFα and IFNγ (Gold et al., 2011) and exhibit a diminished sensitivity to steroid regulation (Fischer et al., 2012). Together, these studies indicate that MS might directly impact neuro-endocrine-immune networks and that this may cause or exacerbate damage to CNS networks important for mood regulation.

Publications

Fischer, A., Otte, C., Krieger, T., Nicholls, R.A., Kruger, S., Ziegler, K.J., Schulz, K.H., Heesen, C., and Gold, S.M. (2012). Decreased hydrocortisone sensitivity of T cell function in multiple sclerosis-associated major depression. Psychoneuroendocrinology 37, 1712-1718.

Gold, S.M., Kern, K.C., O'Connor, M.F., Montag, M.J., Kim, A., Yoo, Y.S., Giesser, B.S., and Sicotte, N.L. (2010a). Smaller cornu ammonis 2-3/dentate gyrus volumes and elevated cortisol in multiple sclerosis patients with depressive symptoms. Biological psychiatry 68, 553-559.

Gold, S.M., Kruger, S., Ziegler, K.J., Krieger, T., Schulz, K.H., Otte, C., and Heesen, C. (2011). Endocrine and immune substrates of depressive symptoms and fatigue in multiple sclerosis patients with comorbid major depression. Journal of neurology, neurosurgery, and psychiatry 82, 814-818.

Gold, S.M., O'Connor, M.F., Gill, R., Kern, K.C., Shi, Y., Henry, R.G., Pelletier, D., Mohr, D.C., and Sicotte, N.L. (2014). Detection of altered hippocampal morphology in multiple sclerosis-associated depression using automated surface mesh modeling. Human brain mapping 35, 30-37.

MARTIN GROUP

1.6 Characterization of JC-Virus-specific lymphocytes from brain biopsies of a PML patient *(Aly, Martin, Sospedra, Yousef)*

One of the most feared complications along the treatment of MS with natalizumab (Tysabri) is the generation of Progressive Multifocal Leucencephalopathy (PML) with an overall lethality of 20%, caused by JC-Virus (JCV). By investigating tissue infiltrating leukocytes from brain biopsies of a PML patient suffering from PML-Immune Reconstitution Inflammatory Syndrome (PML-IRIS) we could show, that mainly $CD4^+$ T lymphocytes are involved which were highly specific for peptides from several JC virus proteins, particularly the major capsid protein VP1. T cell phenotyping revealed $CD4^+$ Th1 and bifunctional Th1-2 cells. The latter secrete large amounts of interferon-γ and interleukin-4 explaining the strong brain inflammation, presence of plasma cells and secretion of intrathecal anti-VP1 antibodies. The functional phenotype of brain-infiltrating JC virus-specific $CD4^+$ T cells was confirmed and extended by examining brain-derived JC virus-specific $CD4^+$ T cell clones. Most of the T cell clones we analysed were able to react with a great variety of MHC II, suggesting to be advantageous in view of the limited MHC expression in the central nervous system. Our data indicate that there exist multiple strategies of JC-Virus recognition in PML-IRIS encompassing the efficient elimination of JC-Virus from the brain. In summary, we provide novel insight into the pathogenesis of PML-IRIS and indicate that JC virus-specific $CD4^+$ T cells play an important role in both eliminating JC virus from the brain, but also in causing the massive inflammation with often fatal outcome.

Publication

Aly, L., Yousef, S., Schippling, S., Jelcic, I., Breiden, P., Matschke, J., Schulz, R., Bofill-Mas, S., Jones, L., Demina, V., et al. (2011). Central role of JC virus-specific $CD4^+$ lymphocytes in progressive multi-focal leucoencephalopathy-immune reconstitution inflammatory syndrome. Brain : a journal of neurology 134, 2687-2702.

1.7 Functional characterization of risk genes for multiple sclerosis *(Jäger, Stürner, Mohme, Martin, Rösner, Schulze)*

According to the current understanding of the etiology of MS several environmental factors are supposed to act together on a complex genetic background of susceptible individuals. Interleukin-7 receptor alpha (IL7RA) is among the top listed candidate genes influencing the risk

to develop MS. In order to analyze the influence of different IL7RA haplotypes on the etiology and pathogenesis of MS we conducted genotyping of four Single Nucleotide Polymorphisms (SNPs) in 600 MS patients as well as 150 healthy donors belonging to the Hamburg MS cohort. Soluble IL-7RA (sIL-7RA) protein and mRNA levels vary among the four common IL7RA haplotypes. Our data show and confirm that protective haplotype carriers have three times lower sIL-7RA serum levels than the other three haplotypes. High sIL-7RA concentrations significantly decrease IL-7-mediated STAT5 phosphorylation in $CD4^+$ T cells. Transcriptome analysis of unstimulated and stimulated $CD4^+$ T cells of MS patients carrying the different IL7RA haplotypes revealed complex and overlapping patterns in genes participating in cytokine signaling networks, apoptosis, cell cycle progression and cell differentiation. Our findings indicate that genetic variants of IL7RA result in haplotype-associated differential responsiveness to immunological stimuli that influence MS susceptibility not exclusively by varying levels of sIL-7RA (Jäger et al., 2013).

Among the risk alleles that have repeatedly been identified by genome-wide association studies in the context of MS, three are located near the Casitas B-lineage lymphoma proto-oncogene b gene (CBLB). The CBLB protein (CBL-B) is a key regulator of peripheral immune tolerance by limiting T cell activation and expansion and hence T cell-mediated autoimmunity through its ubiquitin E3-ligase activity. In this project we showed that CBL-B expression is reduced in $CD4^+$ T cells from relapsing-remitting MS (RR-MS) patients during relapse. The MS risk-related single nucleotide polymorphism of CBLB rs12487066 is associated with diminished CBL-B expression levels and alters the effects of type I IFNs on human $CD4^+$ T cell proliferation. Mechanistically, the CBLB rs12487066 risk allele mediates increased binding of the transcription factor C/EBPβ and reduced CBL-B expression in human $CD4^+$ T cells. Our data suggest a role of the CBLB rs12487066 variant in the interactions of a genetic risk factor and IFN function during viral infections in MS (Stürner et al., 2014.).

The HLA-DR15 haplotype confers the largest part of the genetic risk to develop MS. The mechanisms how certain HLA-class II molecules functionally contribute to autoimmune diseases are still poorly understood, but probably involve shaping an autoimmune-prone T cell repertoire during central tolerance in the thymus and subsequently maintaining or even expanding it in the peripheral immune system. Self-peptides that are presented by disease-associated HLA-class II molecules most likely play important roles during both processes. Here, we examined the functional involvement of the HLA-DR15 haplotype in autologous proliferation in MS and the contribution of HLA-DR15 haplotype-derived self-peptides in an *in vitro* system. We observe increased autologous T cell proliferation in patients with MS in relation to the MS risk-associated HLA-DR15 haplotype. Assuming that the spectrum of self-peptides that is presented by the two HLA-DR15 allelic products is important for sustaining autologous proliferation we performed peptide elution and identification experiments from the MS-associated DR15 molecules and a systematic analysis of a DR15 haplotype-derived self-peptide library. We identified HLA-derived self-peptides as potential mediators of altered autologous proliferation. Our data provide novel insights about perturbed T cell repertoire dynamics and the functional involvement of the major genetic risk factor, the HLA-DR15 haplotype, in MS (Mohme et al., 2013). This project has been conducted in collaboration with Prof. T. Eiermann and Dr. T. Binder (Interdisciplinary clinic of stemcell transplantation, UKE) and HG. Rammensee, University of Tübingen.

Publications

Jäger, J., Schulze, C., Rosner, S., and Martin, R. (2013). IL7RA haplotype-associated alterations in cellular immune function and gene expression patterns in multiple sclerosis. Genes and immunity 14, 453-461.

Mohme, M., Hotz, C., Stevanovic, S., Binder, T., Lee, J.H., Okoniewski, M., Eiermann, T., Sospedra, M., Rammensee, H.G., and Martin, R. (2013). HLA-DR15-derived self-peptides are involved in increased autologous T cell proliferation in multiple sclerosis. Brain : a journal of neurology 136, 1783-1798.

Stürner, K.H., Borgmeyer, U., Schulze, C., Pless, O., and Martin, R. (2014). A multiple sclerosis-associated variant of CBLB links genetic risk with type I IFN function. Journal of immunology 193, 4439-4447.

1.8 Expression analysis of the cation channel P2RX5 during T lymphocyte activation

(Abramowski, Martin, Ogrodwczyk, Pongs)

Members of the P2X family of ligand-gated cation channels (P2RX) are expressed on various cell types including neurons, smooth- and cardiac muscle cells and leukocytes. The channels mediate signaling in response to extracellular ATP. In humans, the subunit isoform P2RX5 exists as a natural deletion mutant lacking amino acids 328-349 of exon 10, which are part of transmembrane ™ 2 and pre-TM2 regions in other organisms like rat, chicken and zebrafish. We performed gene expression analysis and showed that P2RX5 expression of human T lymphocytes is upregulated during activation. P2RX5 is recruited to the cell surface. P2RX5-siRNA-transfected $CD4^+$ T cells produced twofold more IL-10 (an anti-inflammatory cytokine) than controls. Surface and intracellular P2RX5 expression was upregulated in activated antigen-specific $CD4^+$ T cell clones. These data indicate a functional role of the human P2RX5 splice variant in T cell activation and immunoregulation.

Publication

Abramowski, P., Ogrodowczyk, C., Martin, R., and Pongs, O. (2014). A truncation variant of the cation channel P2RX5 is upregulated during T cell activation. PloS one 9, e104692.

1.9 Functional and phenotypical characterization of neutrophils in multiple sclerosis

(Martin, Nägele, Sospedra, Tillack)

Neutrophils are the most abundant circulating leukocyte population and one of the first defenders against invading microorganisms. Among their strategies to eliminate pathogens they release neutrophil extracellular traps (NETs), being chromatin fibers decorated with antimicrobial proteins. NETs trap and kill pathogens very efficiently, thereby minimizing tissue damage. In this project we analysed whole blood from 110 MS patients and 40 healthy controls by flow cytometry for the expression of activation receptors, receptors for chemotactic ligands and adhesion molecules. Our data indicate that neutrophils in MS patients are more numerous and exhibit a primed state based on reduced apoptosis, higher expression of TLR-2, fMLP receptor, IL-8 receptor and CD43, enhanced degranulation and oxidative burst as well as higher levels of neutrophil extracellular traps in serum. The chronic inflammatory environment in MS probably underlies this inappropriate neutrophil priming, which may result in enhanced neutrophil activation during infection. NETs-mediated T cell activation adds to the list of neutrophil functions and demonstrates a novel link between innate and adaptive immune responses. In addition, our data suggests that NETs may underlie gender-specific differences in MS pathogenesis.

Publications

Naegele, M., Tillack, K., Reinhardt, S., Schippling, S., Martin, R., and Sospedra, M. (2012). Neutrophils in multiple sclerosis are characterized by a primed phenotype. Journal of neuroimmunology 242, 60-71.

Tillack, K., Breiden, P., Martin, R., and Sospedra, M. (2012). T lymphocyte priming by neutrophil extracellular traps links innate and adaptive immune responses. Journal of immunology 188, 3150-3159.

Tillack, K., Naegele, M., Haueis, C., Schippling, S., Wandinger, K.P., Martin, R., and Sospedra, M. (2013). Gender differences in circulating levels of neutrophil extracellular traps in serum of multiple sclerosis patients. Journal of neuroimmunology 261, 108-119.

1.10 Investigation of the role of ligands and receptors involved in CNS regeneration-failure *(Martin, Steinbach)*

MS lesions are characterized by inflammation, demyelination and axonal damage. In order to gain better insight into the relatively poor recovery from inflammatory damage in MS lesions, we examined the role of myelin-associated inhibitory factors of axonal damage (Nogo and the Nogo receptor complex) and their interaction partners

NgR1 and NgR2 in the MS model experimental autoimmune encephalitis (EAE) both by antibody blocking experiments, but also in knockout systems of the various Nogo-NogoR components (in collaboration with M. Reindl and C. Bandtlow, University of Innsbruck, and Schwab, ETH Zürich). In this project we could show that genetic deletion of both receptors does not promote functional recovery during EAE and that NgR1 and NgR2-mediated signals also play a minor role in the development of CNS inflammation. Induction of EAE in Ngr1/2-double mutant mice resulted in indifferent disease course and tissue damage when compared to WT controls. Further, the development of encephalitogenic $CD4^+$ Th1 and Th17 immune responses was unchanged. In the absence of NgR1 and NgR2, however, we observed a slightly increased leukocyte infiltration into the CNS, indicating that NgRs might be involved in the regulation of immune cell migration in the CNS. Our study demonstrates the urgent need for a more detailed knowledge on the multifunctional roles of ligands and receptors involved in CNS regeneration failure.

Publication

Steinbach, K., McDonald, C.L., Reindl, M., Schweigreiter, R., Bandtlow, C., and Martin, R. (2011). Nogo-receptors NgR1 and NgR2 do not mediate regulation of CD4 T helper responses and CNS repair in experimental autoimmune encephalomyelitis. PloS one 6, e26341.

1.11 Analysis of immunomodulatory effects of the ether phospholipid edelfosine in experimental autoimmune encephalomyelitis

(Abramowski, Martin, Steinbach)

In order to treat autoimmune diseases several approaches have been considered to induce apoptosis in deregulated, e.g. self-reactive immune cells. The 2-lysophosphatidylcholine analog edelfosine induces apoptosis in highly proliferating cells, e.g. activated immune cells. We examined mechanisms of action of edelfosine on immune functions in experimental autoimmune encephalomyelitis, a well-accepted animal model for MS. We observed activated caspase-3 expression in lymphoid organs and the central nervous system; however, edelfosine did not induce global apoptosis. Edelfosine improved the disease course and led to reduced frequencies of $CD4^+$ T cells infiltrating into the central nervous system. Our data suggest edelfosine as an interesting treatment candidate for MS.

Publications

Abramowski, P., Otto, B., and Martin, R. (2014). The orally available, synthetic ether lipid edelfosine inhibits T cell proliferation and induces a type I interferon response. PloS one 9, e91970.

Abramowski, P., Steinbach, K., Zander, A.R., and Martin, R. (2014). Immunomodulatory effects of the ether phospholipid edelfosine in experimental autoimmune encephalomyelitis. Journal of neuroimmunology 274, 111-124.

2. Clinical research

Translational research aims at evaluating molecular in order to provide (i) safe and convenient treatments for early MS stages when the prognosis is uncertain and (ii) aggressive immunotherapies for very active MS. We pursue investigator-initiated phase I and phase II treatment trials combined with mechanistic laboratory studies for safe treatments in early MS (i.e. boswellic acids, immunological tolerance induction) and highly immunosuppressive approaches for aggressive MS (i.e. autologous hematopoietic stem cell transplantation). In addition, we explore novel neuroprotective treatment approaches (i.e. erythropoietin). Further we develop clinical study designs with take into account the problem of recruiting to trials while licensed treatment already exist, i.e. a justification of baseline-to-treatment designs and adaptive studies designs. As the success of clinical trials critically depends on the availability of appropriate outcome measures, we are conducting research to improve the sensitivity as well as clinical meaningfulness of study endpoints following triangulation of measurements: objective (e.g. MRI, OCT), rater-based (e.g. walking test) and patient-reported (e.g. quality of life).

BIOPHARMA NEU^2 CONSORTIUM

The northern Germany based NEU^2 consortium (www.neu-quadrat.de) was established in 2009 and has created a public-private framework, which applies biological, clinical and technological insight to identify and evaluate novel treatment approaches for MS. The organization integrates existing MS expertise from academic centers (mainly UKE), biotech and pharma companies, with each member contributing one or more of their respective core clinical, scientific, or technical competencies. This provides NEU^2 as a whole with the necessary know-how to discover new therapies and diagnostic approaches for MS and progress them to the clinic in order to benefit patients. Since its inception, NEU^2 has assembled several collaborative discovery and development projects. The projects are partially funded by the Federal Ministry of Education and Research (BMBF) and NEU^2 has extended its initial project portfolio ranging from immunomodulatory approaches to tolerization and neuroprotective treatment modalities in MS and beyond. NEU^2 aims at innovative approaches based on novel mechanisms of action, new ways of delivery, and improved safety. As central academic partner, the INIMS has been involved in several projects within the NEU^2 portfolio:

HEESEN GROUP

2.1 Project “Imaging and clinical platforms and validation study SABA”

Applicant and grantee:
Roland Martin
Christoph Heesen
Funding period: 2009-2015
Participating scientists from the ZMNH:
Roland Martin
Christoph Heesen

Since 2009 a fully operative clinical and imaging Platform has been established with a core personnel team and a state-of-the-art infrastructure for conducting early clinical trials in MS. The clinical platform interfaces closely with the imaging platform, with the Clinical Trial Center North, with the Biomarker and Discovery Biology Laboratory and with select centers outside of Hamburg in order to conduct trials, which require larger patient numbers than those available at UKE. Special attention is payed to the development of new, repsonsive outcomes for neurodegeneration based on MRI as well as

based on ocular coherence tomography. In addition the clinical platform worked on metaanalysis of MRI outcomes and study design issues for early proof-of concept studies.

Publications

Holst, B., Siemonsen, S., Finsterbusch, J., Bester, M., Schippling, S., Martin, R., and Fiehler, J. (2009). T2' imaging indicates decreased tissue metabolism in frontal white matter of MS patients. Multiple sclerosis 15, 701-707.

Reitz, L.Y., Inglese, M., Fiehler, J., Finsterbusch, J., Holst, B., Heesen, C., Martin, R., and Schippling, S. (2012). Quantitative T2' imaging in patients with clinically isolated syndrome. Acta neurologica Scandinavica 126, 357-363.

Stellmann, J.P., Neuhaus, A., Lederer, C., Daumer, M., and Heesen, C. (2014). Validating predictors of disease progression in a large cohort of primary-progressive multiple sclerosis based on a systematic literature review. PloS one 9, e92761.

Stellmann, J.P., Neuhaus, A., Herich, L., Schippling, S., Roeckel, M., Daumer, M., Martin, R., and Heesen, C. (2012). Placebo cohorts in phase-3 MS treatment trials - predictors for on-trial disease activity 1990-2010 based on a meta-analysis and individual case data. PloS one 7, e50347.

Zimmermann, H., Freing, A., Kaufhold, F., Gaede, G., Bohn, E., Bock, M., Oberwahrenbrock, T., Young, K.L., Dorr, J., Wuerfel, J.T., et al. (2013). Optic neuritis interferes with optical coherence tomography and magnetic resonance imaging correlations. Multiple sclerosis 19, 443-450.

2.1.1 Analysis of the heterogeneity of MS with magnetic resonance imaging (MRI), HETOMS-Study *(Reitz, Schippling, Martin, Heesen, Stellmann, Young, Siemonsen).*

Up to now MRI is considered the most sensitive paraclinical measure for MS diagnostics due to its capacity to visualize pathological alterations in brain and spinal cord with high resolution. However, this is challenged by the great variety of different phenotypes within MS patients. Finding algorithms to stratify certain phenotypes corresponding to their pathological features (quantity and quality of CNS inflammation and respectively focal and global tissue destruction) would facilitate diagnosis, treatment and prognosis of individual patients. MS phenotypes can be captured by conventional magnetic resonance imaging (MRI) and correlate with clinical disability evolution. Aim of the current study was to develop further and adapt with respect to clinical applicability a previously proposed MRI algorithm. In addition, we addressed if a newly recognized imaging technique in the field of MS, optical coherence tomography (OCT), supports or extends MRI phenotyping. In collaboration with Prof. Weber (MPI Psychiatry, Munich), we furthermore performed gene expression profiling and gene sequencing in order to correlate these findings with biological data. The results of these studies are expected to be published in 2015.

2.1.2 Platform Validation Study SABA

(Stürner, Stellmann, Siemonsen, Heesen, Martin)

For validation of the running platforms a proof-of-concept Phase I/IIa baseline-to-treatment study SABA („Safety, tolerability and efficacy of boswellia acids (BA) in MS and clinical isolated syndrome (CIS)") has been conducted at the MS Outpatient Clinic of the UKE (coordinator Christoph Hessen) and the Charité Berlin (coordinator Friedemann Paul).

Since orally available drugs exhibiting a safe and favourable side effect profile for the treatment of relapsing-remitting MS (RR-MS) are of high interest for patients and treaters, Boswellic Acids (BAs), the main biologically active compound of frankincense, might offer a new treatment option specially for early MS patients, because they are orally available and known to exhibit anti-inflammatory activities. Preliminary results of the SABA trial, which started in 2011 and will be finished in 2015, show, that the drug seems to be safe, tolerable and efficient. However, final evaluation of the results and further perspectives of this drug candidate will be determined in 2015.

Publication

Stürner, K.H., Verse, N., Yousef, S., Martin, R., and Sospedra, M. (2014). Boswellic acids reduce Th17 differentiation via blockade of IL-1beta-mediated IRAK1 signaling. European journal of immunology 44, 1200-1212.

2.2 ”MS biomarker and platform labs for MS drug discovery and development

Applicant and grantee:
European ScreeningPort GmbH (since 2014 Fraunhofer Institute IME SP)
Funding period: 2011–2018
Participating scientists from the ZMNH:
Friese, Gold, Heesen, Martin

2.3 “Relapse escalation treatment trial in Optic Neuritis (RESCON)”

Applicant and grantee:
Christoph Heesen
Funding period: 2012–2015
Participating scientists from the ZMNH: Heesen
RESCON is a randomized multicenter trial in five German Academic Centers (Hamburg, Berlin, Hannover, Düsseldorf, Heidelberg) to clarify if early plasmapheresis is superior to escalation steroid treatment in treatment refractory optic neuritis.

2.4 “Connectivity Platform: New approaches for the analysis of networks and their function in Multiple Sclerosis (NEUCONN)”

Applicant and grantee:
Andreas Engel
Guido Nolte
Stefan Gold
Christoph Heesen
Funding period: 2012–2015
Participating scientists from the ZMNH:
Gold, Heesen

NEUCONN aims at investigating the course of neuropsychological deficits in a cohort of relapsing remitting MS patients (n = 40) compared to controls (n = 40 in relation to structural (MRI) and functional (fMRI and MEG) measures focussing connectivity and its disturbance as a key mechanism in MS.

2.5 “Nanodeliver: Optimization and clinical testing of a tolerance-inducing drug candidate for Multiple Sclerosis”

Applicant and grantee:
Johannes Herkel
Christoph Heesen
Funding period: 2014–2016
Participating scientists from the ZMNH:
Heesen

Nanodeliver attempts to preclinically and clinically test the antigen-specific induction of immune tolerance by myeline peptide loaded nanoparticles via sinusoidal liver cells and induced regulatory T cells in MS. After proven preclinical safety the drug will be administered to stable MS patients in a safety study.

FRIESE GROUP

2.6 “ASIC 1 inibitors for treatment of Multiple Sclerosis”

Applicant and grantee:
Merck Serono KGaA, Evotec AG
Funding period: 2009–2015
Participating scientists from the ZMNH: Friese

2.7 “Identification of a small molecule inhibitor for ion channel TRPM4”

Applicant and grantee: Manuel Friese
Funding period: 2014–2016
Participating scientists from the ZMNH: Friese

2.8 Evaluation of miRNAs and Metabolites – Discovery of Biomarkers for Neurodegeneration in Multiple Sclerosis”

Applicant and grantee:
Manuel Friese
Ole Pless (Fraunhofer IME SP)
Nikolaus Schauer
(Metabolomic Discoveries GmbH)
Funding period: 2014–2017
Participating scientists from the ZMNH: Friese

MARTIN GROUP

2.9 "Identification of small molecule inhibitors for CD25"

Applicant and grantee: Roland Martin
Funding period: 2010–2011
Participating scientists from the ZMNH: Martin

2.10 "Treating relapsing-remitting Multiple Sclerosis (RR-MS) with a human monoclonal antibody (BT061) against CD4"

Applicant and grantee: Biotest
Funding period: 2010–2015
Participating scientists from the ZMNH: Martin

OTHER CLINICAL PROJECTS

HEESEN GROUP

2.11 Shared-decision making (SDM) and evidence-based patient information (EBPI) in MS *(Heesen, Kasper, Köpke, Rahn, Schäffler)*

Autonomy preferences, risk perception, risk knowledge and factors relevant for medical decision making differ between different patient groups. We have shown that patients are capable of processing risk information and can transfer established risk knowledge to new information. In a multi-center RCT addressing relapsing remitting MS, we found that a four-hour education program can change relapse management in the direction of using less invasive medication and self-administered steroids. Moreover, frequency of relapses decreased indicating patients' strengthened control beliefs (Köpke et al., 2009). Solely delivering printed high-level EBPI did not show an impact on decision making (Kasper et al., 2010). On the other hand two recent RCTs: PEPADIP – Patient education program about diagnosis, prognosis and early MS treatment (Köpke et al., 2014) and PEPIMS – Patient education program about immunotherapy in MS (Köpke et al., 2012) showed an increased number of informed treatment choices and adherence to treatments at 6 and 12 months. Between 2010–2013 the first European collaborative study on autonomy preferences, risk knowledge and shared-decision-making in MS was conducted (www.automs.org), funded by the Hertie's Foundation (C. Heesen) and the Italian MS Society (A. Solari). AutoMS produced linguistically validated and web-based versions of measures of control preferences (Solari et al., 2013), risk knowledge and psychological factors relevant for immunotherapy decision making in German, Italian, Dutch, Estonian, and Serbian. Moreover, the shared decision-making skills of neurologists were assessed in Germany (Kasper et al., 2012) and Italy. Within the multicnter cohort study PERCEPT/CONSIDER we evaluated risk perception among patienst and their neurologists in n = 900 natalizumab-treated MS patients in Germnay through 12 months of FU. Data analysis is ongoing. A cluster-randomised trial on assessing the added value of decision coaching to high-level EBPI through nurses in MS (DECIMS, Decision coaching in MS) with n = 240 patients is currently ongoing (Rahn et al., 2015 submitted). Integrated in the study is a patient information platform tool (www.wiki.kkn-ms.de, access code required) based on a Wikipedia-like format together with workbooks. Online tools are increasingly used; upcoming projects focus on education about the relevance of MRI, motherhood choice and pregnancy management. Moreover, we pursue adherence determining factors and interventions as well as illness narratives as decision support factors.

Publications

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Köpke, S., Solari, A., Khan, F., Heesen, C., and Giordano, A. (2014b). Information provision for people with multiple sclerosis. The Cochrane database of systematic reviews 4, CD008757.

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HEESEN & GOLD GROUP

2.12 Pharmacological and psychological interventions to manage neurospsychiatric-symptoms of MS *(Feddersen, Gold, Heesen, Poettgen)*

Neuropsychiatric symptoms such as depression, fatigue (Möller et al., 2011) and cognitive dysfunction have a considerable impact on activity and participation, presumably more so than mobility problems. However, few therapeutic options are available to effectively treat them. Thus, there is an urgent but unmet need to develop novel approaches including molecular as well as highly standardized psychological interventions that can be implemented at a large scale in MS.

We develop online and group education programmes based on a framework of complex interventions and conduct randomised controlled trials to test their efficacy. We recently conducted a randomized controlled trial to test the potential of an internet-based cognitive behavioral therapy (iCBT) program (Deprexis) to reduce depressive symptoms in MS (Fischer et al., Lancet Psychiatry 2015). During the intervention, the depression scores decreased significantly in the Deprexis group and slightly increased in the control group, yielding a significant treatment effect. Based on these encouraging results, we are currently planning an international, multicenter trial of the Deprexis program in Germany and the US.

Publications

Möller, F., Poettgen, J., Broemel, F., Neuhaus, A., Daumer, M., and Heesen, C. (2011). HAGIL (Hamburg Vigil Study): a randomized placebo-controlled double-blind study with modafinil for treatment of fatigue in patients with multiple sclerosis. Multiple sclerosis 17, 1002-1009.

Fischer A, Schröder J, Vettorazzi E, Wolf OT, Pöttgen J, Lau S, Heesen C, Moritz S, Gold SM (2015). An online programme to reduce depression in patients with multiple sclerosis: a randomised controlled trial. Lancet Psychiatry 2, 217-223.

2.13 Further evaluation and development of novel clinical outcome parameters *(Gold, Heesen, Poettgen, Stellmann)*

In order to evaluate novel intervention approaches in MS – either pharmacological or behavioral – reliable, valid, sensitive, and clinically meaningful outcome measures are needed. Therefore, our research group has focused on the development and evaluation of patient-based rating scales and innovative standardized tests, which can be applied in clinical studies.

We have developed an MS-specific quality of life instrument (the HAQUAMS), which we have continuously used and evaluated for more than a decade now. Our questionnaire has been shown to be sensitive to clinically meaningful change in both observational and interventional studies (Gold et al., 2010) as well as phase II drug trials (Montalban et al., 2011). We have furthermore conducted a longitudinal multicenter (Rostock, Dresden, Berlin, Regensburg, Münster, Gießen)

study on the responsivenss of patient based outcome parameters (REPABO, funded by the Hertie-foundation) comparing HAQUAMS with 2 other rating scales and objective measures. Data analysis is ongoing.

In a pilot study, we were able to demonstrate that social cognition, a set of skills that allow us to understand and adequately respond to the mental states of others (such as intentions, desires, and emotions) is impaired in MS (Pöttgen et al., 2013). Social cognition may be a particularly sensitive tool to study and monitor the clinical correlates of disturbed connectivity and ongoing neurodegeneration in MS.

We work on validation analysis of the accelometry tool „Actibelt“ for the measurement of every day life mobility in MS. Within the monitoring study RESPONSE we applied accelerometry to describe responders under fampyridin treatment (analysis ongoing).

Publications

Gold, S.M., Schulz, H., Stein, H., Solf, K., Schulz, K.H., and Heesen, C. (2010). Responsiveness of patient-based and external rating scales in multiple sclerosis: head-to-head comparison in three clinical settings. Journal of the neurological sciences 290, 102-106.

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Schaffler, N., Schonberg, P., Stephan, J., Stellmann, J.P., Gold, S.M., and Heesen, C. (2013).

Comparison of patient-reported outcome measures in multiple sclerosis. Acta neurologica Scandinavica 128, 114-121.

FRIESE, GOLD & HEESEN GROUP

2.14 Physical activity promotion and exercise to ameliorate progression and neurodegeneration in multiple sclerosis? *(Friese, Gold, Heesen, Schulz, Siemonsen, Stellmann)*

Currently exercise might be the most effective neuroprotective treatment but disease-stage

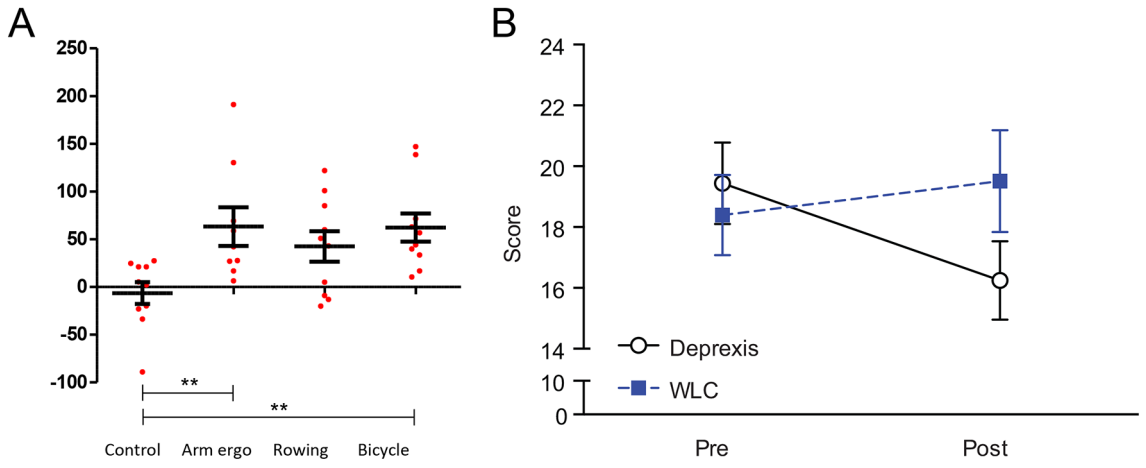

Figure 3. Efficacy of behavioral interventions for neuropsychiatric symptoms in MS. (A) In a randomized pilot trial, a 12-week exercise program significantly increased cognitive function including tests of learning and memory in patients with progressive MS (Briken et al., 2014). (B) An internet-based psychological intervention (Deprexis) significantly reduced depressive symptoms of MS patients in a phase II randomized controlled trial (Fischer et al., 2015).

adapted format and dosing as well as mechanisms and long-term effectiveness are ill defined. We study exercise with clinical, imaging, neurophysiologic and molecular approaches.

Exercise may also enhance cognitive function in humans, so it may be particularly useful for MS patients with pronounced neurodegeneration. In a randomized-controlled pilot trial we investigated the potential of standardized exercise as a therapeutic intervention for progressive MS. Significant improvements were seen in aerobic fitness. In addition, exercise improved walking ability, depressive symptoms, fatigue and several domains of cognitive function (Briken et al., Mult Scler 2014). Based on these findings we recently initiated a larger randomized exercise study to confirm the effect on cognition using novel imaging modalities (AERCONN trial within the NEUCONN project, see translational and clinical projects below), we will also mechanistically underpin by molecular biology in exercised mice.

Publication

Briken, S., Gold, S.M., Patra, S., Vettorazzi, E., Harbs, D., Tallner, A., Ketels, G., Schulz, K.H., and Heesen, C. (2014). Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial. Multiple Sclerosis 20, 382-390.

2.15 Autologous Hematopoietic Stem Cell Transplantation (aHSCT) in Multiple Sclerosis *(Friese, Heesen, Martin, Schippling, Stellmann, Stürner)*

Although aHSCT appears highly efficacious in reducing inflammatory disease activity and relapses in active relapsing-remitting MS in patients followed for up to 10 years and more after aHSCT, a controlled randomized phase III trial comparing aHSCT with approved treatments is still lacking. With close collaboration of the interdisciplinary clinic for stem cell transplantation, UKE (Prof. Zander, Prof. Kröger, Dr. Ayuk) we have been successfully treating patients with this promising approach in the last years. Based on these results we now plan to conduct a multicenter randomized controlled trial to compare Alemtuzumab (an approved drug for active relapsing-remitting MS) and aHSCT in high inflammatory MS.

MARTIN GROUP

2.16 Clinical Phase I/IIa study ETIMS, Establish Tolerance in MS *(Heesen, Lutterotti, Martin, Reinhardt, Sospedra, Stellmann, Stürner, Yousef)*

One of the unmet needs in MS therapy is to stop the pathogenic autoimmune response against target autoantigens in an antigen-specific way without compromising the immune system as a whole and thereby avoiding the potentially severe side effects of general immunosuppression.

This investigator-initiiated first-in-man phase I/IIa study was based on a tolerance inducing approach using peptide-pulsed and fixed autologous antigen presenting cells. In this procedure seven immunodominant myelin peptides, thought to be potentially antigenic in MS, were chemically coupled to the patients' autologous peripheral blood mononuclear cells with a dosis escalation up to 5x10e9 coupled cells, and afterwards reinfused to the patients again. Nine Patients who had T cell responses restricted to at least one of the peptides tested were selected. Indeed, patients who received the highest doses of antigen-coupled cells demonstrated decreases in antigen-specific T cell responses after therapy. Although the patient numbers are small in this first-in-human study, the safety, feasibility, tolerability and early results suggest that this approach may provide a promising avenue for future trials. The operative start of the study was December 2009 and the project, which was supported by the BMBF, was finished in January 2013.

Publication

Lutterotti, A., Yousef, S., Sputtek, A., Sturner, K.H., Stellmann, J.P., Breiden, P., Reinhardt, S., Schulze, C., Bester, M., Heesen, C., et al. (2013). Antigen-specific tolerance by autologous myelin peptide-coupled cells: a phase 1 trial in multiple sclerosis. Science translational medicine 5, 188ra175.

FUTURE PERSPECTIVES

1. Basic Research

Currently, we aim to define the role of conventional CD8+ T cells and MAIT cells in MS and to unravel, how they are regulated and what they recognise. Moreover, by using specific transgenically modified mouse lines and models we currently study how different molecular regulators coordinate the initial activation and function of dendritic cells. This understanding will help us to devise approaches to treat or prevent autoimmune diseases, such as MS. We will expand our translational immunological research efforts into sex differences and the protective effects of pregnancy in MS. Here, we will use clinical cohort studies and relevant animal models to unravel the underlying biological mechanisms by hypothesis-driven and unbiased approaches including immune repertoire sequencing and transcriptomics analyses.

We explore additional neuronal ion channels as contributors of neurodegeneration during CNS inflammation and aim at discovering in an unbiased approach conserved molecular pathways that enhance neuronal resilience. We also use exercise as a neuroprotective intervention and decipher the neurobiological mechanisms underlying this increase in neuronal resistancs. Inhibiting damaging pathways or reinforcing protective pathways may lead to the development of novel interventions for neurodegenerative disorders. We aim at identifying, understanding and modulating these key pathways to ameliorate neurodegeneration in MS. Moreover, we test whether our findings are also applicable in primary neurodegenerative diseases, such as amyotrophic lateral sclerosis.

2. Clinical Research

Clinical research at the INIMS will continue to to develop and rigorously test novel treatments with a comprehensive approach. Therefore, clinical care and research includes assessment and consideration of psychological and psychosocial aspects of MS as well as educational (e.g. evidence-based patient information), behavioral (e.g. psychological) and lifestyle (e.g. exercise and diet) interventions. These interventional startegies will be tested in randomized controlled trials and combined with exploration of underlying biological mechanisms of neurodegeneration and inflammation. Complementing this approach, we conduct research to improve assessment tools, develop novel outcome parameters with clinical relevance, and optimize study designs.

We will further pursue phase I and phase II treatment trials. Continuing the expertise in the area of immune tolerance induction we will increasingly focus on neuroprotection as well as high intensity immunosuppression.

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Gemeinnützige Hertie-Stiftung

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Werner-Otto Stiftung

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- Daniel Mensching
- Konstantinos Patas
- Benjamin Schattling
- Anne Willing

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- Dr. Sabine Rösner (Neurology)
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- Dr. Jan-Patrick Stellmann
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Basic Research Team

Clinical Research Team

Institute for Synaptic Physiology

Thomas G. Oertner

Neurons in the brain communicate through chemical synapses. Depending on the activity of pre- and postsynaptic cells, these communication channels can rapidly and persistently change their strength. These functional adaptations, collectively known as long-term plasticity, involve a large number of intracellular signaling systems. On longer timescales, new synapses are established between previously unconnected cells while other synaptic connections are completely removed. Together, these changes in the efficacy and connectivity of brain circuits are thought to be crucial for information processing and memory storage in the brain.

We develop optogenetic methods to stimulate identified neurons and to optically measure the amplitude of postsynaptic calcium transients in dendritic spines. Two-photon laser scanning microscopy allows us to perform such optophysiological experiments in intact brain tissue with high spatial and temporal resolution. Using genetically encoded probes, we monitor the activity of single synapses over several hundred stimulations and measure parameters such as synaptic potency and the probability of glutamate release. Optical induction of plasticity at individual, identified synapses allows us to investigate the underlying electrical and biochemical processes in great detail. The connectivity of our brain constantly changes in response to sensory experience (Huber et al., 2012). A central aim of our research is to understand the rules and molecular mechanisms that govern our extraordinary ability to learn and to remember.

1. Neuronal silencing with light-gated chloride channels

Simon Wiegert, Iris Ohmert

The discovery of Channelrhodopsin, a directly light-gated cation channel, had a tremendous impact on neuroscience. Expression of this channel in a defined population of neurons allows activating these neurons with millisecond precision (Schoenenberger et al., 2011). We adapted this technique for our work, inducing specific activity patterns to investigate the effects on synaptic strength and stability (Berndt et al., 2011; Wiegert and Oertner, 2013). Light-induced inhibition of neuronal activity would also be useful for loss-of-function experiments, but is technically more difficult to achieve. Light-driven ion pumps hyperpolarize neurons as long as they are illuminated, but they need very high light intensities and are not suitable for sustained inhibition. Collaborating with Peter Hegemann at the Humboldt University in Berlin, we developed and characterized the first directly light-gated anion channel that can keep neurons from spiking at very low light levels (Wietek et al., 2014). We are further improving the ion selec-

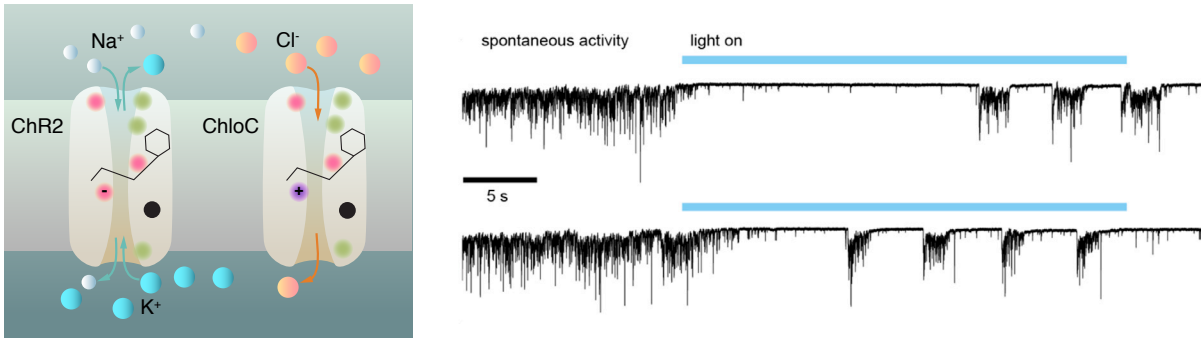

Figure 1. Optogenetik suppression of spontaneous activity in a hippocampal slice culture expressing the improved chloride-conducting channelrhodopsin iChloC in CA3 pyramidal cells.

tivity and kinetics of this new tool to enable optical silencing of individual neurons or brain areas in intact animals (Fig. 1).

2. Activity-dependent regulation of synaptic lifetime

Simon Wiegert, Celine Dürst

While intact synaptic plasticity seems to be essential for our ability to learn and to remember, it is less clear if memories are indeed stored as subtle changes in synaptic strength. Alternatively, the connectivity pattern in certain brain areas could change by removal of existing synapses and formation of novel connections. We know this form of 'binary' memory storage from our digital computers; it has the advantage that small changes in the strength of individual connections do not affect memory stability or recall. Using optogenetic stimulation and read-out (Fig. 2), we could demonstrate that long-term depression indeed had consequences on synaptic lifetime: Synapses with low release probability were efficiently removed from the circuit several days after long-term depression, pointing to a strong correlation between synaptic strength and synaptic lifetime (Wiegert and Oertner, 2013). We have now accumulated evidence that the reverse is also the case: One-time potentiation of individual synapses increases their stability and survival during the following days. Our findings suggest that the connectivity of an adult brain is the direct consequence of a myriad of decisions made at individual synapses.

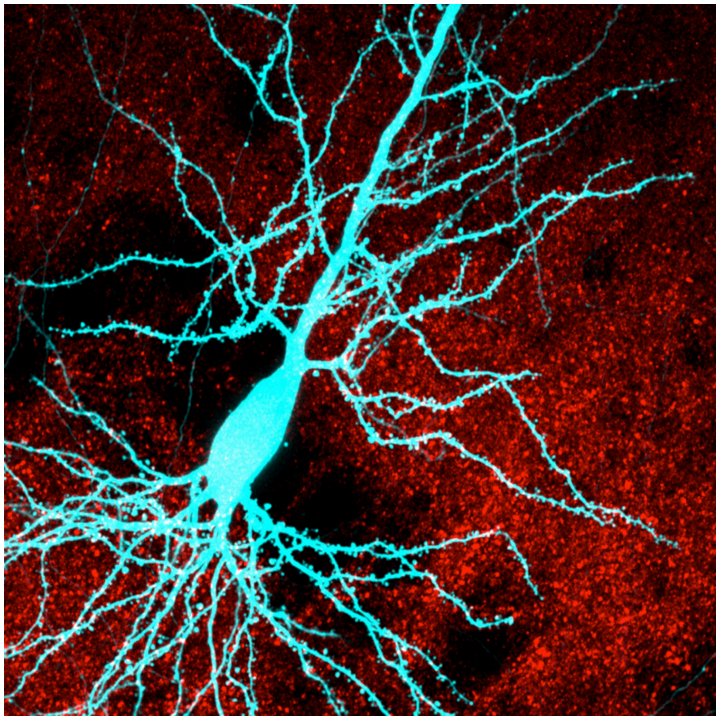

Figure 2. Live pyramidal neuron in CA1 expressing the genetically encoded Ca2+ indicator GCaMP. Red dots are presynaptic terminals that can be activated with blue light (ChR2-ET/TC). This combination enables functional measurements from individual spine synapses over several days (Wiegert and Oertner, 2013).

3. Optogenetic investigation of spike-timing dependent plasticity

Christine Gee, Bas van Bommel

Classic electrophysiological studies of synaptic plasticity consist of a brief induction protocol, followed by low frequency test pulses to assess the stability of synaptic strength over time. The discovery of spike-timing dependent plasticity revealed the possibility that in fact every single action potential changes synaptic strength in a miniscule way, and that synaptic strength tracks temporal correlations between pre- and postsynaptic spike patterns (Hao and Oertner, 2012). This hypothesis is impossible to test with purely electrophysiological approaches, as measuring subthreshold potentials with an electrode perturbs intracellular signaling and eventually kills the recorded neuron. The recent discovery of Channelrhodopsin variants that are sensitive to red light (Klapoetke et al., 2014) enables us to control the timing of action potentials in individual CA3 and CA1 pyramidal cells independently and non-invasively over several days. Using a combination of optogenetic tools with different spectral properties, we are investigating the sensitivity of individual synapses to subtle temporal correlations in pre- and postsynaptic activity patterns.

4. The function of endoplasmic reticulum in homeostatic plasticity

Alberto Perez-Alvarez, Clemens Blumer, Shuting Yin

Neurons contain a tubular network known as the *endoplasmic reticulum* (ER) that stretches throughout the entire cell, including the axon and most of the dendrite. The ER is involved in the delivery of proteins and lipids as well as calcium homeostasis. In pyramidal cells, a small subset of dendritic spines contains stable ER in the form of a *spine apparatus*, while most spines are briefly sampled by single ER tubules from time to time. We could show that synapses on spines containing stable ER express a specific form of plasticity, mGluR-dependent long-term depression (Holbro et al., 2009). We are now using time-lapse two-photon imaging to investigate movements of dynamic ER in hippocampal neurons. Analysis of large 3D time series on the level of individual synapses is not trivial, and we have developed a machine learning approach to detect dendritic spines automatically and to follow them over time (Blumer et al., 2015). To our surprise, ER movements were correlated with changes in spine volume and could be triggered by strong synaptic stimulation, suggesting that ER selectively visits highly active synapses (Fig. 3). Understanding the physiological role of ER in the visited spines is the goal of this project.

5. Cyclic nucleotide signaling in synaptic plasticity

Daniel Udwari, Christine Gee

An important second messenger system in neurons is based on the conversion of ATP into cAMP, a reaction catalyzed by the enzyme adenylyl-cyclase (AC). Stimulation of endogenous AC with pharmacological agents (forskolin) triggers the potentiation of synapses, a protocol known as 'chemical LTP'. Such pharmacological manipulations affect all cell types in the tissue, making it difficult to interpret the results and distinguish between pre- and postsynaptic signaling. In collaboration with the group of Peter Hegemann, we could show that a photoactivated AC from a marine bacterium (bPAC) can be used to control cAMP levels in individual neurons by light (Stierl et al., 2011). To investigate the effects of cAMP elevation on synaptic plasticity, we expressed bPAC in postsynaptic neurons. To our surprise, even strong and sustained cAMP elevation did not induce long-term plasticity of active synapses. As pharmacological elevation of cAMP in all cells is known to induce synaptic plasticity, we suspect the critical compartment to be in the presynaptic neuron or in non-neuronal cell types. Using cell-type specific expression of bPAC, we will dissect the precise location of cAMP action. Furthermore, we develop new tools to control cAMP and cGMP signaling in subcellular compartments.

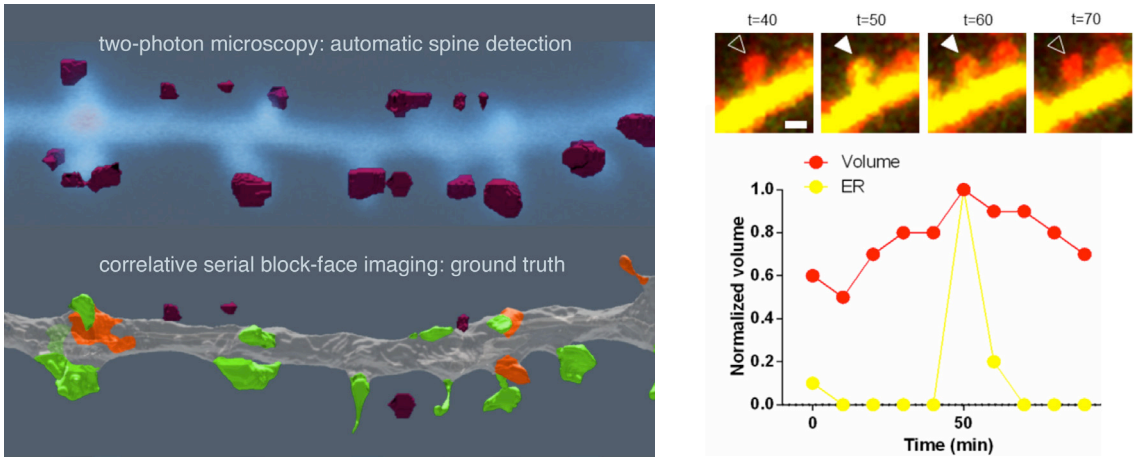

Figure 3. Automatic spine detection and ER dynamics in CA1 pyramidal cell dendrites. At t = 50 min, a spine is invaded by ER. 20 minutes later, the ER has retracted. Interestingly, ER invasion is typically preceded by a period of spine head expansion (red curve).

6. Vesicle cycling at Schaffer collateral synapses

Tobias Rose, Iris Ohmert

Studies in dissociated neuronal culture have suggested that not all vesicles in the presynaptic terminal can be mobilized by electrical stimulation. The pool of vesicles that are never used, even during periods of intense stimulation, has been termed the 'resting pool'. We set out to revisit the question in a more physiological preparation, organotypic slice cultures of rat hippocampus. In order to calculate the fraction of vesicles released from individual Schaffer collateral boutons, we developed a ratiometric sensor based on pH-sensitive GFP and a dimeric red fluorescent protein. In immature cultures, we could indeed detect a resting pool of vesicles, but this pool completely disappeared after 2-3 weeks in culture (Fig. 4). Mature Schaffer collateral synapses also displayed much faster endocytosis, making these synapses capable of sustained high frequency transmission during place cell firing *in vivo* (Rose et al., 2013).

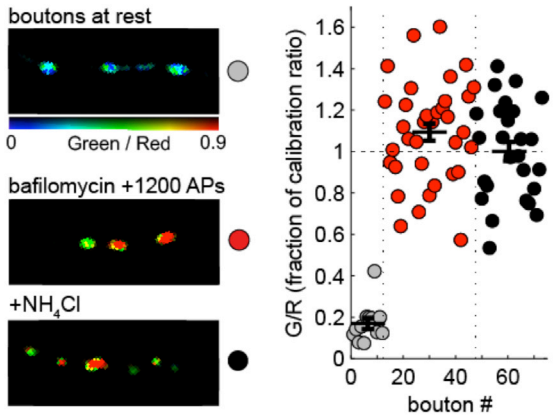

Figure 4. Imaging vesicular glutamate release from individual Schaffer collateral boutons in mature organotypic culture. At rest, transmitter vesicles are acidic and green fluorescence is quenched. After stimulation with 1200 action potentials, green fluorescence increases as vesicles are released. Chemical neutralization of vesicular pH (+ NH4Cl, calibration ratio) does not lead to further increase in green fluorescence, indicating that all vesicles were already used during electrical stimulation (Rose et al., 2013).

7. Diffusional isolation of dendritic spines as a mechanism for metaplasticity

Shuting Yin, Christian Schulze

Dendritic spines act as miniature bio-reactors, trapping activated enzymes close to their targets for up to a second. It is thought that this biochemical isolation enables rapid modification of individual synapses while minimizing the impact on immediate neighbors (Wiegert and Oertner, 2011). We set out to test this hypothesis, comparing the plasticity of synapses on spines with long and thin necks, which are well isolated from the dendrite, to the plasticity of synapses on short and stubby spines. We have previously shown that the spine neck enables stronger depolarization of active synapses, boosting the influx of calcium ions during synaptic transmission (Grunditz et al., 2008; Holbro et al., 2010). On the other hand, diffusion of fresh glutamate receptors from the dendrite into the spine would favor less isolated synapses for potentiation. Plasticity induction by two-photon uncaging of glutamate in combination with optical calcium measurements enables us to compare the plasticity of isolated vs connected synapses.

8. Modulation of synaptic signaling by TRPM4 channels

Christine Gee, Brenna Fearey, collaboration with Institute for Neuroimmunology and Multiple Sclerosis

TRPM4 channels are calcium-activated cation channels. Under conditions where calcium concentrations in neurons are high, they are further depolarized by activation of these channels, leading to a very dangerous situation. Indeed, pharmacological blockade or knock-out of TRPM4 channels makes neurons resistant to apoptosis-inducing stimulation, raising the question of the physiological function of these channels (Schattling et al., Nat. Med. 18, 1805–1811, 2012). We use a knock-out mouse model, optogenetic stimulation and pharmacology to investigate the physiological role of TRPM4 channels in synaptic function and plasticity.

Future Perspectives

The focus of the institute will remain on synaptic function and plasticity with the ultimate goal to understand the entire life cycle of a synapse, from formation to removal. We will continue to develop novel optogenetic tools that allow us to monitor and manipulate intracellular signaling in individual neurons with light. The power of optogenetics allows us to follow the fate of individual synapses over several weeks and simultaneously interfere with electrical activity and biochemical signaling in a controlled and quantitative fashion. For high speed imaging in 3D, we have constructed a two-photon microscope with advanced scanning mechanisms which allows us to sample functional signals from a large number of synapses near simultaneously. A new line of research will investigate the consequences of altered synaptic plasticity for network function. In collaboration with Fabio Morellini, we will study the role of hippocampal synaptic plasticity in rodent foraging and spatial learning.

Support

Research projects in our institute are supported by the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm SPP 1665), a start-up grant from the Federal State of Hamburg (Landesforschungsförderung), the Marie Curie Actions research fellowship program, and an EMBO long-term fellowship.

Collaborations

We collaborate with the group of Prof. Peter Hegemann at the Humboldt University in Berlin in the development of novel optogenetic tools. With the group of Prof. Karel Svoboda at HHMI's Janelia Farm, we have completed a project on genetically encoded calcium indicators. We collaborate with Prof. Thomas Vetter at the Computer Science Department in Basel to develop software for the automatic segmentation of two-photon microscopy images.

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Institute for Structural Neurobiology

(established in May 2011)

Michael Frotscher

The peculiar structures of nerve cells determine their specific functions in the nervous system. Examples for this are the unusually long processes of neurons that transmit signals to remote locations, and the synapses, highly specialized structures for the signal transfer from one neuron to the next. In the Institute for Structural Neurobiology we study nerve cell structures in relation to their functions at different levels. At the level of large neuronal assemblies, such as the cerebral cortex, we investigate the signaling mechanisms controlling the formation of laminated structures, using the neocortex and hippocampus as model systems. In turn, using mouse mutants deficient in molecules essential for neuronal lamination, we study the functional consequences of altered cortical or hippocampal organization (Kowalski et al., 2010). In recent years we have been focusing on Reelin, a large extracellular matrix protein, known to be important for cortical lamination, and on interaction partners of Reelin that play important roles in such different processes as cell motility and synaptic transmission (Chai et al., 2009; Sibbe et al., 2009; Leemhuis et al., 2010; Hellwig et al., 2011; Bouché et al., 2013; Chai et al., 2014, 2015). One interaction partner of Reelin is cofilin, an actin depolymerizing protein, which is important for the reorganization of the cytoskeleton. When phosphorylated at serine3, cofilin is no longer capable of depolymerizing actin, which stabilizes the cytoskeleton. We have shown that Reelin phosphorylates cofilin thereby stabilizing the leading processes of migrating neurons, which is required for the translocation of the nucleus during the migratory process (Chai et al., 2009). Reelin, a developmental molecule, is synthesized and secreted by Cajal-Retzius (CR) cells in the marginal zone of the cortex. However, Reelin is also expressed in the postnatal period, and we provided evidence for a role of Reelin in the maintenance of cortical architecture in the mature brain (Frotscher, 2010).

At a higher resolution, we study structural and functional plasticity of identified synapses. An easily identifiable synapse in the hippocampus is the synapse formed by the axons of the granule cells, the mossy fibers, and their target cells, mossy cells and CA3 pyramidal neurons. Our current knowledge about the fine structure of synapses is largely based on nervous tissue that was fixed using aldehyde solutions. Aldehyde fixation results in the denaturation of proteins and is followed by dehydration and embedding of the tissue in resin. It has remained an open question to what extent protein denaturation and tissue shrinkage caused by the dehydration process alter the molecular and structural components of a synapse. Moreover, subtle structural changes at synapses may not be preserved when the tissue is subjected to fixation and dehydration. In recent years we have established high-pressure freezing (HPF) in the lab, which allows shock freezing of tissue samples without the application of aldehydes and avoids robust dehydration. We used this procedure to study fine-structural changes associated with functional changes such as long-term potentiation (LTP), a form of functional synaptic plasticity (Zhao et al., 2012; Studer et al., 2014; Frotscher et al., 2014).

Finally, we study functional synaptic plasticity at hippocampal mossy fiber synapses by using two-photon microscopy and calcium-sensitive dyes. In particular, we compare mossy fiber synapses from control animals with those from mouse mutants lacking synaptopodin, a molecule essential for the formation of the spine apparatus in dendritic spines. We want to find out to what extent the spine apparatus organelle contributes to synaptic plasticity in the hippocampus (Korkotian et al., 2014).

1. Role for Reelin in stabilizing cortical architecture

Xuejun Chai, Shaobo Wang, Jiawei Li, Shanting Zhao

During development late-generated neurons destined to superficial layers of the cerebral cortex have to bypass their predecessors in deep cortical layers. It has been known for some time that Reelin plays a role in this process, but the underlying molecular mechanisms have remained elusive. The leading processes of migrating cortical neurons, which later become their apical dendrites, get in contact with Reelin in the marginal zone of the cortex. By phosphorylating cofilin, Reelin stabilizes the actin cytoskeleton in the leading processes and their branches and anchors them to the cortical surface (Chai et al., 2009; 2015). In contrast, in *reeler* mutants deficient in Reelin the leading processes are not attached to the surface of the cortex, pointing to all directions, often towards the white matter, and directed neuronal migration to upper layers is compromised.

Reelin does not only stabilize the leading processes during the development of the cortex. There is evidence that Reelin is also important for the stabilization of mature hippocampal architecture. In human temporal lobe epilepsy and in Kainate-induced experimental epilepsy in animals Reelin expression is dramatically decreased associated with a secondary loss of granule cell lamination in the dentate gyrus (granule cell dispersion; Frotscher, 2010, review). How to explain this secondary "migration" of fully differentiated granule cells leading to granule cell dispersion? Low levels of Reelin might lead to relative large amounts of active (non-phosphorylated) cofilin, increasing its severing activity. We hypothesized that decreased Reelin expression would increase cytoskeletal reorganization in the granule cells leading to increased cell motility and granule cell dispersion.

In order to test this hypothesis, we exposed hippocampal slice cultures to the glutamate receptor agonist Kainate, which like *in vivo* induced epileptic activity associated with granule cell dispersion and decreased Reelin expression (Fig. 1; Chai et al., 2014).

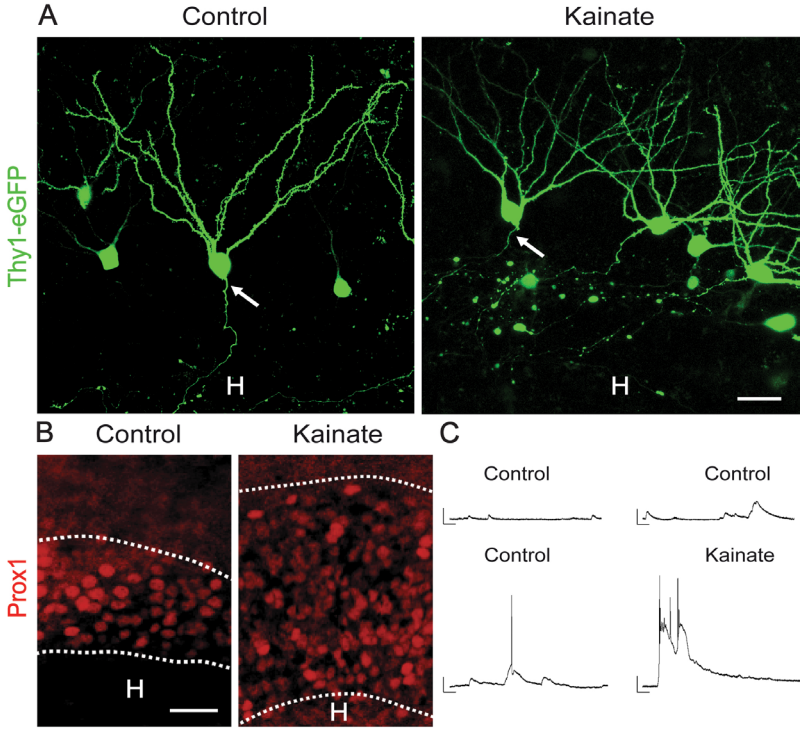

Figure 1. Kainate-induced granule cell dispersion in hippocampal slice culture. (A) Thy1-eGFP-labeled differentiated granule cells showing dendrites, spines and axon (arrows) in a control culture (incubated *in vitro* for 11 days) and in a culture incubated for 10 days, followed by incubation in the presence of Kainate for 24 h. H, hilus. Scale bar: 15 µm. (B) Immunostaining for Prox1, a marker of dentate granule cells, revealed an expansion of the granule cell layer (dashed lines) in Kainate-treated slice cultures when compared to control cultures. H, hilus. Scale bar: 50 µm. (C) Examples of current clamp recordings of granule cells from control slice cultures and a Kainate-treated slice culture at resting membrane potential. While only excitatory postsynaptic potentials (EPSPs, upper trace) and single action potentials (lower trace) were recorded from control granule cells, all Kainate-exposed granule cells showed bursts of action potentials. Scale bars: 50 ms, 20 mV (from Chai et al., 2014).

In order to study this increased granule cell motility, we took advantage of Thy1-EGFP mice, which allowed us to monitor the actual migratory activity of the labeled granule cells following Kainate application to the slice culture. When we imaged these neurons, we observed that Kainate application indeed increased the motility of granule cell nuclei, which moved into granule cell apical dendrites for some distance. This displacement of the nucleus resulted in a dispersion of the normally compact granule cell layer when visualized in Nissl stain. Moreover, the movement of the cell body into one apical dendrite resulted in the reorientation of other apical dendrites that now originated from the basal pole of the granule cell soma (Fig. 2). These recurrent basal dendrites are a characteristic feature of granule cells in the human epileptic hippocampus and are not formed *de novo* but result from the reorientation of the dendrite following increased motility of the cell nucleus (Chai et al., 2014).

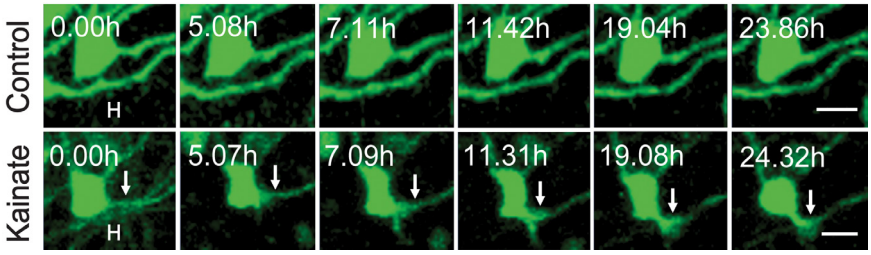

Figure 2. Somal translocation and dendritic reorientation following kainate application. Following kainate application the nucleus of a granule cell moves into an apical dendrite, shifting the origin of another dendrite (arrow) towards the basal pole of the cell body; it becomes a recurrent basal dendrite. H, hilus. Scale bars: 10 µm (from Chai et al., 2014).

2. Role for Reelin signaling in radial glial cells of the dentate gyrus

Jasmine Pahle, Jo Kristin Welzel, Shaobo Wang, Janice Graw, Saskia Siegel, Bettina Herde, Bianka Brunne

In this project we aimed at determining the effects of Reelin signaling in radial glial cells (RGCs). In the past we were able to show that Reelin is important for the establishment of a radial glial scaffold during the development of the dentate gyrus and for adult neurogenesis in this region (Brunne et al., 2010, 2013). Secondary RGCs (also called radial glia-like cells in the adult brain) are the most affected RGC population in the brain

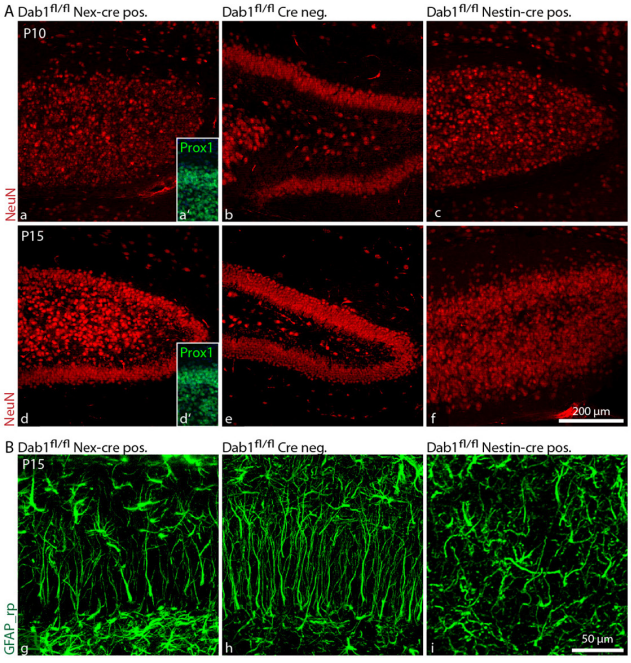

Figure 3. Secondary radial glial cells and granule cell compaction in Nex Cre-Dab1fl/fl mice. NeuN staining for postmitotic neurons (A) and GFAP staining (GFAP_rp) for secondary radial glial cells (B) in Dab1fl/fl Nex-cre positive mice lacking Dab1 in neurons but not glial or radial glial cells at P10 and P15. Nestin-cre positive Dab1$^{fl/fl}$ mice (c,f,i), with cre expression in neurons and glial cells, showing a Dab1 knockout phenotype, and cre-negative Dab1$^{fl/fl}$ mice (b,e,h) showing a wildtype phenotype, are used as controls. At P10 Dab1$^{fl/fl}$ Nex-cre positive mice (a) show a dentate gyrus phenotype which resembles Dab1 knockout mice or Nestin-cre positive Dab1$^{fl/fl}$ mice (c). In contrast at P15 (d) an intermediate phenotype can be observed between mice that have Dab1 (e) and mice lacking Dab1 in neurons and glial cells (f). Staining for Prox1 identifies dislocated cells as granule cells (insets in a and d). GFAP staining is depicted as high magnification extended focus images (Z-stack 26x1µm), revealing the partially rescued secondary radial glial cell morphology in Nex Cre-Dab1$^{fl/fl}$ mice (g). For comparison Cre negative (h) and Nestin-cre positive Dab1$^{fl/fl}$ mice (i) are shown.

of the *reeler* mutant with severely impaired positioning and radial morphology. Reelin signaling to radial glial cells, but not neurons, partially rescued neuronal positioning in the dentate gyrus (Brunne et al., 2013; Fig. 3). This is in contrast to experiments in the neocortex and underlines the importance of Reelin signaling to glial cells especially in the dentate gyrus. However, the underlying mechanisms, the involvement of the two Reelin receptors ApoER2 and VLDLR, and the mutual interactions between RGCs and neurons during development as well as in adult neurogenesis in the dentate gyrus have remained elusive.

In ongoing projects we will address these issues. First, we aim to determine the exact locations and differential functions of the two Reelin receptors on RGCs. For this purpose, we established two new mouse mutants using the zinc finger nuclease technology. These mice carry tagged Reelin receptors, which will allow us to localize the two receptors in immunohistochemical experiments and real-time microscopy studies. In an additional step we aim at visualizing the migratory activities of both RGCs and granule cells and a potential glia-guided granule cell migration in hippocampal slice cultures. Of particular interest is our recently produced conditional Reelin mutant in which Reelin expression is selectively switched off in GABAergic interneurons after the animals were allowed to undergo normal ontogenetic development (Fig. 4). In the adult brain, Reelin has been associated with the stabilization of neuronal architecture, synapse modification, long-term potentiation and adult neurogenesis, and a decrease in Reelin levels has been observed in a variety of neuropsychiatric diseases such as schizophrenia, depression and epilepsy (Frotscher, 2010, review). Due to the severe developmental defects in the *reeler* mutant, it has been difficult to distinguish between direct effects of Reelin in the adult brain and indirect effects caused by the malformation of brain structures resulting in severely altered anatomical organization. We are eager to address these questions soon using our new conditional Reelin mutant.

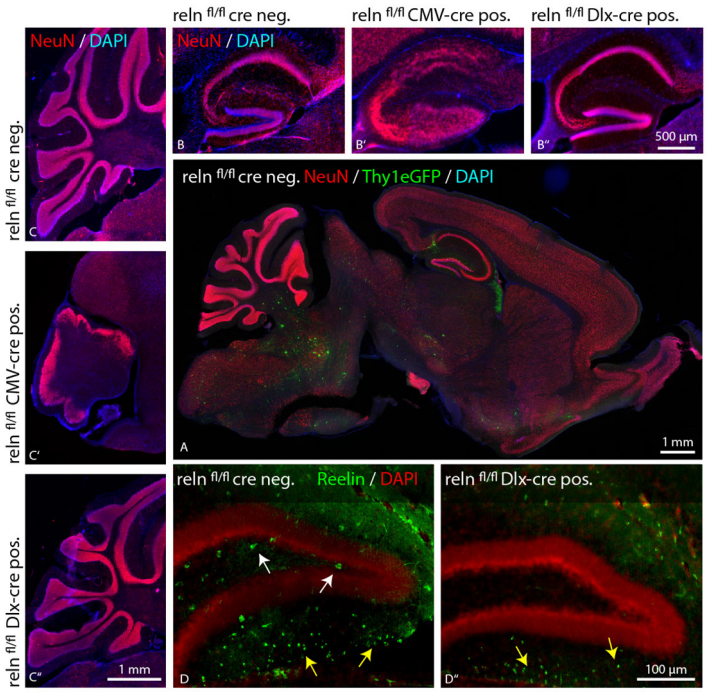

Figure 4. Characterization of the Reelin flox – Dlx5/6 cre mouse line.
In our newly generated mouse line the first exon of Reelin is flanked bei loxP sites. Cre negative mice show normal brain structure (A) and Reelin expression (D). Combined with a ubiquitously cre expressing mouse line (CMV promotor) the mice show a *reeler* phenotype with neuronal dispersion in layered structures such as the hippocampus (B') and a severly altered hindbrain (C'). In contrast, when combined with a mouse line expressing cre recombinase only in interneurons (Dlx5/6 promotor) brain morphology is nomal (B'' and C'') since Reelin expression by Cajal-Retzius cells is normal (yellow arrows in D''). Reelin expression in interneurons (white arrows in D) develops around P14 in the dentate gyrus and is not required for proper brain development. With this model, we will now be able to investigate the role of Reelin in interneurons in the adult brain that has undergone normal development.

3. Fine-structural changes associated with LTP

Shanting Zhao, Dagmar Drexler, Xuejun Chai, Michael Frotscher

LTP is a characteristic form of synaptic plasticity discovered as early as in 1973 by Bliss and Lomo. It has remained an open question whether LTP is associated with learning and memory processes; however, modifications at synapses are likely to occur in circuits that are involved in learning and memory processes. While synaptic plasticity in LTP is principally defined as an increase in synaptic strength, several studies have shown that LTP is also associated with changes in synaptic structure. Previous studies took advantage of two-photon microscopy to monitor the time course of such structural changes. Alternatively, electron microscopy (EM) was used to determine structural changes at the actual synaptic contacts. However, relatively few fine-structural analyses attempted to avoid artifacts associated with chemical fixation by aldehydes. To this end, we established high-pressure freezing in the lab, which allowed us to avoid chemical fixatives and dehydration in ethanol (see above). Briefly, in organotypic slice cultures of hippocampus we induced chemical LTP (cLTP) with tetraethylammonium (TEA), which resulted in the robust potentiation of mossy fiber synapses 10 minutes after TEA application as revealed by patch-clamp recordings in the whole cell mode. After 10 minutes of exposure to TEA the slice cultures were immediately subjected to HPF. Following shock freezing, the tissue water was freeze-substituted by methanol or acetone while being in a solid phase. This contrasted to traditional dehydration in ethanol, which takes place while the tissue water is in a liquid phase, resulting in the shrinkage of the various tissue components depending on their water content. With high-pressure freezing we not only achieved a very good preservation of fine-structural detail but were also in the position to monitor subtle structural changes induced by cLTP (Zhao et al., 2012; Studer et al., 2014; Frotscher et al., 2014).

We used the easily identifiable mossy fiber synapse in the hippocampus as a model. The thin preterminal mossy fiber axon enlarges to form a giant bouton that establishes synaptic contacts with large, often branched complex spines on the proximal dendrites of mossy cells in the hilar

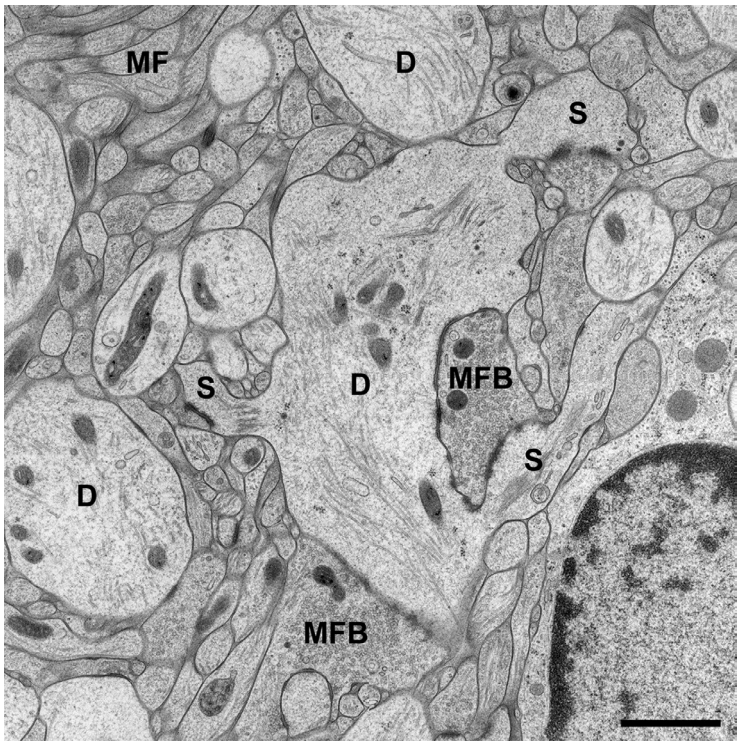

Figure 5. CA3 region of hippocampus in a slice culture incubated for 2 weeks *in vitro*. The tissue was high-pressure frozen in the absence of chemical fixatives, subjected to freeze substitution, osmicated, and finally embedded in Epon (see Studer et al. 2014, for details on the method). Note that all tissue components of stratum lucidum are well preserved after the incubation period and subsequent freezing procedure. As known from many studies in perfusion-fixed material, the *stratum lucidum* mainly contains the thin unmyelinated axons of the mossy fibers (MF) and their giant boutons (MFB). The postsynaptic elements, the proximal dendrites (D) of CA3 pyramidal cells, are located in between the bundles of mossy fibers and give rise to large complex spines (S) for the synaptic contact with MFBs. Scale bar: 1 µm (from Frotscher et al., 2014)

region and pyramidal neurons in the *stratum lucidum* of CA3. In Fig. 5, all structural details of *stratum lucidum* are shown in a control slice culture subjected to high-pressure freezing.

Following LTP induction by TEA, we observed that these giant spines gave rise to numerous newly formed spine-like protrusions that formed new, short synaptic contacts. A quantitative analysis accordingly showed a significant increase in the number and area of spines/mossy fiber bouton area and an increase in the number of synaptic release sites, which were, however, smaller than active zones in control slice cultures, likely because they were still growing after the 10-minute stimulation period. Of note, when we studied slice cultures from Munc13-1 mouse mutants in which priming and docking of synaptic vesicles is compromised, we were unable to find these TEA-induced structural changes at mossy fiber synapses (Zhao et al., 2012). Taken together, we regard our fine-structural findings at mossy fiber synapses in the hippocampus as an example of the high structural plasticity of central synapses under conditions of synaptic potentiation.

4. Role of the spine apparatus as a calcium store

Alexander Drakew, Urban Maier, Anja Tippmann, Bettina Herde, Dung Ludwig

The spine apparatus is an enigmatic organelle that is regularly observed in the large complex spines postsynaptic to mossy fiber boutons. We have shown some time ago that these organelles are not formed in mouse mutants deficient in synaptopodin, an actin-associated cytoplasmic protein found in kidney and brain. Hence, synaptopodin knockout mice allowed us to study synaptic transmission in brain tissue lacking a spine apparatus. Since the spine apparatus is assumed to be a calcium store we established two-photon glutamate uncaging and two-photon calcium imaging at individual spines in the lab (Fig. 6). In brief, our results showed that basal synaptic transmission is not different between control tissue and tissue from synaptopodin-deficient mouse mutants. Calcium transients at large complex spines of mossy fiber synapses were similar between genotypes. However, after intense stimulation known to induce synaptic

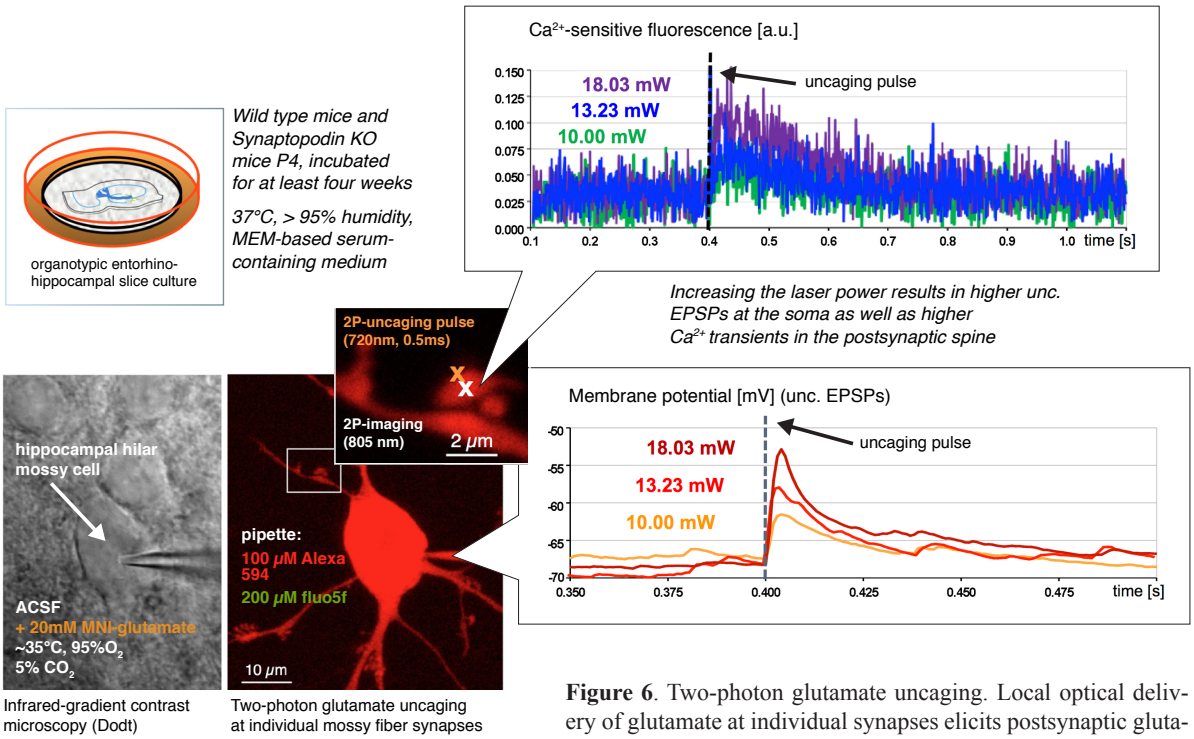

Figure 6. Two-photon glutamate uncaging. Local optical delivery of glutamate at individual synapses elicits postsynaptic glutamatergic responses in single spines of mossy fiber synapses.

potentiation (pairing of glutamate uncaging with back-propagating action potentials at mossy fiber synapses) we found calcium transients in slice cultures from wild-type animals significantly increased when compared to cultures from synaptopodin-deficient mutants. These results not only confirm that the spine apparatus is an intracellular ER-derived calcium store, they also suggest that the spine apparatus plays a crucial role in synaptic plasticity.

Future perspectives

Application of HPF to immunocytochemical studies using immunogold labeling

David Lutz, Dagmar Drexler, Saskia Siegel, Xuejun Chai, Michael Frotscher

When subjecting tissue to high-pressure freezing, proteins are not denaturated and the tissue water is not removed by robust dehydration known to result in tissue shrinkage. Moreover, it is well known that aldehyde fixation results in decreased tissue antigenicity. Hence, we set forth to study immunogold labeling in high-pressure frozen tissue samples. In a preliminary study using an antibody against p-cofilin, we found a much larger number of gold grains at active zones (where p-cofilin is located) when compared to tissue fixed conventionally by aldehydes (Studer et al., 2014). Of note, background staining was not increased. We hypothesize that antigenicity was much improved in the absence of chemical fixation. We will now use cLTP as a model and study a variety of candidate molecules that are likely involved in the structural changes we had observed following cLTP. We will use immunogold labeling to determine quantitative changes in transmitter receptor subunits, synaptopodin, and brain-derived neurotrophic factor (BDNF; Dieni et al., 2012), and will also study appropriate mouse mutants for structural and functional deficits if we find quantitative changes in these candidate molecules. We expect that these studies will enable us to unravel molecular changes associated with the structural changes observed at mossy fiber synapses after the induction of cLTP.

Functional characterization of synaptic transmission at mossy fiber synapses

Alexander Drakew, Urban Maier, Saskia Siegel, Dung Ludwig

Mossy fiber synapses are known for their specific morphological characteristics of presynaptic and postsynaptic components (see above). In our future projects we aim at understanding how these characteristic structural features are

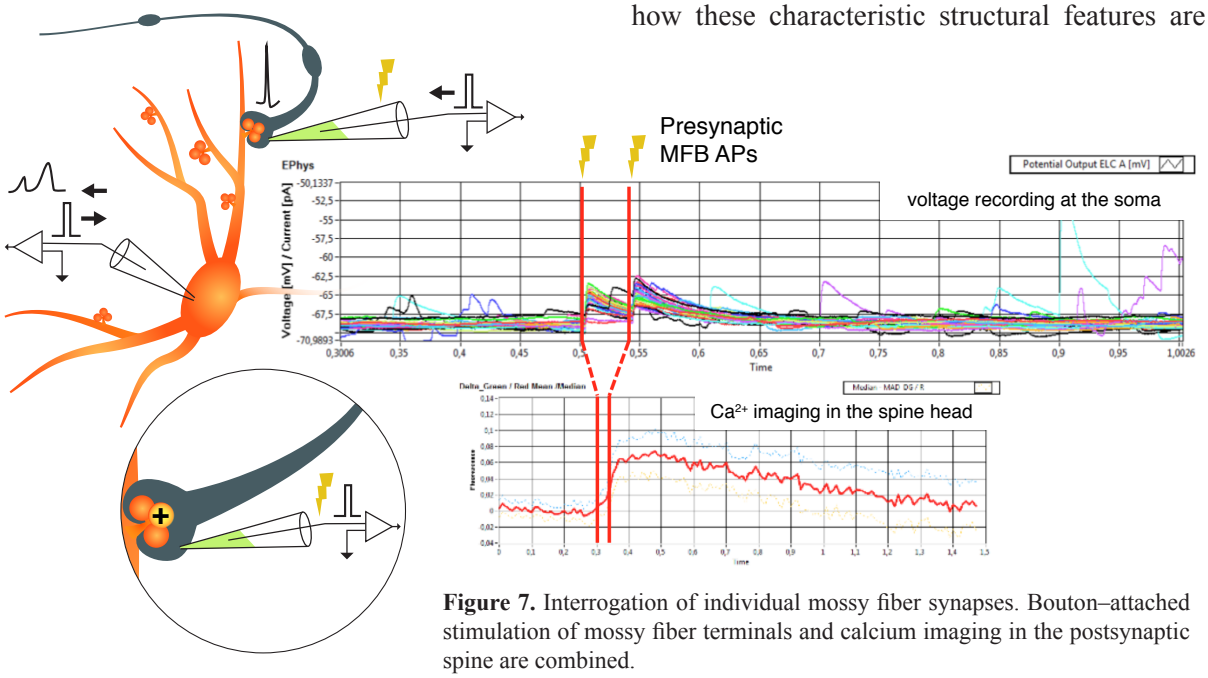

Figure 7. Interrogation of individual mossy fiber synapses. Bouton–attached stimulation of mossy fiber terminals and calcium imaging in the postsynaptic spine are combined.

used in synaptic transmission at this particular synapse. For this purpose, we want to stimulate individual presynaptic mossy fiber boutons using the patch-clamp technique and will record the calcium response in individual postsynaptic spines. This will be correlated to the electrical response at the somatic patch pipette. Alexander Drakew and Urban Maier adopted the technique of *shadow patching,* which was developed to patch cell bodies, to the giant presynaptic mossy fiber boutons. We hope to get closer to an understanding of the functional characteristics of this particular synapse using this novel approach of stimulating and recording from pre- and postsynaptic compartments of an identified central synapse (Fig. 7).

Support

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Institute for Molecular Neurogenetics

(established in February 2010)

Matthias Kneussel

(2002-2010 Head of the ZMNH Research Group Protein Trafficking and Synapse Formation)

Our group is interested in understanding molecular and cellular mechanisms of synaptic plasticity, which is thought to be the cellular basis of learning and memory. The strengthening and weakening of synapses requires the delivery of plasticity-related proteins (PRPs) and adaptive changes of various synaptic components. These processes involve both the dynamic movement of molecules through active cytoskeleton transport and Brownian diffusion at the plasma membrane. To deliver newly synthesized neurotransmitter receptors, neurons use kinesin family proteins (KIFs) to power vesicular transport of AMPARs, NMDARs, $GABA_A$Rs, and GlyRs along microtubules into dendrites. Myosins often mediate the final steps of plasma membrane delivery, using actin filaments as tracks that are highly abundant underneath the plasma membrane and in dendritic spines. Upon surface delivery though exocytosis, receptors undergo diffusion movement and reversible trapping by receptor-scaffold interactions. These interactions are in turn regulated through signaling mechanisms, following neuronal activity changes. Adjustment of synaptic receptor numbers also involves internalization through endocytic processes. Initial steps of receptor endocytosis are mediated by actin and myosins. The transport of receptors downstream of the sorting endosome is powered by the microtubule motor dynein. Alternatively, myosins transport receptors from recycling endosomes back to the plasma membrane. Thus, the dynamic routes of postsynaptic receptors involve alternate steps of transport, diffusion, and confinement that are regulated by neuronal activity and are specialized to rapidly adapt synaptic receptor numbers in regulating synaptic strength.

Transport regulation also involves cytoskeletal proteins that form and stabilize the cytoskeletal tracks along which motors move. The cell cortex on the inner face of the plasma membrane (PM) is an actin-rich layer. In dendritic spines, the spine head and its neck contain a dense network of actin filaments. Electron microscopy failed to detect microtubules in spines. However, dynamic microtubules, labeled by the microtubule tip-tracking protein EB3, were reported to transiently enter spines in an activity-dependent manner. At the base of the spine, actin filaments associate with microtubules that are highly abundant in dendrites. Furthermore, tubulin in microtubules is highly modified by different posttranslational modifications (PTMs), such as acetylation, polyglutamylation and tyrosination/de-tyrosination. Some tubulin PTMs affect transport in neurons and are thought to act as traffic signs that may have the potential to direct cargo to specific subcellular destinations ("tubulin code" hypothesis). Recent evidence points toward an activity-dependent regulation of tubulin PTMs in neurons, suggesting that they might participate in the crosstalk between neuronal activity and intracellular transport. In this respect, they provide a candidate system to understand the preferential delivery of tagged over untagged synapses in synaptic tagging. In addition to intracellular transport, excitatory and inhibitory ionotropic receptors traffic rapidly at the surface of the neuronal PM by thermally driven Brownian diffusion. Synaptic receptor numbers result from a dynamic equilibrium between synaptic and extrasynaptic sites. Receptors constantly switch between mobile and immobile states, with a mobile rate of about 0.1 μm2/s to 0.5 μm2/s. The reversible binding of mobile receptors to immobile submembrane scaffolds or cytoskeletal elements leads to diffusion trapping and, consequently, to an immobilization of receptor molecules. Diffusion trapping is regulated by posttranslational modifications of receptors or scaffold elements, as well as by membrane compartmentalization or the extracellular matrix (ECM). We

recently characterized the protein radixin as an activity-dependent regulator of receptor diffusion in the plasma membrane (discussed below).

Our group aims to understand molecular mechanisms that regulate the transport and turnover in neuronal plasticity. We combine molecular/biochemical techniques with spinning disk time-lapse microscopy and fluorescence recovery after photobleaching (FRAP) imaging in living neurons. Dissociated hippocampal and cerebellar neurons as well as slice cultures are used to study these processes. We investigate the consequences of molecular manipulations on excitatory post-synaptic potentials (EPSPs), long-term potentiation (LTP) and long-term depression (LTD) using genetic mouse mutants of different synaptic and transport components. This work is complemented by mouse behavioral analysis to understand the contribution of synaptic transport to learning and memory.

KIF21B - a microtubule-based kinesin motor powering protein transport to synapses

Mary Muhia, Jürgen Schwarz, Edda Thies

The gene encoding the kinesin KIF21B has been identified as a susceptibility locus for neuronal disease. KIF21B protein levels were five-fold increased in Alzheimer´s disease and in MS patients, KIF21B correlated with the extent of grey matter demyelination. We found that KIF21B is a processive kinesin that moves along neuronal microtubules. Its motility is regulated by the E3 enzyme TRIM-3 (Labonté et al., 2013), whereas KIF21B powers the delivery of γ2 subunit- containing $GABA_AR$s heading to synapses (Labonté et al., 2014). We recently generated a KIF21B conditional knockout mouse to study the consequences of KIF21B depletion. Strikingly, AMPARs are significantly reduced at the neuronal plasma membrane if KIF21B is

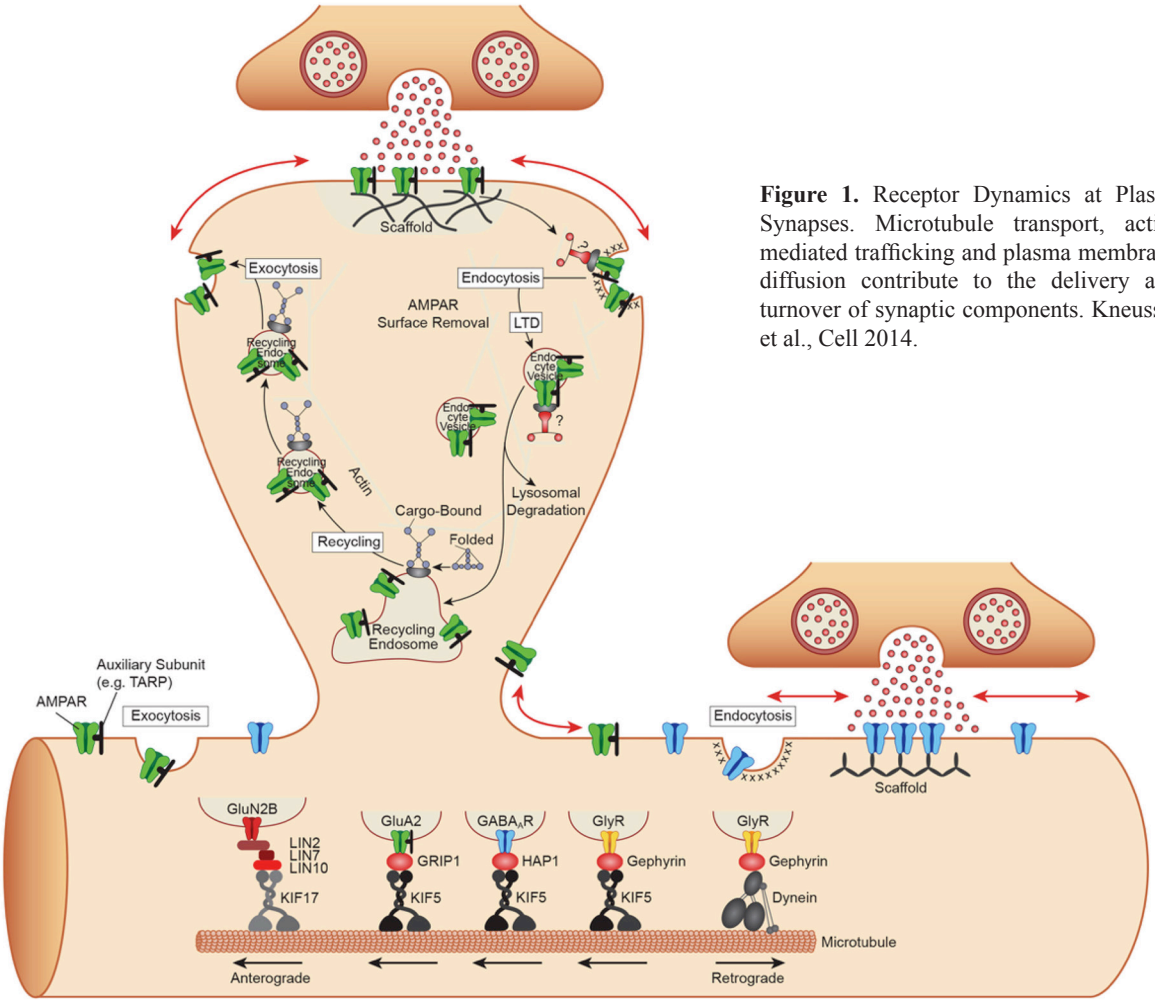

Figure 1. Receptor Dynamics at Plastic Synapses. Microtubule transport, actin-mediated trafficking and plasma membrane diffusion contribute to the delivery and turnover of synaptic components. Kneussel et al., Cell 2014.

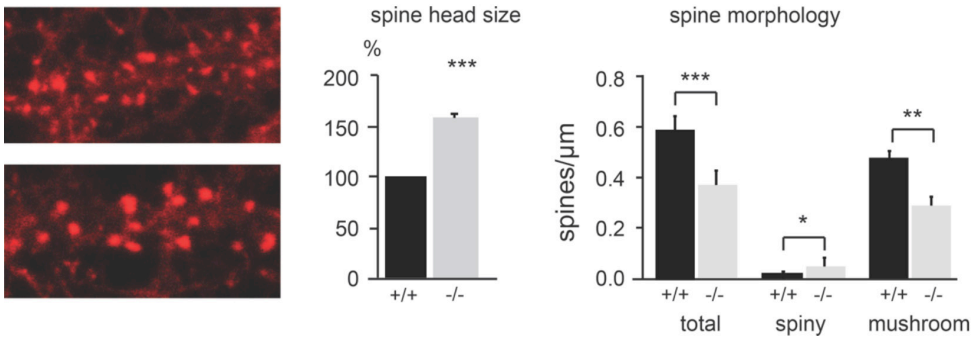

Figure 2. Depletion of the kinesin motor KIF21B leads to a reduction of mushroom-type dendritic spines with a larger spine head size.

absent. Knockout mice further exhibit changes in dendritic spines and dendrite branching, suggesting that the motor is critical in neuronal development and plasticity.

Loss of KIF21B alters LTP and LTD in the hippocampus. At the behavioral level, KIF21B knockouts exhibit altered anxiety-related behavior (Fig. 3), as well as impairment in the proper acquisition of conditioned fear and spatial learning. They further show deficits in social recognition. Hence, KIF21B mouse models are instrumental in elucidating the molecular control over specific cognitive faculties in which plasticity and subsequent spine re-structuring are implicated.

GRIP1, Muskelin and Neurobeachin: adapters and regulators of synaptic transport

Kira Brune, Sandra Freitag, Frank F. Heisler, Mary Muhia, Yvonne Pechmann

Motor cargo complexes consist of the motor protein, the cargo adapter that connects the motor to its cargo and several accessory proteins, which regulate transport. Since a limited number of motors transport a large variety of cargoes across cells, cargo adapters mediate the specificity of transport by "telling" the motor which cargo is attached.

GRIP1 is a multi PDZ domain protein that connects AMPARs with the kinesin KIF5. Using yeast two-hybrid screening, we could show that GRIP1 also couples the cell adhesion protein N-Cadherin to KIF5-AMPAR transport complexes. Both the neurotransmitter receptor and the cell adhesion protein undergo simultaneous transport towards glutamatergic synapses (Heisler et al., 2014). This finding is consistent with the fact that AMPARs and N-Cadherins physically connect at the synaptic plasma membrane. Quantification of AMPAR and N-Cadherin transport by time-lapse and electron microscopy revealed that about 30% of both proteins undergo combined synaptic transport, whereas both proteins also reach the synapse by separate transport routes (Heisler et al., 2014). Our data suggest that GRIP1 acts as a central intracellular hub to organize the transport of synaptic components heading to the same synapse.

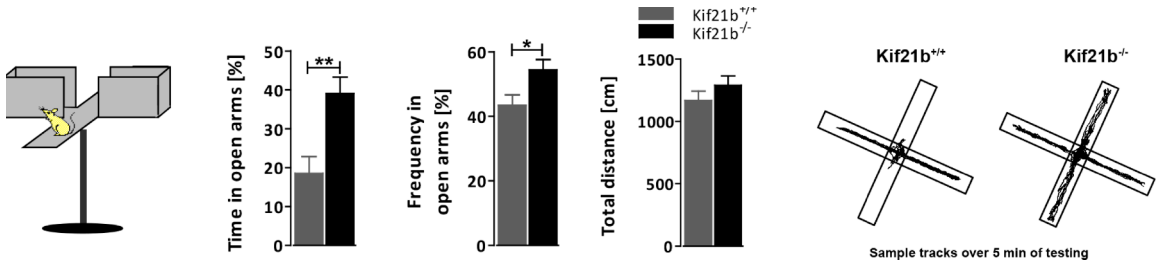

Figure 3. Elevated plus maze test for anxiety-related behavior. Loss of KIF21B results in an anxiolytic phenotype, suggesting that KIF21B motor function may regulate anxiety-related behavior. Knockouts spend significantly more time, as well as increased frequency into open aversive arms.

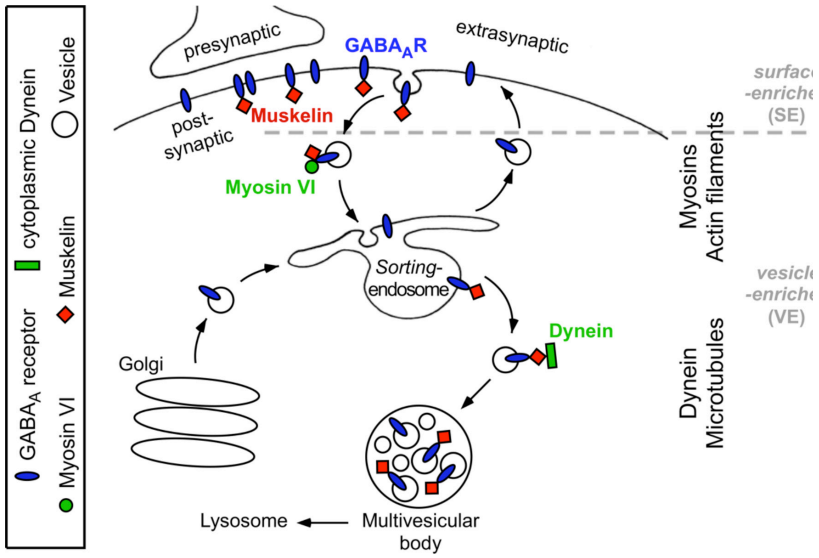

Figure 4. Model of muskelin function in intracellular trafficking pathways. Heisler et al., Neuron, 2014.

Other factors that connect motor and cargo include the protein muskelin (Heisler et al., 2011). Muskelin connects α1-containing GABA$_A$Rs to both the microtubule motor dynein and the actin motor myosin VI. In this respect muskelin accompanies receptor internalization along the actin- and microtubule cytoskeleton from the synaptic plasma membrane towards intracellular lysosomes that degrade GABA$_A$Rs (Fig. 4). To our knowledge muskelin is the first transport factor that functionally interacts with both cytoskeletal elements, suggesting that it might be involved in switching cargo vesicles from one to the other cytoskeleton (Heisler et al., 2011).

In a collaboration with the laboratory of Hermann Schindelin from Würzburg University, we recently obtained structural data showing that muskelin forms a tetrameric assembly via dimerization of its LisH domain in combination with a head-to-tail interaction. Mutagenesis to interfere with the individual dimerization motifs revealed that muskelin is differentially localized to either the cytoplasm or the neuronal nucleus (Delto et al., 2015). Muskelin is therefore a candidate protein to travel between the synapse and the nucleus in order to regulate gene expression. Current investigations therefore study the gene expression profiles of wildtype versus muskelin knockout mice to identify downstream targets of muskelin nuclear shuttling.

In behavioral assays, muskelin KO mice display specific cognitive phenotypes. While short-term memory retention is intact, muskelin knockouts show a significantly decreased exploration of the Y-maze novel arm after a 24h delay interval, compared to wildtype controls. In the Morris water maze test for reference memory acquisition and reversal learning, the loss of muskelin leads to enhanced reversal learning, suggesting that muskelin may regulate specific aspects of cognitive function involving cognitive/behavioral flexibility.

Polyglutamylated Tubulin, Spastin and Katanin: regulation of microtubules, the tracks along motor-cargo complexes move

Petra Breiden, Torben J. Hausrat, Franco Lombino, André Teixeira Lopes

In addition to the regulation of transport at the level of motor-cargo complexes, transport reactions are regulated by the tracks along which motors move. Tubulin dimers consisting of α- and β-tubulin represent the building blocks of microtubules. Both tubulins are highly modified by posttranslational modifications (PTMs), such as acetylation, polyglutamylation and tyrosination/de-tyrosination (Fig. 6). Recent evidence from our laboratory has shown that tubulin polyglutamylation is sensitive to neuronal activity changes and regulates the number of gephyrin molecules that undergo KIF5-mediated delivery into neurites (Maas et al., 2009). Furthermore, we found that behavioral preconditioning in mice affects tubulin PTMs, suggesting that they might be functionally associated with neuronal plasticity.

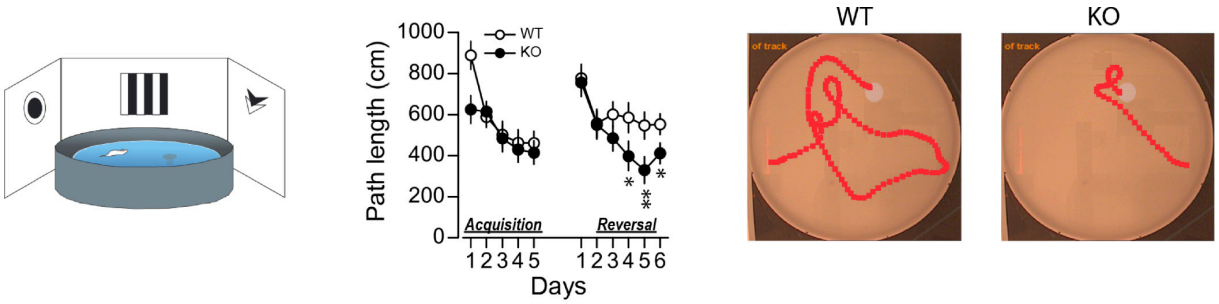

Figure 5. Left: Water maze test for spatial acquisition and reversal learning. Middle: Required path length to find the hidden platform over the individual days of training. In the reversal training phase (platform at opposite position), muskelin knockouts find the platform significantly faster. Right: Representative traces of WT and KO mice during the late phases of reversal training. Hidden platform position indicated by white circle.

To study the role of polyglutamylation, we generated three conditional knock-in mouse mutants with mutations in the tubulin C-terminal tail. Glutamate residues, known to be subject to polyglutamylation, were exchanged to aspartate to prevent polyGlu-tubulin. In this respect, we focused on three tubulin genes that are highly expressed in the postnatal brain. In collaboration with Thomas Oertner, ZMNH Institute for Synaptic Physiology, we further apply optogenetic methods to study activity-dependent transport in the presence and absence of specific tubulin PTMs.

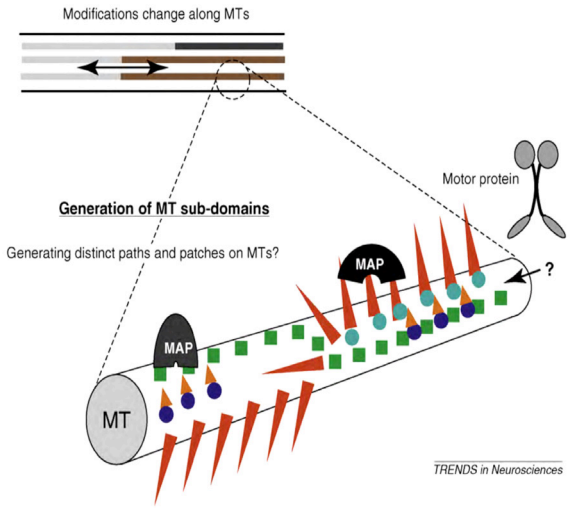

Figure 6. Tubulin posttranslational modifications (PTMs) modify microtubules. The individual patterns of tubulin PTMs are suggested to write a pattern of information into the cytoskeleton and have been discussed as the "tubulin code". Janke and Kneussel, Trends Neurosci. 2010.

Other proteins that regulate microtubules are the microtubule severing enzymes spastin and katanin, which cut microtubules in the regulation of microtubule turnover. For instance, spastin cuts preferably microtubules that carry polyglutamylated tubulin C-termini. In addition, spastin-mediated cleavage is required to grow microtubules into new neurite branches. Recent evidence in the field has also shown that microtubules transiently enter dendritic spines, dependent on neuronal activity. To study the role of microtubule severing with respect to synaptic delivery and synapse function, we generated conditional knock-out mice of spastin and katanin. Preliminary analysis of the mutants revealed significant changes at the synapse and neuronal network level.

Myosin VI – an actin based motor powering AMPA receptor transport in dendritic spines

Wolfgang Wagner

Actin filaments are the major cytoskeletal element in dendritic spines and serve as tracks for the myosin family of motor proteins. For example, myosin V transports AMPAR-containing recycling endosomes into spines. Myosin VI is also involved in AMPAR trafficking. However, it is unclear how precisely this myosin promotes AMPAR trafficking and whether synaptic transmission and plasticity depend upon myosin VI. In order to clarify these issues, we study cerebellar Purkinje cells (PCs) as a model system. We use

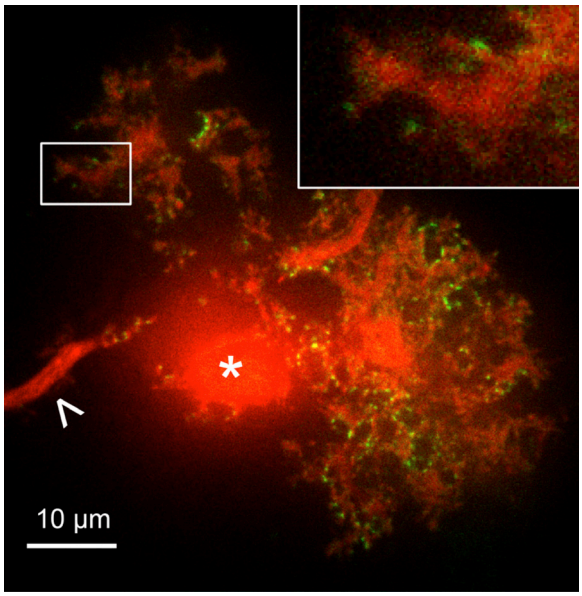

Figure 7. Surface-exposed AMPARs in a live Purkinje cell. A cultured Purkinje cell expressing pHluorin-tagged GluA1 AMPAR subunit (green) and mCherry (to visualize cell volume; red). Cell body (indicated by star), axon (indicated by arrow head) and dendritic tree are visible. A magnified view of the boxed region is shown at the top, right.

cell biological assays such as FRAP imaging of pHluorin-tagged AMPARs to dissect how myosin VI affects AMPAR delivery and turnover at the postsynaptic plasma membrane of PCs (Fig. 7). We also measure AMPAR-mediated synaptic transmission in PCs via electrophysiological recordings. Furthermore, we generated a conditional myosin VI knockout mouse that we use in collaboration with Chris de Zeeuw (Erasmus Medical Center, Rotterdam) to elucidate if myosin VI is required in PCs for postsynaptic plasticity and for PC-dependent motor learning.

Radixin - regulation of synaptic receptors that undergo surface diffusion at the plasma membrane

Torben J. Hausrat, Mary Muhia, Jürgen Schwarz

Receptors that have reached the plasma membrane also undergo trafficking by alternate surface membrane diffusion and trapping though submembrane scaffold proteins. We identified radixin as a clustering factor that anchors α5 subunit-containing $GABA_A$ receptors at extrasynaptic sites outside of inhibitory synapses. Radixin undergoes phosphorylation through the Rho kinase pathway, which determines whether radixin exists in its open or closed conformation. Notably, the open conformation acts as an extrasynaptic anchor to keep receptors outside of synapses that otherwise reach the synapse via membrane diffusion (Fig. 8). Our current model suggests that extrasynaptic radixin-receptor clusters may be plasma membrane reserve pools to rapidly exchange receptors at synaptic sites.

Future perspectives

Although much progress in characterizing the exchange of neurotransmitter receptors at synapses has been made, many questions remain. (1) How is the active transport of plasticity-related proteins (PRPs) directed to those dendrites that contain active or tagged synapses? (2) What regulatory mechanisms exist to switch transport complexes between microtubules and actin filaments in order to enter a dendritic spine? (3) Which signals unload cargoes from the

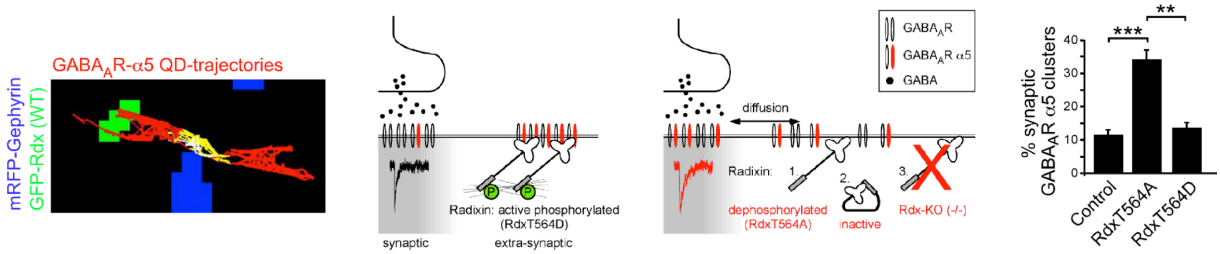

Figure 8. Left: Alternate surface membrane diffusion and trapping of α5 subunit-containing GABAA receptors between gephyrin clusters (blue) and radixin clusters (green) (in collaboration with Antoine Triller). Middle: Model of radixin function. The phosphorylated form of radixin binds to receptors and F-actin. If radixin is inactive (closed conformation) or absent (knockout mouse), receptors are released and diffuse across the plasma membrane. Right: the radixin T564A mutant that leads to the closed conformation is unable to trap receptors at extrasynaptic sites. Instead receptors diffuse and reach the synapse. The open and active T564D conformation normalizes this effect.

motor complex to deliver receptors to an excitatory versus an inhibitory synapse? (4) How is the exchange of receptors between intracellular vesicles and the plasma membrane regulated? (5) Which posttranslational modifications control the diffusion trapping of cell-surface receptors? (6) How are neuronal activity changes translated to crosstalk with the trafficking machinery?

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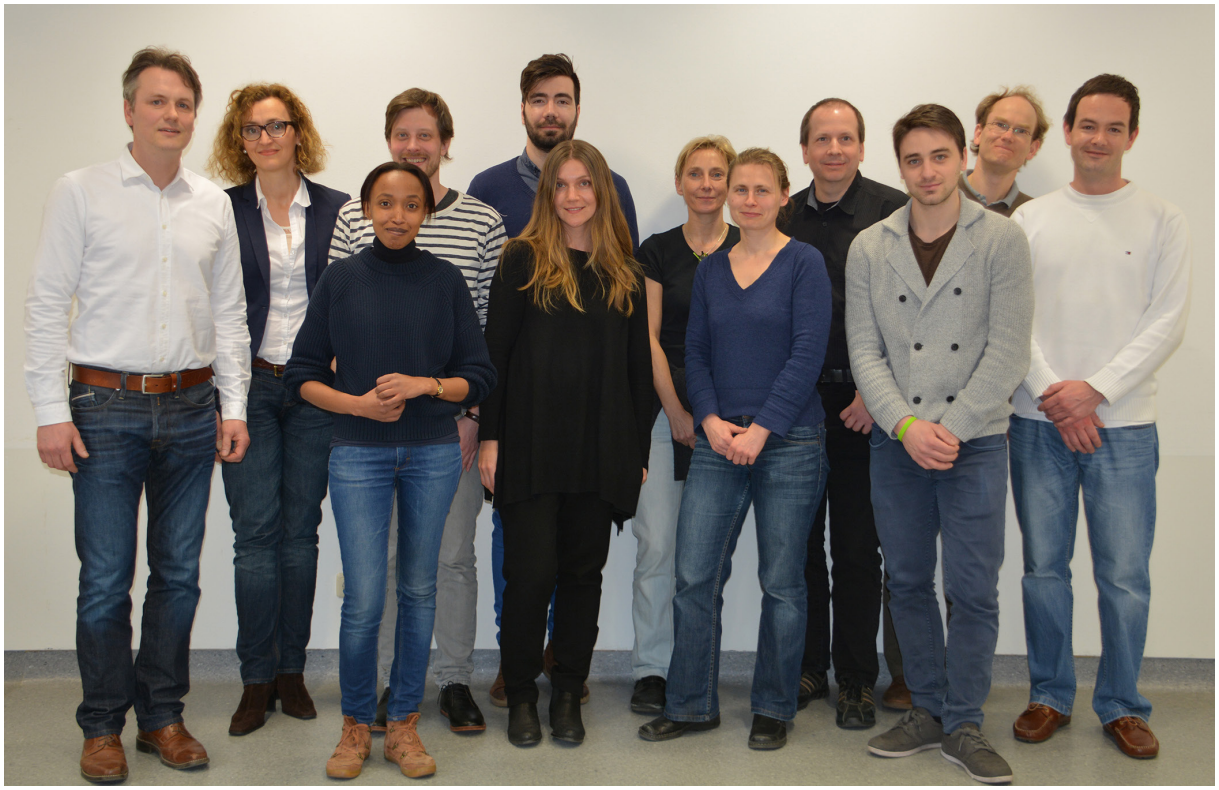

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Administration: Angelika Kneussel
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Sandra Freitag
Torben Hausrat
Frank Heisler
Mary Muhia
Wolfgang Wagner
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André Teixeira Lopes
Technicians:
Petra Breiden
Yvonne Pechmann
Edda Thies
Student/Trainee:
Irina Schäfer
Guest scientists:
Jürgen R. Schwarz
Sönke Hornig
Alumni 2009-2014
Wiebke Hirdes
Dorthe Labonté
Han Kyu Lee
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Guest scientist group Jürgen R. Schwarz

(established in 2006)

Since my retirement in 2006 from the position as head of the "Institut für Angewandte Physiologie" (UKE) I have been a guest scientist, first in the group of Prof. Pongs (Institute of Neural Signal Transduction), and since 2011 in the group of Prof. Kneussel (Institute of Molecular Neurogenetics).

Function of erg K channels in Purkinje cells

Dragos Niculescu, Wiebke Hirdes, Sönke Hornig, Olaf Pongs, Matthias Kneussel

We are studying voltage-dependent ion channels (Na, K, Ca and Cl channels) to understand the basic mechanisms underlying neuronal excitability. The aim of our main project is to understand the function of ether-à-go-go-related gene (erg) K channels in the brain. This field is relatively unexplored, since erg channel function has mainly been studied in the heart, where they are involved in repolarizing the cardiac action potential. HERG (human erg) malfunction prolongs the QT-interval in the electrocardiogram, thereby increasing the incidence of heart arrhythmia and sudden death.

The erg channel family consists of three members (erg1-3), all of which are differentially expressed in the brain. Since erg channels are strongly expressed in the brainstem, olfactory bulb and cerebellum, we have previously studied erg channel function in raphe neurons and mitral cells of the olfactory bulb (Hirdes et al., 2010). The aim of our present project is to analyse erg channel function in Purkinje cells of the cerebellum and their importance for motor control and coordination. In Purkinje cells erg K channels are already activated at the resting potential, therefore they contribute to the maintenance of the resting potential and dampen excitability by elevating the threshold potential. Blockage of erg channels in Purkinje cells by a selective

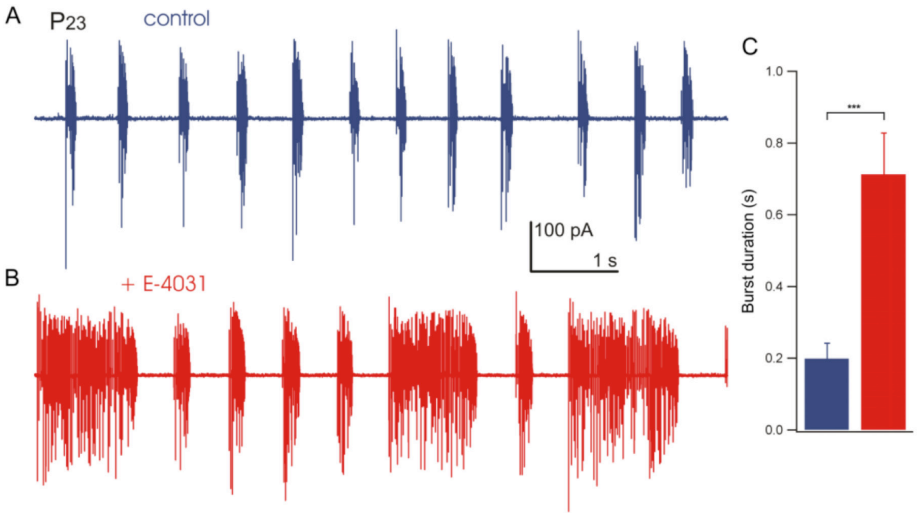

Figure 1. Burst activity of a Purkinje cell of a 4 week old mouse before (A) and during (B) application of 5 µM E-4031. On-cell recording from a purkinje cell in an acute slice preparationof the cerebellum. 5 mM KCl in ACSF, $GABA_A$ and Glutamate receptors were blocked. Following blockage of erg channels the duration of bursts was prolonged from 200 to about 700 ms (C, $p<0.001$).

blocker (E-4031) depolarizes the neuron and decreases the threshold potential. Another important finding is that activation of the metabotropic glutamate receptor (mGluR1) blocks erg channels in Purkinje cells, thereby lowering the threshold potential and increasing the frequency of action potentials. The biophysical properties of the native erg current together with results from quantitative PCR and experiments with toxins selective for the different erg channel subunits indicate that the native erg channels are presumably heteromeric channels, constructed from erg1 and erg3 channel subunits. These data were recently published (Niculescu et al., 2013).

Application of the erg channel blocker E-4031 increased the frequency of action potential firing as well as the length of action potential bursts (Fig. 1). To analyse erg channel function for motor behaviour, we study the effect of erg channel blockage on spontaneous activity of Purkinje cells at body temperature. To understand how erg channels affect motor behaviour and coordination, we are about to knock-down erg channels in Purkinje cells with siRNA. We constructed rAAVs containing the Purkinje cell specific L7 promotor, GFP, and siRNA for inhibiting erg channel expression. In preliminary experiments we have injected the viral solution into the lateral ventricle of P1 mice. After 14 days Purkinje cells were selectively stained. We still need to do control experiments before we can perform behavioural tests to detect potential deficits in motor coordination after successful reduction of erg channel expression.

Future perspectives

Our research has two important aspects. First, we want to understand the function of erg channels for neuronal excitability on a cellular and a systemic level. Second, after successful implementation of the siRNA-induced knock-down of erg K channels in Purkinje cells this method will provide a suitable tool to knock-down other types of ion channels in Purkinje cells to study their function for motor behaviour.

Projects completed between 2009 and 2014

Erg channels in gonadotropes

Shuping Wen, Dragos Niculescu, Wiebke Hirdes, Crenguta Dinu, Ulrich Boehm, Jürgen R. Schwarz

Previously, U. Boehm constructed a mouse model at the ZMNH which allowed to visualize gonadotropes in the anterior pituitary. This method allowed us to distinguish gonadotropes from the other cell types in cultured anterior pituitary cells. We investigated the biophysical properties of the erg current present in gonadotropes and studied erg current modulation by GnRH (Hirdes et al., 2010).

Inhibition of erg channel protein expression decreases cell proliferation of lung cancer cells

Jürgen R. Schwarz. Collaboration with Prof. Udo Schumacher (Institute of Anatomy, UKE) and Prof. Christiane Bauer (Physiologisches Institut, UKE)

Small cell lung cancer is a malignant variant of lung cancer. In a cell line (SW2) derived from this type of cancer we investigated the effect of HERG channels on cell growth. These cells transform to neurons in the presence of indomethacin and IMBX (Lange et al., 2011). We also showed, that erg current reduction by itself did not influence cell proliferation. In contrast, the reduction of the expression of the HERG channel protein induced by siRNA induced a significant reduction of cell proliferation. Presumably, this finding has an important clinical implication (Glassmeier et al., 2011).

KCNQ2/3 K channels of the node of Ranvier

Jürgen R. Schwarz. Collaboration with Prof. Peter Grafe (Physiologisches Institut, Universität München)

Recently we have described in the mammalian node of Ranvier a slowly activating K current which is mediated by KCNQ2/3 K channels. In collaboration with Prof. Grafe we now showed that flupirtine a substance known to activate KCNQ channels and used as an analgesic dampens excitability as expected from an activator of KCNQ current (Sittl et al., 2010).

Aromatase inhibition reduces LTP

Jürgen R. Schwarz. Collaboration with Prof. Gabriele Rune (Institute of Anatomy, UKE, University of Hamburg)

Inhibitors of aromatase, the final enzyme of estradiol synthesis, used to treat breast cancer after surgery, are suspected of inducing memory deficits in women. We studied the effect of letrozole, an inhibitor of aromatase, on the generation of LTP in organotypic slices of mice hippocampus. We showed that letrozole applied for 1 week induced a reduction of LTP which was stronger in female as compared to male mice (Vierk et al., 2012).

Micrurotoxin from coral snake venom modulates GABA(A) receptor activity

Yvonne Pechmann, Olaf Pongs, Matthias Kneussel, Jürgen R. Schwarz. Collaboration with Prof. Pierre Bougis, Aix Marseille university

Two micrurotoxins, MmTX1 and MmTX2, were discovered and isolated from the venom of a Costa Rican coral snake. Both toxins bind to $GABA_A$ receptors at nanomolar concentrations. Our experiments with recombinant and synthetic toxins in cultured hippocampal neurons and in HEK cells heterologously expressing $GABA_A$ receptors showed that the toxins potentiate the GABA current at low GABA concentrations, whereas at higher concentrations no effect was visible. In cultured hippocampal neurons MmTX1 induced a transient inhibition of activity and a subsequent increase in spontaneous activity. This work was recently published (Rosso et al., 2015).

Dynamics of postsynaptic Neuroligin

Jürgen R. Schwarz. Collaboration with Matthias Kneussel

Neuroligin is a cell adhesion protein which is incorporated in the postsynaptic membrane of spines. It binds to ß-neurexin, which is important for the formation of synapses. We have shown that the density of neuroligin increases upon induction of LTP and decreases upon induction of LTD. We also showed that upon treatment with forscolin/rolipram all signs of increased excitability occurred (Schapitz et al., 2010).

Physiological importance of lateral diffusion of GABA(A) receptors containing α5-subunits (manuscript submitted)

Torben Hausrat, Wiebke Hirdes, Jürgen R. Schwarz, Matthias Kneussel

$GABA_A$-α5 receptors are trapped extrasynaptically through the actin-binding protein radixin,

thereby providing pools of $GABA_A$ receptors outside the synapse. RhoA/ROCK signalling uncouples $GABA_A$-α5 receptors from their extrasynaptic anchor, thereby increasing synaptic $GABA_A$ receptor density. We have contributed to this work results from measurements of GABA-mediated mIPSCs. These data demonstrate a significant increase in the number of mIPSCs with a slow time course of desensitization (Hausrat et al., 2015).

Ongoing projects

Function of Myosin VI in Purkinje cells

Wolfgang Wagner, Sönke Hornig, Jürgen R. Schwarz, Matthias Kneussel

Myosin VI is a molecular motor involved in intracellular vesicle and organelle transport. Myosin VI knock-out mice (Snell's waltzer) are deaf and show circling behaviour indicative of vestibular dysfunction. We are doing patch-clamp recordings from cultured Purkinje cells lacking myosin VI and find that in these neurons chemically induced LTD is affected. We are also measuring spontaneous mEPSCs as well as EPSP current responses to application of high glutamate concentrations to estimate AMPA receptor density.

Effects of kif21b on AMPA receptors

Edda Thies, Mary Muhia, Jürgen R. Schwarz, Matthias Kneussel

In kif21b knock-out mice the number of dendritic branches is reduced and – correspondingly - the density of AMPA receptors in cultured hippocampal neurons. We have done preliminary measurements of mEPSCs to detect functional correlates of these morphological and cell biological data.

Modulation of KCNQ1 by intracellular calcium

Vitya Vardanyan, Olaf Pongs, Jürgen R. Schwarz

This project (funded by the VW foundation) supports the scientific re-integration of Dr. V. Vardanyan in Yerevan, Armenia. Dr. Vardanyan successfully equipped a laboratory in the Institute of Molecular Biology of the National Academy of Sciences in Yerevan. The equipment now allows to perform two-electrode voltage clamp experiments in oocytes of Xenopus laevis as well as patch-clamp experiments on dissociated cells. Since summer 2014 successful experiments on mutated KCNQ1 channels have been performed in Yerevan. The point mutations of the KCNQ1 channels have been done at the ZMNH. The aim of this project is to study the modulation of KCNQ1 function by intracellular calcium.

Ion channel course

An "Ion channel course" took place from May 5 – 9, 2014 in Yerevan. The course consisted of lectures in the morning and practical exercises in the afternoon.
Organizers: V. Vardanyan, J.R. Schwarz.
Attendance: 10 PhD students from different life science institutes in Yerevan.

Support

External support: DFG (Az: Schw292/14-1, Schw292/15-1, Schw292/16-1, Schw292/16-2) and Volkswagen Foundation (Az: 86659).

Internal support: Since 2006 by Prof. Pongs (Institute of Neural Signal Transduction), and since 2011 by Prof. Kneussel (Institute of Molecular Neurogenetics). The support and help by the other ZMNH research groups as well as by the administration of the ZMNH is gratefully acknowledged.

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Prof. Frank Bosmans, Department of Physiology, Johns Hopkins University School of Medicine, Baltimore, USA

Prof. Pierre E. Bougis, Aix Marseille Université, CNRS, Marseille, France

Prof. Peter Grafe, Institut für Physiologie, Ludwig-Maximilian-Universität, München, Germany

Prof. Olaf Pongs, Physiologisches Institut, Universität des Saarlandes, Homburg, Germany

Prof. Gabriele Rune, Institut für Anatomie, UKE, University of Hamburg, Germany

Prof. Udo Schumacher, Institut für Anatomie, UKE, University of Hamburg, Germany

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Publications

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Structure of the Group

Head: Jürgen R. Schwarz

Postdoctoral fellows:

Wiebke Hirdes

Sönke Hornig

Graduate students:

Dragos Niculescu

Crenguta Dinu

Institute of Molecular and Cellular Cognition (IMCC)

(established in October 2008)

Dietmar Kuhl

Memory binds our mental world together and allows us to have continuity in our lives. Much of what we know about the outside world and about ourselves we have learned. To a good measure we are who we are because of what we have learned and remember. Conversely, the loss of memory, as can be seen in many diseases, leads to the loss of our live history and of our immediate self. Scientists of the IMCC are taking an integrative approach to the studies of learning and memory building on their expertise in mouse genetics, biochemistry, molecular and cellular physiology, and behavioral analysis. Several of the activity-regulated genes first identified in our laboratory code for proteins that can directly modify the physiology of neurons. Our research moves from the identification of activity-regulated genes that are induced during learning to the analysis of synaptic plasticity in the brain and wants to assess which consequences they convey on the behavior of animals and their capability to learn and store information. We bring to these problems a multi-disciplinary approach that includes (i) genomic and proteomic approaches, (ii) reverse genetic approaches in the animal and primary neuronal cultures, (iii) electrophysiological recordings from hippocampal and cortical neurons *in vivo* and *in vitro*, and (iv) analysis of acquisition and consolidation of memory traces using behavioral learning tasks. We anticipate that this analysis will provide insights into how expression of genes that are activated in coordinated biochemical pathways may contribute to the formation of synaptic plasticity. In as much as the identified genes bear the potential to act as direct effectors of neuronal physiology, they become promising targets for the therapeutic intervention of the devastating diseases that disturb synaptic plasticity and memory.

1. Profiling of the activity regulated transcriptome

Guido Hermey, Jakob Gutzman, Claudia Mahlke**

Neurons have the capacity to undergo activity-dependent changes in their molecular composition and structure in order to adjust their synaptic strength. Such synaptic plasticity underlies learning and memory and dysfunctions of synaptic plasticity contribute to brain diseases such as epileptogenesis, responses to ischemia, drug addiction, and neuropsychiatric disorders. Since enduring forms of synaptic plasticity, like long-term potentiation (LTP) and long-term memory require activity-dependent gene induction that is important in defining neuronal connectivity in the brain, it is anticipated that many forms of mental disabilities, including neurodegenerative processes and cognitive disturbances will be understood as cortical or limbic cognates of disturbed activity-dependent gene transcription.

We therefore have focussed much attention on the identification and functional characterization of the specific genes that are induced by patterned synaptic activity. In the past we used differential screening and subtractive cloning strategies to identify the first activity-regulated genes (e.g. Nature (1993) 361, 453-457; Proc. Natl. Acad. Sci. USA (1995) 92, 5734-5738; EMBO J. (1999) 18, 3359-3369 and EMBO J. (1999) 18, 20, 5528-5539). More recently we have been using transcriptional profiling technologies to monitor changes in mRNA expression on a whole-genome scale in an unbiased way by comparing gene-expression before and at several time points after neuronal stimulation (Nature (2010) 465:182-187; PLoS One (2013) 8:e76903).

This allowed us in a first step to establish a comprehensive library of activity-regulated genes. These genes are then searched for common elements, such as being present in the same pathway, sharing interactions or functions, or having similar DNA-motifs in their promoter region. In this way we can identify pathways of genes involved in synaptic plasticity and transcription factors mediating the activity-dependent

expression programs. Moreover, by comparing knock-out animals with wild-type animals, or by using time-resolved measurements we are now beginning to unveil causal upstream-downstream relations between these genes. As these techniques allow us to discover novel pathways that so far have been elusive, we begin to understand the neuron specific genomic response to synaptic activity.

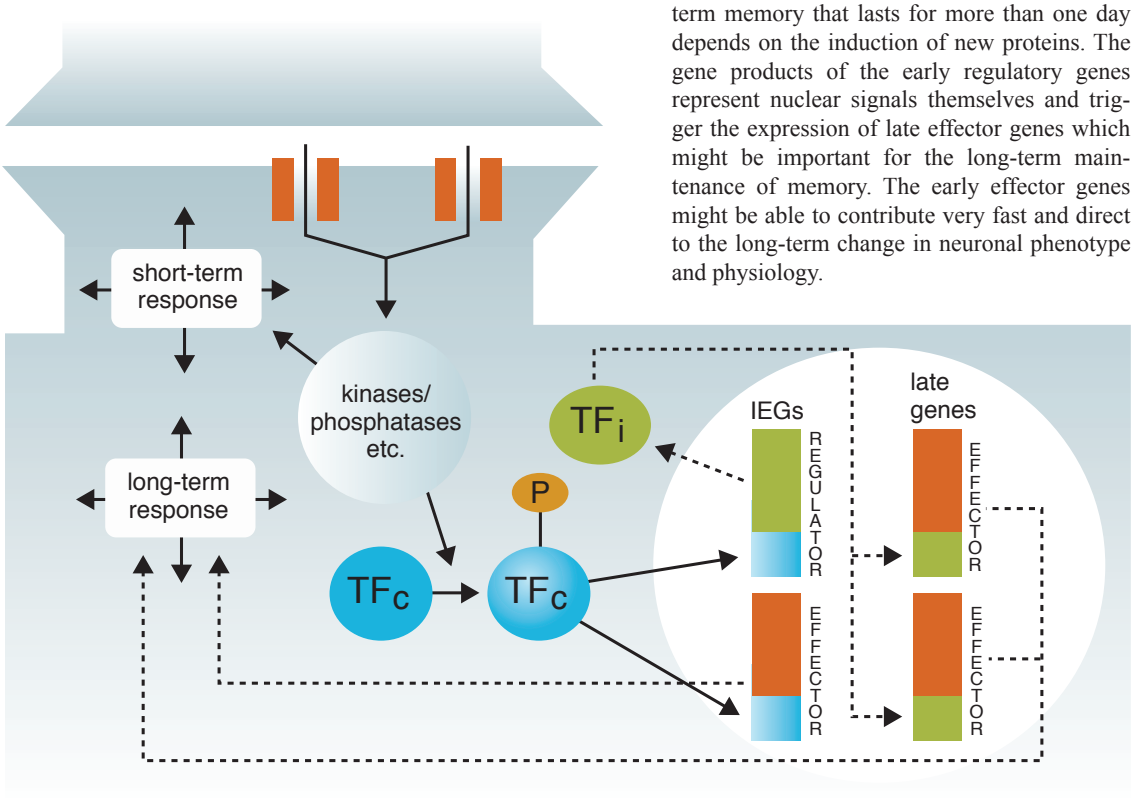

Figure 1. Activity-regulated gene expression is required for the formation and consolidation of long-term memory
A common extracellular signal, a transmitter released by a presynaptic neuron, acts on the postsynaptic neuron to initiate separate memory processes with different durations. Short-term memory has a time course of minutes to hours and involves covalent modification of preexisting proteins. The duration of these covalent modifications determines the duration of the short term response. Unlike these covalent modification mechanisms, acquisition of long-term memory that lasts for more than one day depends on the induction of new proteins. The gene products of the early regulatory genes represent nuclear signals themselves and trigger the expression of late effector genes which might be important for the long-term maintenance of memory. The early effector genes might be able to contribute very fast and direct to the long-term change in neuronal phenotype and physiology.

2. Analysis of specific activity-regulated genes in the physiology and pathophysiology of synaptic plasticity

2.1 small G-Protein (AR-Arl)

Daniel Mensching, Ora Ohana, Guido Hermey*

One of the genes we identified in the whole genome Chip survey is a novel activity-regulated gene encoding an ADP-ribosylation factor-like small G-Protein (AR-Arl). Transcription of AR-Arl is increased in the hippocampus 1 and 2 hours after kainic acid induced seizures. Moreover, 1 hour after *in vivo* LTP stimulation AR-Arl transcript levels are elevated in the dentate gyrus. We found that the small GTPase AR-Arl shares many characteristics with proto-typical Arf proteins. We demonstrate that N-terminal myristoylation of AR-Arl is required for GTP-dependent attachment to membranes of the Golgi apparatus and endosomes. Moreover, we can induce the recruitment of AR-Arl to vesicles by Brain-Derived-Neurotrophic-Factor (BDNF) and AR-Arl co-localizes with the BDNF receptor TrkB in late endosomes. In addition, we find that AR-Arl functions in long-range axonal retrograde endosomal transport. A dominant-negative AR-Arl variant deficient in GTP-mediated activation impaired

fast retrograde trafficking of late endosomes in cultured hippocampal neurons. Conditional AR-Arl knock-out mice that we generated exhibit a reduced activation of ribosomal protein S6, indicating an impairment of BDNF induced translation required for synaptic plasticity. In line with these observations, AR-Arl-deficient mice show a distinct memory deficit and spent less time exploring an unknown object in the novel object recognition task compared to wild type littermates.

2.2. SorCS1

Guido Hermey, Sandra Oetjen, Abuzar Kaleem**

SorCS1 belongs to the Vps10p-Domain receptor family, which defines a group of receptors binding neuropeptides and trophic factors (Cell. Mol. Life Sci. (2009) 66, 2677-2689). SorCS1 has been related to the genetically complex disorders type 2 diabetes and Alzheimer's disease (Ann. Neurol., (2011) 69, 8-10). We identified SorCS1 and the highly homologous SorCS3 as activity-regulated genes and showed that SorCS1, SorCS2, and SorCS3 are expressed in a combinatorial mostly non-overlapping pattern in the developing and adult nervous system (J. Neurochem. (2004) 88, 1470- 1476; PLOS One (2013) 8 (10), e76903; J. Comp. Neurol. (2014) 522, 3386-402). One shared function among Vps10p-Domain receptors is their proteolytic processing and our recent studies demonstrate that alternative processing can adjust receptor activity. Thus, differential processing of SorCS1 modulates the interaction with the receptor Sortilin and thereby its function (Biochem. J. (2014) 457, 277-288). In addition SorCS2 exhibits disparate functions in neurons and glia depending on its cell specific proteolytic processing (Neuron, (2014) 82, 1074-87). Another proposed shared characteristic of Vps10p-Domain receptors is the sorting and intracellular targeting of ligands. In agreement, we localized SorCS3 to hippocampal dendrites and postsynaptic vesicles and demonstrated that it conveys endocytosis of ligands (J. Comp. Neurol. (2014) 522, 3386-402). Currently we extend our studies by analyzing how adaptor proteins identified by us convey activity dependent dendritic targeting of SorCS1 and SorCS3.

2.3. Sgk1

Ralf Scholz, Claudia Mahlke**

Using subtractive cloning strategies we identified the serum and glucocorticoid-inducible kinase 1 (*Sgk1*) as an activity-regulated gene in the brain.

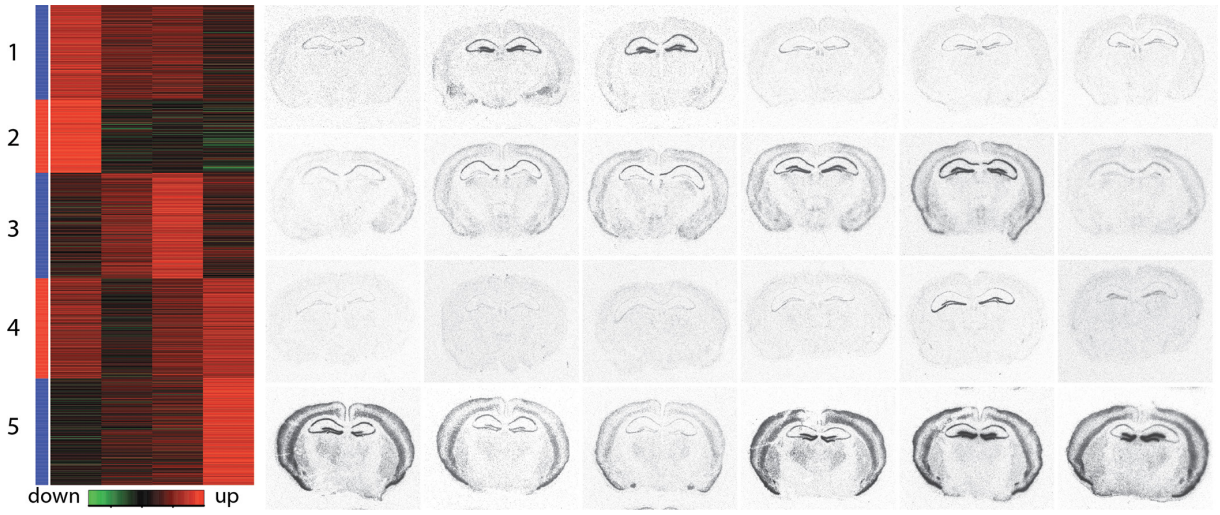

Figure 2. Gene expression profiles induced by neuronal activity
Heatmap to visualize expression kinetics observed by microarray analysis (left) and in situ hybridizations demonstrate temporal and spatial changes in gene expression (right).

Based on the constitutive knockout mouse model generated in our laboratory (J. Clin. Invest. (2002) 110, 1263-1268), we found that the *Sgk1* gene product has a very short half-life (Biochem J. (2006), 399, 69-76) and lack of *SGK1* is causative for a variety of non-neuronal deficits. In collaboration with Florian Lang's group (University of Tübingen) we identified defects in renal function (e. g. Am. J. Physiol. Renal Physiol. (2009) 297, 704-712), mast cell activation (J. Immunology (2009) 183, 4395-4402), hemostasis (Blood (2012), 119, 251-261) and muscle homeostasis (EMBO Mol. Med. (2013), 5, 80-91) in *Sgk1* null mice. In the brain of wild type animals we observed an activity-dependent induction of *Sgk1* in two different cell types. In oligodendrocytes induction is dependent on glucocorticoid release, whereas in dentate granule neurons transcriptional activation is independent of glucocorticoids but strictly dependent on synaptic activity. Our initial behavioral studies using complete knockout animals revealed strongly reduced locomotor and exploratory activity. To dissect the cellular basis for the behavioral phenotype and exclude non-neuronal influence we generated conditional *Sgk1* knockout mice. These animals will allow us to analyze the consequences of cell type specific deletions of *Sgk1*. In a complementary approach, we set out to identify novel interaction partners to elucidate the molecular function of *SGK1* in the brain. Employing the yeast two-hybrid system to screen mouse cDNA libraries, we identified several interaction candidates. Selected interaction partners were validated biochemically and currently we proceed to understand the molecular function underlying these interactions and link them to phenotypes found in the *Sgk1* knockout mice.

2.3. Arc/Arg3.1

Lars Binkle, Xiaosong Mao, Jerome Gruhlich*, Jakob Gutzmann*, Joachim Novock, Guido Hermey, Uwe Borgmeyer, Tiemo Marquarding*, Johanne Klässchen*, Karin Kähler*, Lilianne Kucharczyk*, Xiaoyan Gao*, Sergio Castro-Gomez*, Jasper Grendel*, Francesca Xompero* Ora Ohana*

Among activity-dependent genes Arc/Arg3.1 stands out. Only few show the exquisite regulation and breadth of functional importance as this immediate early gene. Arc/Arg3.1 was discovered in our laboratory and independently of us by Paul Worley and colleagues. The implications from the original discovery of Arc/Arg3.1 have now been borne out in studies establishing a function for the protein in multiple forms of protein synthesis-dependent synaptic plasticity, regardless of the polarity of change. Mice in which we have disrupted the Arc/Arg3.1 gene show altered synaptic plasticity and severe deficits in hippocampus-dependent and -independent cognitive tasks, which require the consolidation of newly encoded memories (Neuron (2006) 52, 437-444; Nat. Neurosci. (2010) 13:1082-1089; Neuron (2011) 69:437-444). Further evidence demonstrates that the expression of Arc/Arg3.1 is important for homeostatic synaptic scaling (Proc. Natl. Acad. Sci. USA (2011) 108: 816-821;. J. Neurosci. (2010) 30:7168-7178). Conversely, aberrant Arc/Arg3.1 expression has been implicated in psychiatric and neurodegenerative diseases, including Alzheimer's disease (Cell (2011) 147:615-628).

2.3.1 Functional consequences of the subcellular localization of Arc/Arg3.1

Xiaosong Mao, Joachim Novock, Tiemo Marquarding*, Johanne Klässchen*, Karin Kähler*, Lilianne Kucharczyk*, Francesca Xompero*, Ora Ohana*

Previous experiments established a strong link between gene expression and physiological and pathological neuronal plasticity; however, it remains an open question how transcriptional activation taking place in the nucleus can selectively modify stimulated synaptic sites in the distant dendritic compartment of the neuron. Such selective modifications of synapses that have experienced coincident activity are required by the Hebbian rule and might be a prerequisite for input specificity of LTP. The analysis of Arc/Arg3.1 might guide our thinking and provide insights into this problem. Most strikingly, following LTP-producing stimulation Arc/

Arg3.1 mRNA is localized to the dendrites of neurons that received patterned synaptic activity.

Consequently, Arc/Arg3.1 mRNA may be locally translated at activated synapses and may have a key role in synapse specific modifications during plastic events in the brain. To test this hypothesis we have generated a phage artificial chromosome harboring mutations that completely abolish the targeting of Arc/Arg3.1 mRNA but leave all other properties intact. Mice carrying these mutations have plasticity and memory deficits. The impairments are severe but distinct from those observed in the complete Arc/Arg3.1 Ko mice. In a complementary approach we generated knock-in mice in which Arc/Arg3.1 protein is only somatically and dendritically localized but not found in the nucleus anymore. The consequences of this mutation on behavior and physiology are currently under investigation.

Arc/Arg3.1 function

Lars Binkle, Jakob Gutzmann, Uwe Borgmeyer, Guido Hermey, Francesca Xompero*, Xiaoyan Gao*, Sergio Castro-Gomez*, Ora Ohana*

We find that Arc/Arg3.1 can regulate AMPA receptor trafficking by binding to proteins of the endocytic machinery. To get a more complete understanding of the post-synaptic protein networks Arc/Arg3.1 interacts with, we generated TAP-tagged animals and conducted conventional as well as split ubiquitin Y2H screens. These screens yielded several proteins that are resident in the endosomal system. This is in agreement with the proposed function of Arc/Arg3.1 in endocytosis and might help to explain the versatile role of Arc/Arg3.1 in synaptic plasticity. We focused our attention on a new transmembrane protein and a so far uncharacterized sorting nexin. Members of this large protein family are of central importance in regulating the endosomal sorting of membrane cargo. As a first step to further study the functional importance of the identified interactions on receptor trafficking and plasticity we will virally express binding-deficient mutants in neurons of conditional sorting nexin mice that we have recently generated.

Conditional Arc/Arg3.1 KO mice

Xiaoyan Gao, Sergio Castro-Gomez, Jasper Grendel, Francesca Xompero, Ora Ohana

Following memory encoding and retrieval, Arc/Arg3.1 expression increases in various areas of the hippocampus and cortex, suggesting their mutual contribution to memory formation. In addition, we have recently found that Arc/Arg3.1 is expressed in the brain during the first 4 weeks

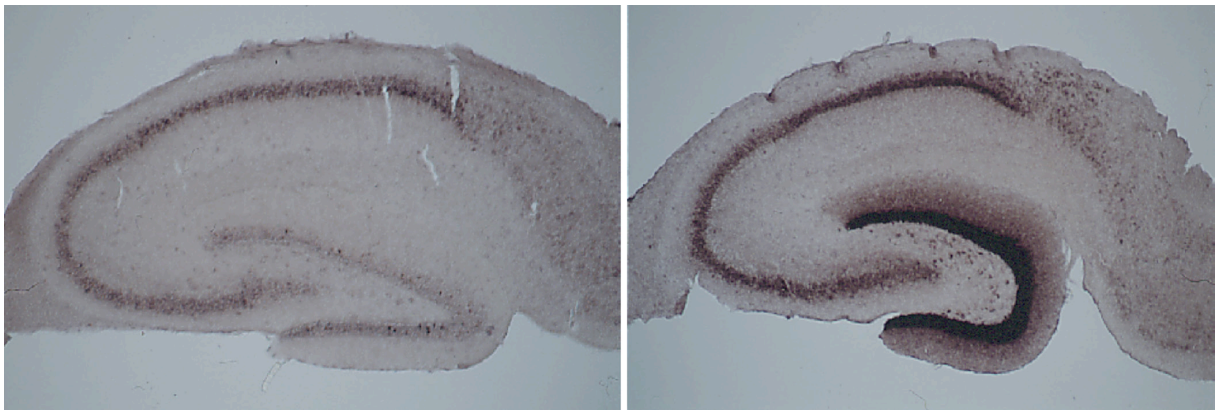

Figure 3. Arc/Arg3.1 mRNA is rapidly distributed to dendrites of activated neurons
Non-isotopical in situ hybridization of a non-stimulated and stimulated hippocampus. Arc/Arg3.1 transcript levels are very low before stimulation (left). Following synaptic activity Arc/Arg3.1 mRNA dramatically increases in the granule layer which contains the somata of the granule cells. Most remarkably, a very unusual localization of the transcripts is observed in the molecular layer, which contains the dendrites of the granule cells (right).

of the critical period of development. To dissect the spatial- and temporal roles of Arc/Arg3.1 in development and in adult memory-formation we generated conditional Arc/Arg3.1 (cKO) mice and remove Arc/Arg3.1 in specific brain regions or time points by injecting rAAV- Cre viruses or by breeding with Cre-transgenic mice. We investigate the impact of Arc/Arg3.1 ablation on memory performance, network structure and function and on synaptic plasticity in the brain.

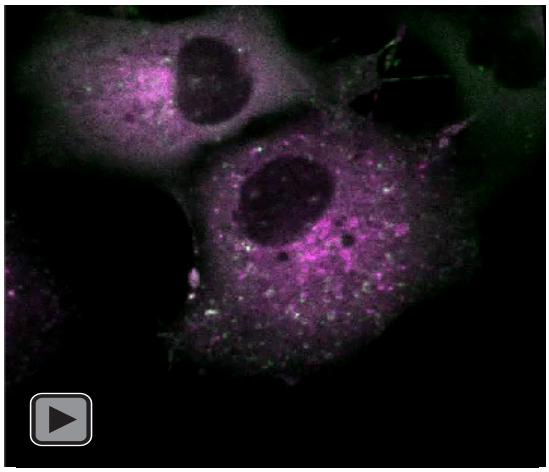

Figure 4. Trafficking of membrane cargo at early endosomes. Still and video show membrane tubulation mediated by a newly identified Arc/Arg3.1 interaction partner.

3. Physiology and pathophysiology of cortical plasticity

3.1. Functional circuits in primary sensory cortex

Ora Ohana

Sensory information arriving in the cortex is encoded and processed by complex algorithms in the local cortical circuitry. These algorithms require distinct interactions between excitatory and inhibitory neurons and between different layers of the cortex. These interactions had been the focus of our investigations for the last decade. In particular we focused on the thalamocortical-corticothalamic circuitry entailing L4, L6 and L5 (J Physiol (1998) 513, 135-48 ; J Neurophysiol (2008) 100, 1909-1929; PLoS One (2012) 7 e40601). We study these interactions using several complementary techniques: multi-electrode patch clamp recordings from cortical neurons in acute slices of sensory cortex, glutamate uncaging, 3-D reconstructions of the recorded neurons and computational modelling. In the future, we plan to further investigate the connectivity within and between these layers and their contribution to specific behaviors.

4. Future perspectives

The several findings described above open up new avenues and pave the way to investigate mechanisms of plasticity, or when disturbed are the cause of mental diseases, psychiatric disorders or play roles e.g. in addiction, epileptogenesis, ischemia, and Alzheimer disease. The main focus of our research, however, will remain on the analysis of learning and memory. Much progress has been made, within discrete levels of analysis, characterizing biophysical, molecular and cellular adaptations associated with plasticity and cognitive functions. However, it has proven difficult to integrate these findings and translate the specific knowledge at each level into an understanding of information processing and storage. A long-term goal of our research is to elucidate how mental functions

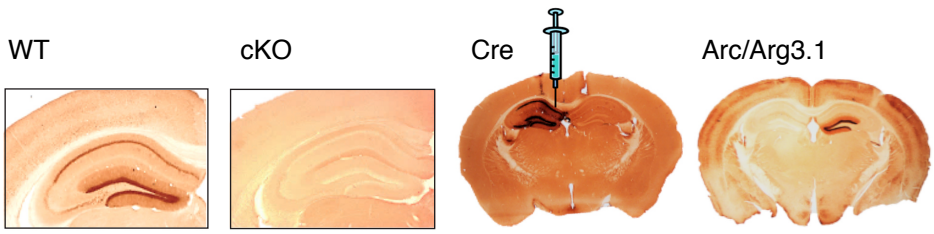

Figure 5. Conditional Arc/Arg3.1 KO mice. Complete loss of Arc/Arg3.1 in brains of adult cKO mice expressing a CaMKIIa-Cre transgene (left). Injection of Cre-harboring rAAVs into one hippocampus results in high expression levels of Cre and complete ablation of Arc/Arg3.1 in the injected but not control hippocampus (right).

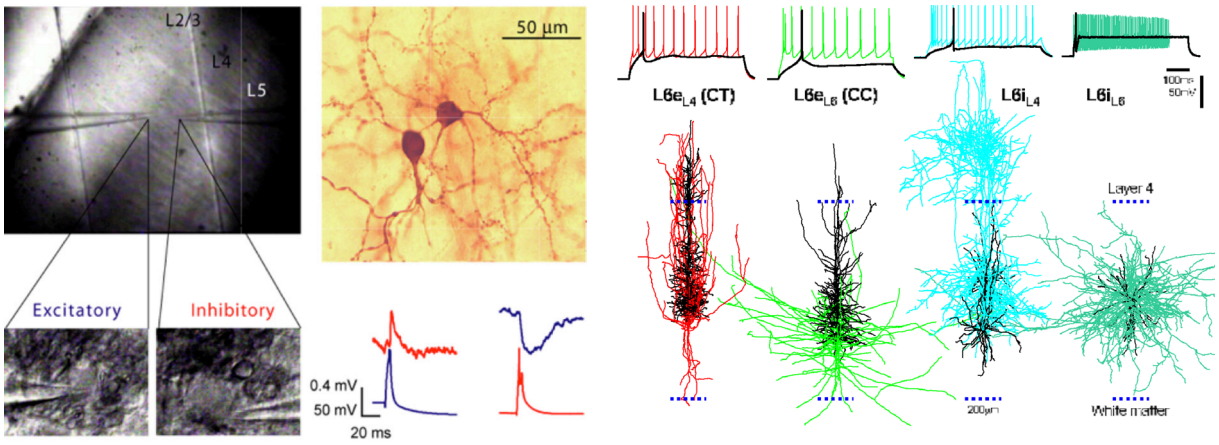

Figure 6. Synaptic circuits in sensory cortex. Recurrent excitatory-inhibitory connections in L4 (left). Subcircuits within L6 divide into L4-projecting and L6-connecting excitatory and inhibitory neurons (right).

emerge from specific changes at molecular levels. We see the use of mouse genetics as an important means of building bridges between molecular biology and systems neurobiology and between systems neurobiology and behavior. This provides the rationale for an integrated approach to follow the flow of information from excitatory events in the dendrite through neural networks in behaving animals. We hope in this way to extract some of the fundamental rules that govern dendritic information processing in the activity-driven refinement of networks that underlies learning and memory.

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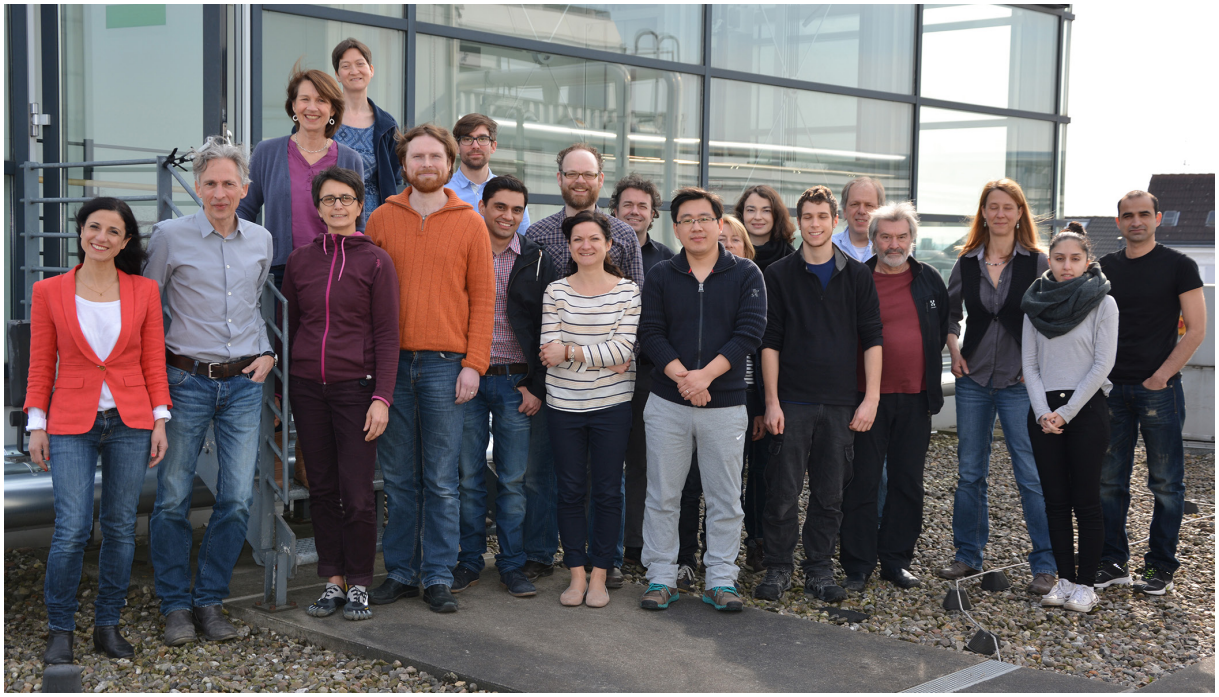

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Biosynthesis of Neural Structures

(established in 1995, since 2011 Emeritus Group)

Melitta Schachner Camartin

Cell adhesion molecules are important functional ingredients not only during nervous system development, but also in synaptic plasticity and regeneration after trauma in the adult. With the discovery of the first vertebrate neural cell adhesion molecule NCAM by Gerald Edelman and Urs Rutishauser, this molecule was viewed to be sufficient for development in its spatial and temporal variations of expression, together with its glycan polysialic acid. Furthermore, NCAM's main function was considered to be a 'glue' between cells.

However, this deemed to be too simple an interpretation, leading to efforts to discover other functions of neural cell adhesion molecules. The transmembrane cell adhesion molecules NCAM and L1 indeed function as bona fide signal transducers, when triggered at the cell surface. The differential distribution of the 180kD isoform of NCAM in synapses led to the hypothesis that this most immobile, highly cytoskeleton-linked isoform of NCAM enriched in postsynaptic densities was involved in regulation of synaptic plasticity. That adhesion molecules and their carbohydrates impinge on synaptic plasticity was followed up by the first electrophysiological and behavioral studies on adhesion molecules on synaptic plasticity *in vitro* and learning and memory *in vivo*. Adhesion molecules were then found to influence and even associate with or be integral parts of ion channels. A link between adhesion molecules and neurotransmitter receptors also became apparent. The generation of mice defective in or missing adhesion molecules led to the first discovery that these mice can represent animal models of human diseases: The mouse deficient in the prominent structural and functional glycoprotein P0 of peripheral nervous system myelin, is an experimental animal counterpart of the polyneuropathy Charcot-Marie-Tooth disease type 1B in humans. Deficiency in the adhesion molecule L1 was then recognized to represent a mouse model of the human L1 syndrome which is characterized by severely affected neural structures and behavioral symptoms.

First indications regarding the importance of glycan moieties other than polysialic acid became apparent with the discovery that a complex carbohydrate, initially called L2 and later found to be identical to the human natural killer cell antigen HNK-1, was a structurally and functionally unusual glycan shared by many neural adhesion molecules with important functions in synaptic plasticity via interactions with neurotransmitter receptors and in peripheral nervous system regeneration, allowing preferential motor reinnervation by the femoral nerve - after complete transection of the nerve before its bifurcation – regrowing into the motor, but avoiding the inappropriate sensory branch. Identification of the HNK-1 synthesizing sulfotransferase sequence not only led to the generation of mice deficient in this enzyme, but also to the identification of other sulfotransferases within this family which generate chondroitin and dermatan sulfates that are important in central and peripheral nervous system development and regeneration after injury.

Progress in studying the importance of the HNK-1 carbohydrate depended on finding compounds that mimic the functions of this carbohydrate. This deemed to be important, since this unusual carbohydrate is very difficult to synthesize chemically or to isolate in sufficient and pure enough quantities from natural sources. HNK-1 mimicking peptides were isolated using phage display techniques which were initially met with considerable skepticism by carbohydrate chemists who doubted that a carbohydrate could be modeled structurally by a peptide and functionally induce similar effects as the carbohydrate itself. Similar arguments were put forward for peptides mimicking polysialic acid. This glycan, called colominic acid in bacteria, is labile in biological environments which contain potent hydrolases. The polysialic acid mimicking

peptides turned out to be very helpful in studying nervous system regeneration and encouraged the isolation of small organic compounds that mimic this carbohydrate.

Results

1. Cell adhesion molecules and associated interaction partners

Mehrnaz Azami-Movahed, Harshita Chaudhary, Igor Jakovcevski, Gunjan Joshi, Jelena Katic, Nicole Karl*, Ralf Kleene, Kristina Kraus, Gabriele Loers, Bibhudatta Mishra*, Daniel Novak*, Thomas Theis*, Nina Westphal, Mei-Fang Xiao*, Jin-Chong Xu**

NCAM. Cell adhesion molecules do not act by themselves, but in context with other molecules in cis- and trans-interactions, i.e. on the membrane of one cell and between different cells, respectively. NCAM is functionally associated with the dopamine D2 receptor and affects receptor signaling (Xiao et al., 2009). This interaction increases internalization of this receptor, thereby leading to decreased availability of receptor sensitization. Another important functional association of NCAM relates to the direct interaction of NCAM's intracellular domains with the receptor tyrosine kinase TrkB (Cassens et al., 2010). Associated with this complex is the inwardly rectifying K+ channel KIR 3.3 (Kleene et al., 2010). Association of NCAM with calmodulin leads to NCAM-mediated neurite outgrowth (Kleene et al., 2010). NCAM's interaction with the fibroblast growth factor receptor regulates growth cone functions (Chernyshova et al., 2011). An important ingredient in NCAM's functions is its unusual carbohydrate polysialic acid. This carbohydrate interacts with the intracellularly localized myristoylated alanine-rich C kinase substrate (MARCKS) (Theis et al., 2013). This interaction is noteworthy, since polysialic acid from the extracellular space penetrates the surface plasma membrane of live cells to interact with MARCKS attached to the inner surface of the plasma membrane. This interaction was shown by fluorescence resonance energy transfer (FRET) analysis. Penetration of polysialic acid through the plasma membrane alters the membrane capacity of an artificial lipid bilayer. (This finding touches on the generally held view that carbohydrates are hydrophilic and avoid hydrophobic microenvironments, such as plasma membranes.) Polysialic acid-carrying NCAM also associates with histone H1, which is commonly regarded as a nuclear protein, but has been localized by others and us also in the extracellular space, where it functionally interacts with polysialic acid to enhance neurite outgrowth (Mishra et al., 2010).

Close homolog of L1. The cell adhesion molecule close homolog of L1 (CHL1), which has been linked to mental disorders, binds to a short peptide stretch in the third intracellular loop of the serotonin 2c (5-HT2c) receptor via its intracellular domain. CHL1 deficiency in mice leads to reduced 5-HT2c receptor-related locomotion. This behavioral phenotype is associated with increased levels of serotonin in the striatum, enhanced 5-HT2c receptor levels in striatal endosomal and lysosomal fractions as well as plasma membranes. In contrast, endosomal and lysosomal fractions from total brain of CHL1-deficient mice showed elevated 5-HT2c receptor levels. In CHL1-deficient brains enhanced binding of phosphatase and tensin homolog (PTEN) and of G-protein-coupled receptor kinase 6 (GRK6) to 5-HT2c receptor and reduced levels of the phosphorylated receptor and of receptor-associated β-arrestin 2 were observed. These results link CHL1 to 5-HT2c receptor functions and to serotonergic modulation.

CHL1 is also associated with the extracellular matrix molecule vitronectin and its integrin receptors resulting in CHL1-mediated neurite outgrowth and neuronal migration (Katic et al., 2014).

Since we showed that CHL1 enhances synaptic vesicle recycling we were interested to investigate its association with the SNARE complex and found that CHL1 organizes the presynaptic assembly of this complex (Andreyeva et al., 2010).

L1 and L1 family members. The highly glycosylated adhesion molecule CD24 associates with L1

family members, such as contactin/F3/F11, and L1 itself. This association is mediated by Lewis^x and alpha 2,3-sialyl glycans which are highly present on CD24 which consists of a peptide backbone of only nine amino acids in mice, with the carbohydrate moieties leading to an apparent molecular mass of kDa 24 (Lieberoth et al., 2009). Analysis of the carbohydrate composition of CD24 was carried out and showed that the HNK-1 and oligomannosidic carbohydrates are also carried by CD24 (Bleckmann et al., 2009).

2. Novel proteases cleaving L1

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Proteolytic cleavage of L1 by cognate proteases is a prerequisite for L1-mediated functions, such as neurite outgrowth. We identified myelin basic protein (MBP), cathepsin E and reelin as proteases that generate distinct L1 fragments with distinct functional roles. MBP and cathepsin E only cleave sumoylated membrane-bound full-length L1 to generate 70 and 30 kDa L1 fragments, respectively, which are transferred from the plasma membrane to the nucleus of L1 expressing neurons and Schwann cells. Generation of both fragments promotes neurite outgrowth, neuronal survival, Schwann cell process formation and myelination of dorsal root ganglion axons. MBP binds to L1 in a Lewis^x glycan-dependent manner and cleaves sumoylated L1 in its extracellular domain at R^{687} (Lutz at al., 2014a) yielding a transmembrane fragment that promotes neurite outgrowth and neuronal survival in cell culture. L1-induced neurite outgrowth and neuronal survival are reduced in the MBP-deficient *shiverer* mouse mutant and in wild-type cerebellar neurons treated with MBP antibody or L1 peptide containing the MBP cleavage site, thus showing a novel function of MBP.

Cathepsin E cleaves L1 at E^{1167} and generates a sumoylated intracellular L1 fragment resulting in promotion of neuronal and Schwann cell migration as well as myelination (Lutz et al., 2014b). Stimulation of cultured mouse cerebellar neurons by a function-triggering L1 antibody leads to cathepsin E-mediated generation of a sumoylated 30 kDa L1 fragment (L1-30) and to import of L1-30 into the nucleus. Mutation of the sumoylation site at K^{1172} or the cathepsin E cleavage site at E^{1167} abolishes generation of L1-30, while mutation of the nuclear localization signal at K^{1172} prevents nuclear import of L1-30. The aspartyl protease inhibitor pepstatin impairs the generation of L1-30 and inhibits L1-induced migration of cerebellar neurons and Schwann cells as well as L1-dependent *in vitro* myelination on axons of dorsal root ganglion neurons by Schwann cells.

The sumoylated transmembrane 70-kDa fragment comprising the intracellular and transmembrane domains and part of the extracellular domain is generated by function-triggering L1 antibodies (Lutz et al., 2012). This fragment is transported from the plasma membrane to a late endosomal compartment, released from endosomal membranes into the cytoplasm, and transferred from there into the nucleus by a pathway that depends on importin and chromatin-modifying protein 1. Mutation of the sumoylation site or of the nuclear localization signal at K^{1147} inhibits L1-stimulated generation or nuclear import of the 70-kDa fragment, respectively. 70-kDa fragment levels are altered during development and after adult spinal cord injury, or in a mouse model of Alzheimer's disease.

The extracellular matrix protein reelin acts as a serine protease and cleaves L1 at ^{840}RKHSKR^{845} to generate a 80 kDa transmembrane fragment, which signals independently of the 'canonical' reelin signaling pathway. Perturbed reelin-L1 interactions not only impair neuronal migration *in vivo*, but also neurite outgrowth and polarization *in vitro*.

3. Glycans in nuclear localization, regeneration and synaptic functions

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Because of the importance of glycans in adhe-

sion molecule-mediated functions *in vitro*, we further investigated the mechanisms underlying their functions as well as their functional implications *in vivo*. Polysialic acid is carried to the cell nucleus after stimulation of neurons with NCAM function-triggering antibodies. This translocation is not seen when neurons are not NCAM-stimulated. The ability of polysialic acid to enhance regeneration was investigated in peripheral nerve (Mehanna et al., 2009, 2010) and spinal cord (Marino et al., 2009) injuries, and application of PSA mimetics enhanced repair. Important for these studies was that a peptide mimic of polysialic acid was available. As for the HNK-1 glycomimetic peptide, phage display libraries encoding 12- and 15-mer peptides were screened and led to the identification of peptides that could mimic PSA (Mehanna et al., 2009). Polysialic acid was also found to be important in blocking extrasynaptic NR2B NMDA receptors, thereby enhancing the functions of the synaptic NR2A receptors impinging on promotion of long-term potentiation (Kochlamazashvili et al., 2012). Furthermore, the glycan hyaluronic acid beneficially influences synaptic plasticity in the mouse hippocampus by modulating postsynaptic L-type calcium channels (Kochlamazashvili et al., 2010). The HNK-1 carrying extracellular matrix glycoprotein tenascin-R was found to be important for perineural net function (Morawski et al., 2014). Application of the HNK-1 glycan mimetic peptide alone or functionalized on collagen enhanced repair and preferential motor reinnervation after mouse and monkey femoral nerve injury (Irintchev et al., 2011; Masand et al., 2012a,b; see also Bhunia et al., 2010). Dermatan sulfate generated by the HNK-1 sulfotransferase family member sulfotransferase Chst 14 was shown to be inhibitory for peripheral nerve regeneration (Akyüz et al., 2013), but enhances proliferation and neurogenesis of progenitor cells, whereas Chst11 was ineffective (Bian et al., 2011). The chondroitin sulfate degrading human enzyme arylsulfatase B enhanced regeneration when applied acutely after injury (Yoo et al., 2013). As late as during the secondary stages after injury the combination of L1 and bacterial chondroitinase ABC enhanced spinal cord regeneration (Lee et al., 2012).

4. L1 in Alzheimer's disease and autism

*Nevena Djogo, Igor Jakovcevski, Gabriele Loers, David Lutz, Ralf, Kleene, Yin-Chong Xu**

Since application of L1 via different carriers is beneficial for functional recovery in spinal cord regeneration and in Parkinson's and Huntington's diseases, the influence of L1 on the pathology of Alzheimer's disease was tested in a mouse model of this disease (Djogo et al., 2013). Application of L1, but not CHL1 led to amelioration of plaque load. L1 could be shown to interact with amyloid beta 42 more so than with amyloid beta 40, but not with the amyloid precursor protein.
L1 was also shown to be beneficial in the RETT syndrome of autism spectrum disorders in that neurally-induced reprogrammed human stem cells from a RETT syndrome person which do not express L1 and are mutated in the MeCP2 transcription factor could be induced to express L1 when transfected with wild type MeCP2 and full-length human L1. The RETT syndrome cells which did not show neurite outgrowth in culture could be induced to extend neurites when transfected with wild type MeCP2 and L1. Interestingly, the intracellular domain of L1 binds to MeCp2. The consequences of this interaction are presently under study.

Female mice hemizygous for the X-chromosome linked L1 gene are born with more neurons than their wild type and L1-/y littermates, mitigating the general experience that hemizygous animals show an intermediate phenotype (Schmid et al., 2013). This phenotype is interesting with regard to autism, since overproduction of neurons has been observed in some persons with autism. The L1+/- mice do not show pronounced deficits in behavior, except for a slight abnormality in assessing time intervals (Gallistel et al., 2014). However, they are abnormal in accepted mouse models of autistic behavior.

5. Function-triggering L1 antibodies and small organic compound mimetics for L1 and for glycans

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It has become more widely known that antibodies cannot only be inhibiting, but they can trigger functions when directed against appropriate epitopes. Whereas antibodies against the immunoglobulin-like L1 domains inhibit adhesion, neurite outgrowth, and neuronal migration and survival (Wang et al., 2012), we found that antibodies directed against the transition between the second and third fibronectin type III homologous repeat of L1 (now designated the amino terminus of the third repeat) are function triggering in that they promote neurite outgrowth and neuronal survival *in vitro*. The previously identified function-triggering monoclonal antibody 557 against mouse L1 is now available as Fab fragment and enhances functional recovery after adult mouse spinal cord injury, thus showing that clustering of L1 at the cell surface via bivalent or multivalent L1 antibodies is not required for functional benefit (Loers et al., 2014a). Since the Fc domain of antibodies can be functionally counteractive because of its ability to attach to microglia/macrophages thereby activating the production of pro-inflammatory cytokines, the availability of endotoxin free Fab fragments represents a step forward in using function triggering L1 antibodies in neurological diseases.

A peptide comprising the third fibronectin type III homologous repeat of L1 was coupled to gold nanoparticles as drug delivery platform, and cell culture experiments showed that these nanoparticles are function triggering in that they promote neurite outgrowth and neuronal survival (Schulz et al., 2013).

We have also succeeded in finding small organic compounds from the commercially available NIH library that mimic the functions of L1 using the 557 antibody for screening by competitive ELISA targeting the 12-mer peptide that this antibody recognizes. These small organic compounds stimulate the beneficial functions of L1 *in vitro*, and are now being tested in mouse spinal cord injury by topical, but also systemic injection after injury. Furthermore, recovery from spinal cord injury is being measured in larval and adult zebrafish in the presence of the mimetic compounds in the aquarium water. First results are very encouraging in that these compounds enhance the recovery time and thereby the natural ability of zebrafish to regenerate.

Finally, small organic compounds mimicking the functions of polysialic acid have been obtained and shown to be beneficial for neuronal functions *in vitro* and for regeneration after injury of mouse peripheral and central nervous systems (Bushman et al., 2014; Loers et al., 2014b; Pan et al., 2014).

Support

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BMBF (German Federal Ministry of Education and Research) and the Polish Ministry of Education and Research. German-Polish Research Projects in Neuroscience. Project 01GZ0705 "Combinatorial therapeutic approaches targeting molecules, neurotrophins and locomotor exercise for spinal cord repair". Subproject "*In vitro* and *in vivo* Studien zur Evaluierung von L1 und Nogo-A zur Kombinationstherapie von Läsionen des Rückenmarks"

BMBF. International Collaboration in Education and Research with India. Project IND 10/050 "Untersuchungen des therapeutischen Potentials von PSA-Mimetika in Zellkultur- und Mausmodellen von Verletzungen und Erkrankungen des zentralen

Nervensystems”

Hamburg Ministry of Science and Research (Behörde für Wissenschaft und Forschung der Freien und Hansestadt Hamburg).

Hamburg Excellence Initiative 2009 Project “Nanotechnology in Medicine” Schachner-Camartin-Stiftung

Collaborations

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Selected Publications

Akyüz, N., Rost, S., Mehanna, A., Bian, S., Loers, G., Oezen, I., Mishra, B., Hoffmann, K., Guseva, D., Laczynska, E., Irintchev, A., Jakovcevski, I., and Schachner, M. (2013). Dermatan 4-O-sulfotransferase1 ablation accelerates peripheral nerve regeneration. Exp. Neurol. 247, 517-530.

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Structure of the Group

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- Igor Jakovcevski*
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Institute for Neural Signal Transduction

Olaf Pongs *(1991 until September 2011)*
Dietmar Kuhl *(Provisional Director: October 2011 until dissolution of the Institute effective January 1, 2015)*

Support

All research projects of Olaf Pongs and Ulrich Boehm supported by the DFG (German Research Foundation) are listed in the online information service "GEPRIS – Project Funded by the DFG".

Publications

see pages 169/170

Theses and Dissertations

see pages 186/187

Research projects funded in the framework of coordinated programmes

see pages 193/194

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Emeritus Group Cell Biochemistry and Clinical Neurobiology

(established in 2005)

Dietmar Richter (*Founding Director of the ZMNH)*

Due to my retirement in 2005 the Institute for Cell Biochemistry and Clinical Neurobiology at the University Medical Center Hamburg-Eppendorf (UKE) was closed down. The help of the directorate of the Center for Molecular Neurobiology Hamburg (ZMNH) by providing space for the continuation of my scientific activities is greatly acknowledged. Most of the ongoing research was carried out in collaboration with my former co-workers Stefan Kindler and Hans-Jürgen Kreienkamp, now group leaders at the Institute for Human Genetics, UKE. Research has been focused on how nerve cells manage to respond to external and internal signals in order to maintain and regulate their cellular architecture. As shown earlier signal transduction processes involving neurotransmitter receptors are mediated by a series of defined protein-protein interactions. We have identified specific interacting proteins for the C-terminal, intracellular regions of each subtype of G-protein coupled somatostatin receptors (SSTR1-5). Some interacting partners, such as the PDZ domain protein PIST, have a function in membrane targeting of SSTR3 and SSTR5. Others such as the tight junction protein MUPP1 or the postsynaptic scaffold proteins PSD-95 (interacting with SSTR4) or SSTRIP/shank (interacting with SSTR2) link the receptors to large signaling complexes, such as the postsynaptic density (PSD) in excitatory synapses of the central nervous system.

We have also continued our work on the structure and function of the members of the shank protein family which represents master scaffold proteins of the PSD and appears to play a central role in neuronal morphogenesis and synaptogenesis. We have shown that shank proteins interact directly or indirectly with neurotransmitter receptors, actin binding proteins and other prominent postsynaptic scaffold proteins such as PSD-95. More recently, we have studied the pathogenesis of the fragile X-mental retardation syndrome (FXS). To date, the molecular events leading from the loss of the fragile X mental retardation protein (FMRP) to the diverse devastating symptoms of FXS, including cognitive impairment and autism, are still poorly understood. Much research on the cellular causes for FXS has been focused on synaptic dysfunction. In brain neurons of wild-type mice, FMRP is found in the proximity of synapses where it primarily represses translation of mRNAs at postsynaptic sites. This translational block can be abolished via stimulation of metabotropic glutamate receptors (mGluRs). Thus, lack of FMRP leads to excessive mGluR-dependent protein synthesis at synapses which may be the major cause for synaptic malformation and dysfunction. Indeed, in FMRP deficient mice several FXS symptoms can be corrected by a reduction of neuronal mGluR levels.

While mGluRs act *upstream* of FMRP in the signal cascade regulating local synaptic protein synthesis, the *downstream* components involved in FXS pathogenesis are less well described. Recently, we reported that the PSD is altered in FMRP deficient mice. We could show that several mRNAs encoding components of the PSD are *in vivo* associated with FMRP. Via this interaction FMRP controls dendritic mRNA translation and postsynaptic protein levels, but not local transcript stability. In particular, FMRP was shown to repress the translation of shank 1-mRNA in an mGluR-sensitive manner by binding to the 3’ untranslated region (3’UTR). Thus, our data suggest that the mGluR/FMRP pathway controls shank 1 levels in the PSD. In agreement with this idea is the finding by Durand et al., 2007, that mutations in the gene encoding shank 3 are associated with autism spectrum disorders and mental retardation. Based on our hypothesis that elevated shank 1 levels in PSDs represent key molecular events of the FXS pathology we presently try to reduce synaptic shank 1 levels in FMRP deficient mice *(Fmr1-/-)* by genetic manipulation followed by analyzing various

structural, molecular and behavioral parameters of the mutant mice. We expect that similar to a reduced concentration of mGluR5 (Dölen et al., 2007), an *upstream* component of the FMRP-dependent synaptic protein synthesis pathway, the genetically induced reduction of postsynaptic levels of shank 1, a *downstream* signaling molecule, will correct at least some of the pathogenic alterations observed in *Fmr1-/-* mice. Thus, shank 1 may emerge as an attractive novel drug target for the treatment of FXS patients.

We also extended our previous work on allatostatin receptors in invertebrates, a G-protein coupled receptor (GPCR) family initially identified by a reverse pharmacological approach in Drosophila melanogaster (Birgül et al., 1999). Recently, we described allatostatin receptors from Periplaneta americana and Aedes aegypti, all are structurally related to vertebrate galanin/somatostatin/opioid receptors. Expression studies revealed that allatostatin receptors are widely expressed in adult insect tissues and in early larval instars. The spatial expression supports the known pleiotropic activity of allatostatins and a role as a paracrine effector.

Support

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Collaborations

Prof. Stefan Kindler and Prof. Hans-Jürgen Kreienkamp, Institute for Human Genetics, UKE, Hamburg, Germany. (Topics: shank family; FXS)

Prof. Dietmar Kuhl, ZMNH, UKE, Hamburg, Germany. (Topic: FXS)

Prof. Fernando G. Noriega, Department Biology Sciences, Florida International University, Miami, USA and Prof. Wolfgang Meyerhof, Department of Molecular Genetics, German Institute of Human Nutrition, Potsdam, Germany. (Topic: allatostatin receptors in insects)

Selected Publications

Studtmann, K., Ölschläger-Schütt, J., Buck, F., Richter, D., Sala, C., Bockmann, J., Kindler, S. and Kreienkamp, H.-J. (2014). A non-canonical initiation site is required for efficient translation of the dendritically localized shank1 mRNA. Plos One 9: e88518.

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Books

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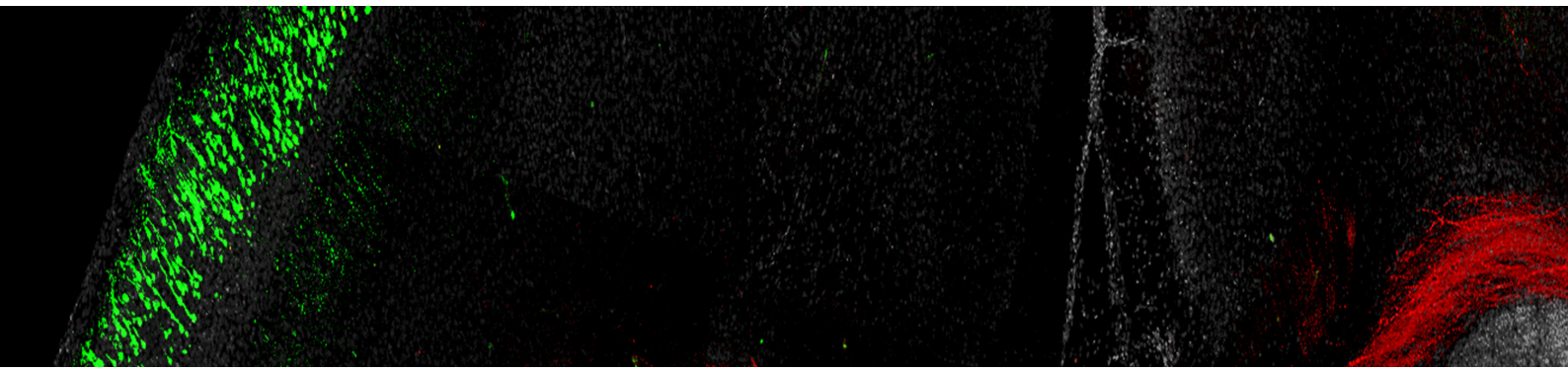

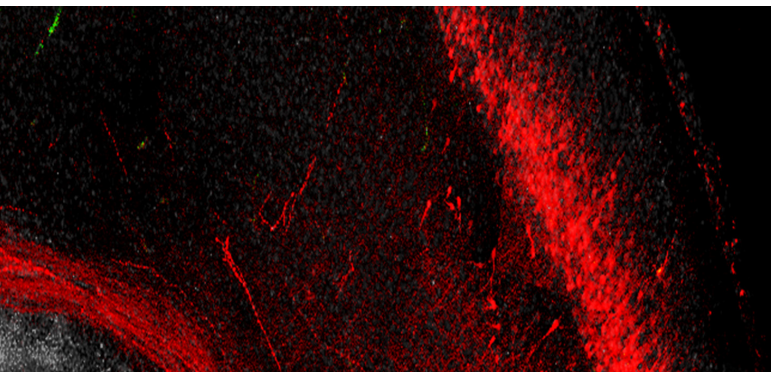

Research Reports of the ZMNH Junior Research Groups

Behavioral Biology

(established in October 2013)

Fabio Morellini

The Behavioral Biology group was founded to strengthen and support system neurosciences at the ZMNH by investigating how behavior develops, is controlled and finally degenerates under pathological conditions. Behavior is, indeed, an essential functional correlate for molecular and cellular processes of interest. Noteworthy, behavioral analyses are fundamental to determine to which extend findings obtained in the mouse can be extrapolated to understand the human brain. Our group combines the ethological perspective and experimental psychology to understand how (ultimate causes) and why (proximate causes) determined behavioral responses are used by mice. In terms of functions, our studies focus to cognition, novelty-induced behaviors, coping strategies, social behavior, sensory-motor functions, as well as addiction- and depressive-like behaviors (Fig. 1). Briefly, our research has three general aims and approaches: 1) understanding how and why certain behaviors are expressed, 2) implementing throughout and validity of behavioral analyses, 3) investigating molecular and neuroendocrinological causations by means of transgenic and pharmacological approaches.

Figure1. Some behavioral paradigms in our group

Cognitive function in mice

Navigation strategies and spatial learning and memory.

The analysis of spatial learning in rodents is commonly used to investigate the mechanisms underlying certain forms of human cognition and to model their dysfunction in neuropsychiatric and neurodegenerative diseases. Proper interpretation of rodent behavior in terms of spatial memory and as a model of human cognitive functions is only possible if various navigation strategies controlling the performance of the animal in a spatial task are taken into consideration. In the last years, we thoroughly investigated navigation strategies in mice and identified that geometry is the primary spatial information used by this species to navigate (Fellini and Morellini, 2011). Thanks to this knowledge, we could not only designed appropriate conditions to test spatial learning and memory in mice (Morellini et al., 2010; Fellini and Morellini, 2013; Morellini, 2013), but also formulate precise hypothesies on the computational and cognitive processes used by this species to create and use a cognitive map (Morellini, 2013).

Episodic-like memories in mice.

Complex forms of learning and memory are attracting more and more interest within the scientific community because of their importance in understanding human autobiographical knowledge and sense of self. On the other hand, the validity of studying episodic-like memories in mice has been questioned. We performed several experiments to test whether mice possess episodic-like memory. Using an ecologically relevant paradigm for spontaneous learning we found that mice, indeed, create episodic-like memories of unique experiences. We showed that mice can distinguish at which time of the day they have encountered, in the same location of the arena, either a female mouse or a dominant male, demonstrating that they flexibly process "what-where-when" information, in agreement

with the definition of episodic-like memory for non-human animals (Fellini and Morellini, 2013). Thus, our results encourage the use of the mouse for the investigation of neuronal and cellular processes underlying episodic memory in humans. Moreover, we validated a new behavioral paradigm for referencing spatial memory which has several advantages compared to other cognitive tasks. By means of this task we could show that expression of the snoRNA host gene GAS5 in the hippocampus does not regulate, as previously suggested, spatial learning and memory, but affects novelty-induced behaviors and is regulated by activation of the stress response (Meier et al., 2010).

Reversal learning and extinction.

Memories can undergo deterioration, reversal learning or extinction. The dynamic nature of memory has a relevant adaptive value because it allows the update of existing knowledge in light of new information. The investigation of the dynamics of memory change is important for understanding the cellular and molecular processes underlying cognitive function. We therefore established several new behavioral paradigms and protocols to test two major forms of memory modification, namely extinction and reversal learning. Noteworthy, we validated different types of paradigms in which extinction and reversal learning could be tested for different types of learning requiring different sensory stimuli and reward systems such as emotional, spatial, social and olfactory learning (Haaker et al., 2013; Fellini and Morellini, 2013; Morellini et al., 2011). By applying these paradigms, we found that reversal learning is facilitated in mice deficient for the extracellular matrix glycoprotein tenascin-R and that this cognitive ability positively correlates with amount of inhibition in the dentate gyrus, suggesting that enhanced GABAergic inhibition and reduced LTP in the dentate gyrus support working memory and relearning abilities in mice (Morellini et al., 2010). In collaboration with Raffael Kalisch we searched for pharmacological approaches to boost the effects of cognitive behavioral therapies for panic disorders. We reported that administration of L-DOPA boosts extinction of fear memories in mice and humans. Noteworthy, the behavioral effects of L-DOPA were accompanied with reduced neuronal activity in amygdala and prefrontal cortex in both species (Haaker et al., 2013). Moreover, we found that consolidation of memories is enhanced in mice injected with L-DOPA 20 min before the learning trial of the fear conditioning test (unpublished data, Fig. 2). These data suggest that dopamine facilitates consolidation of new memories as well as modification of old memories.

Inter-individual variability in trait anxiety and coping strategy

A proper balance between novelty-seeking and risk assessment is fundamental for the fitness of an animal. To understand the function and origins of specific coping strategies, we investigated how

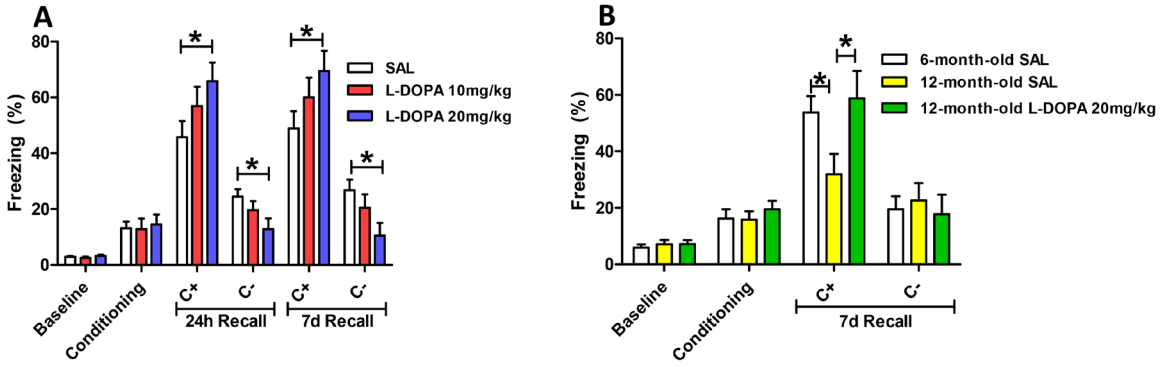

Figure 2. A, The L-DOPA group spent more time freezing during the recall trials in the conditioned context (C+) and less time freezing in the unpaired context (C-) compared to saline mice. B, 12-month-old mice spent less time freeing compared to 6-month-old mice during the recall trials. Injection of L-DOPA improved memory retrieval in 12-month-mice.

anxiety evolves in C57BL/6 mice. We showed that trait anxiety, determined by the emergence latencies in the free choice open field test, positively correlates with the long-term behavioral and neuroendocrinological changes induced by a stressor. We showed that this interindividual variability is caused by a different reactivity of the hypothalamus-pituitary-adrenal (HPA) axis upon exposure to a stressor. In search of the molecular mechanisms underlying these differences, we found that under non-stressed conditions mRNA and protein levels of the glucocorticoid receptor in the hippocampus were higher in mice with high trait anxiety compared to mice with low trait anxiety. Also, systemic injection of a glucocorticoid receptor antagonist decreased the stress-induced activation of the HPA axis and the long-term anxiogenic effects of stress observed in mice with high trait anxiety. Finally, the rewarding properties of cocaine were enhanced in mice with high trait anxiety, suggesting a causal link between trait anxiety, stress activity and the behavioral responses to drugs of addiction (Jakovcevski et al., 2011). Recently we observed that variability in the coping strategy of a mouse are epigenetically determined during the first week of life and are apparent at least already at the age of four weeks and remain constant till adulthood (unpublished data).

Role of HCN/h channels in entorhinal cortex during learning and memory (*K. Meier)*

Together with Dirk Isbrandt we investigated the effects of the ablation of subthreshold-activating ion HCN/h channels in specific neuronal populations on the functional connectivity between the entorhinal cortex and hippocampus during learning and memory processes. The project combined behavioral analyses with *in vivo* electrophysiological recordings in transgenic mouse lines with ablation of HCN/h in specific brain regions. We identified specific learning-dependent local field potential changes in entorhinal cortex-hippocampus communication that occur in control mice but not in mice without HCN/h current. Ablation of HCN/h current in the medial entorhinal cortex (Fig. 3) affected both acquisition and retrieval of long-term reference and episodic-like memories in mice. Noteworthy, cognitive impairments correlate with altered entorhinal cortex-hippocampal network activity during the acquisition and consolidation phases.

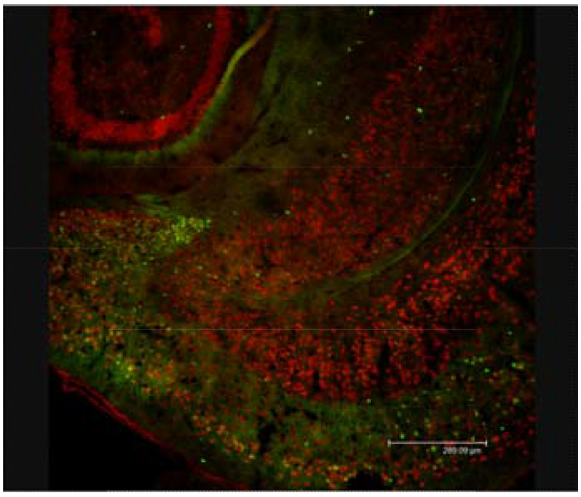

Figure 3. EGFP positive cells in the intorhinal cortex have impaired HCN/h current.

Nocebo/placebo in mice

We recently developed a new paradigm to test nocebo hyperalgesia in mice. The behavioral test is based on a conditioning protocol so that nocebo hyperalgesia is induced by a specific context. Currently, we are validating the test for placebo analgesia. To our knowledge, our data are the first evidence that nocebo hyperalgesia can be induced in rodents by means of behavioral conditioning. This project was stimulated by the scientific exchange, within the SFB936, with the group of Chrsitian Büchel at the UKE who intensively studies the cognitive processes regulating nocebo/placebo in humans by means of fMRI. The final aim of the project is to use the mouse as model to investigate, by means of transgenic and pharmacological approaches, the molecular and neural mechanisms regulating nocebo hyperalgesia and placebo analgesia.

Analysis of transgenic mice

In the last years we performed several experiments to analyze possible behavioral alterations in transgenic mice provided by our collaborators at the ZMNH (Duncan, Calderon de Anda, Friese, Schachner) and UKE (Kreienkamp, Kindler,

Meyer-Schwesinger, Windhorst, Glatzel). The behavioral analyses comprised a longitudinal battery of paradigms covering several behavioral functions. By these means, we could provide our collaborators with alternative hypotheses on the behavioral functions, brain regions and developmental stages in which their molecule of interest may play a role (Sawallisch et al., 2009; Morellini et al., 2010; Choe et al., 2013).

Future perspectives

Our group has four major goals for the near future. First, we want to implement our collaborations with scientists at the UKE performing neuroimaging studies in humans. Specifically, we will validate new behavioral paradigms in mice that can model the human studies. The use of appropriate behavioral mouse models will be of paramount importance for the investigation of the molecular and neural substrates regulating behavior and will enormously help translational research. For instance, we will collaborate with Tobias Sommer at the UKE to study the effects of the interaction between estradiol and dopamine on synaptic and network activities underlying cognitive function in mice and humans. Second, we will continue our collaboration with scientists at the ZMNH and UKE in terms of behavioral and *in vivo* analyses of transgenic or pharmacologically treated mice. Third, we planned to collaborate with Thomas Oertner at the ZMNH to investigate the neuronal substrates of reversal spatial learning by combining optogenetics and behavioral analyses. This project should extend our knowledge on the role of the interaction between entorhinal cortex and hippocampus on cognitive function as started with our project B3 within the SFB936. Finally, we will further investigate the environmental factors determining the coping strategies of a mouse, the underlying epigenetic mechanisms and the relevance of the effects on the adaptive behavior and fitness of a mouse.

Support

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Selected Publications

Hochgäfe, K., Sydow, A., Matenia, D., Cadinu, D., Könen, S., Petrova, O., Pickhardt, M., Goll, P., Morellini, F., Mandelkow, E., Mandelkow., E.M. (2015). Preventive methylene blue treatment preserves cognition in mice expressing full-length pro-aggregant human Tau. Acta Neuropathol. *(in press)*.

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Haaker, J., Gaburro, S., Sah, A., Gartmann, N., Lonsdorf, T.B., Meier, K., Singewald, N., Pape, H.-C., Morellini, F.*, and Kalisch, R.* (2013). Single dose of L-dopa makes extinction memories context-independent and prevents the return of fear. Proc.

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Neuronal Development

(established in July 2012)

Froylan Calderon de Anda

We are interested to understand by what means neurons form a functional unit in the neocortex. How neurons acquire their morphology is a fundamental topic in developmental neurobiology since the shape of a neuron supplies valuable clues to its function. Little is known about the mechanisms of axon and dendrites specification *in vivo* and how intracellular and extracellular programs cooperate to define the site of axon elongation and dendrite formation. Furthermore, it is now conceivable that neuronal cytoarchitectural abnormalities might lead to neurological disorders. Therefore, we are particularly interested in understanding how neurons develop axons and dendrites *in vivo*, in order to gain insight into the cellular and molecular events that may underlie neuropsychiatric diseases.

In our lab we are studying three aspects of neuronal development:

1. How do neurons attain a post-mitotic stage in the developing cortex?
2. How do neurons decide where to form an axon?
3. The role of Autism Spectrum Disorder susceptibility gene TAO2 in neuronal development.

1. How do neurons attain a post-mitotic stage in the developing cortex?

A longstanding orthodoxy in neurobiology is that once formed, neurons never divide. Indeed, neurons are the quintessential 'post-mitotic' cell. Attempts to induce neurons to proliferate by either expressing oncogenes or by inactivating tumor suppressors are well documented in the literature, but have generally resulted in neuronal death instead. In addition, aberrant cell cycle re-entry precedes neuronal loss under various neurotoxic conditions, and cell cycle re-entry by neurons is elevated in certain neurodegenerative disorders such as Alzheimer's disease. Together, these observations reinforce the notion that cell division is essentially incompatible with the survival of mature neurons. However, precisely when and how during its genesis a neuron attains this irreversibly post-mitotic state is still poorly understood. The cell cycle machinery has a role during neuronal development: genes, which regulate phases of the cell cycle, also modulate neuronal migration, axon formation, and dendrite growth and branching. However, comparatively little is known about the timing in which neurons define the terminally differentiated state, in other words: when a neuron truly becomes a post-mitotic cell. It has been proposed that during the acquisition of morphological features that define a neuron (i.e. axon and dendrites formation), proteins associated with cell cycle regulation participate in these morphological changes as part of another developmental machinery different from the cell cycle control. It is also possible, however, that newly born neurons have a mixed identity between progenitors and neurons and that the post-mitotic state is still not defined.

Our preliminary data show the precise time in which upper layer neurons attain a clear post-mitotic identity. Cortical neurons labeled *in utero* at embryonic day 15 (E15) and tracked at E18-postnatal day 5 (P5) elongated axons while migrating in the CP (E18-E19) and initiated dendrite formation after completing migration (P3-P5). However, still at P3, these neurons drive gene expression under the Ta1-promoter, which is active in neurogenic intermediate neuronal progenitors, suggesting that post-mitotic neuronal identity is still not well defined even at this developmental stage. Transcriptome analysis of upper cortical neurons at P3 and P5 supports a gradual transition to the post-mitotic state, with cell cycle genes up regulated at P3 and tumor suppressors expressed at P5. Furthermore, we demonstrate that controlled calcium influx in CP-migrating neurons at E18-E19 divided and accumulated mAG-hGem (Fig. 1), which selectively accumulates in cells that are in the S/G2/M phases of the cell cycle. At P3, however, mAG-hGem is also expressed upon calcium influx, but subsequent cell divisions were not detected. Finally, calcium

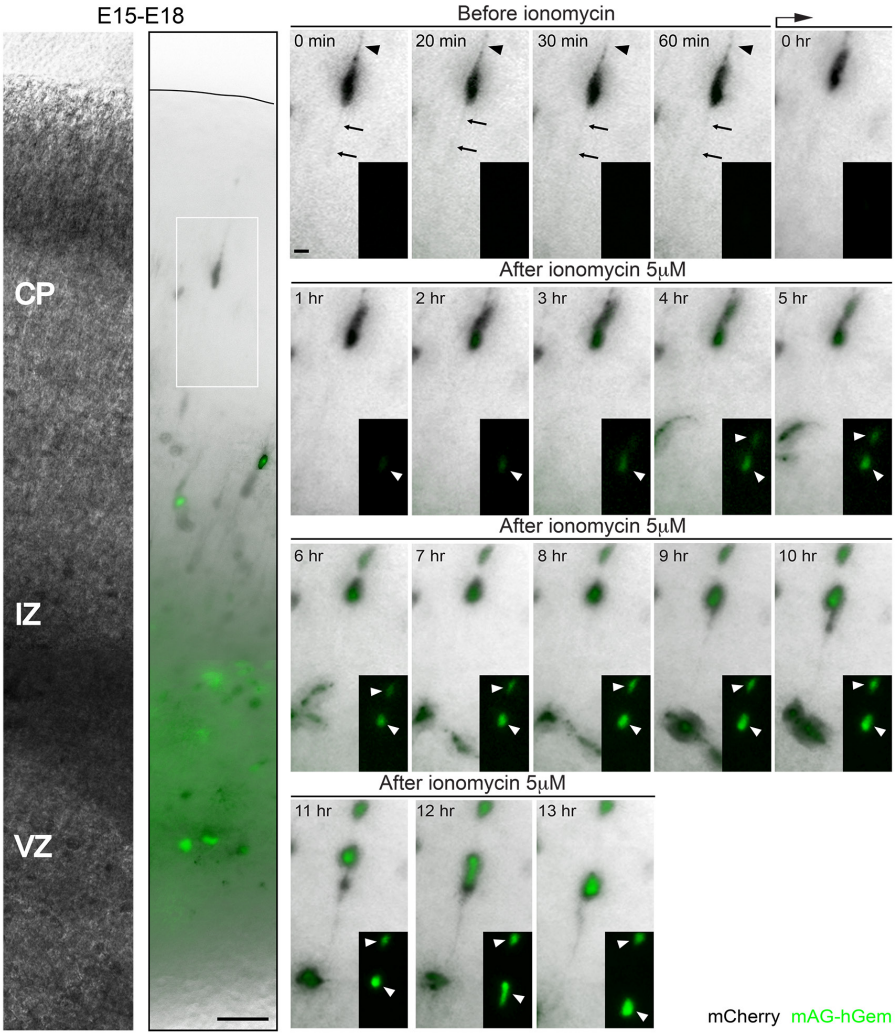


Figure 1. Calcium influx induces cell cycle re-entry and cell division in developing neurons from the CP. Neuron with a leading process and trailing process or axon (arrowhead and arrow respectively) in the CP re-enter the cell cycle upon ionomycin treatment (5 μM) and express the S/G2/M marker mAG-hGem (white arrowheads, insets from time-lapse sequence) and divide. Scale bar: 50 μm (Left panel) and 10μm (time-lapse sequence).

influx at P5 induced cell death in upper layer neurons. We conclude that upper layer neurons attain an irreversible post-mitotic state only after P5. Our data suggest that during the formation of axons and dendrites, neurons do not have a terminally defined post mitotic state. In fact, the post-mitotic or terminally differentiated state might be a gradual process that starts with neuronal migration and becomes well defined only when neuronal connectivity is achieved. Altogether, our results shed light on potential regulatory programs that function later on to maintain this terminally differentiated state.

2. How do neurons decide where to form an axon?

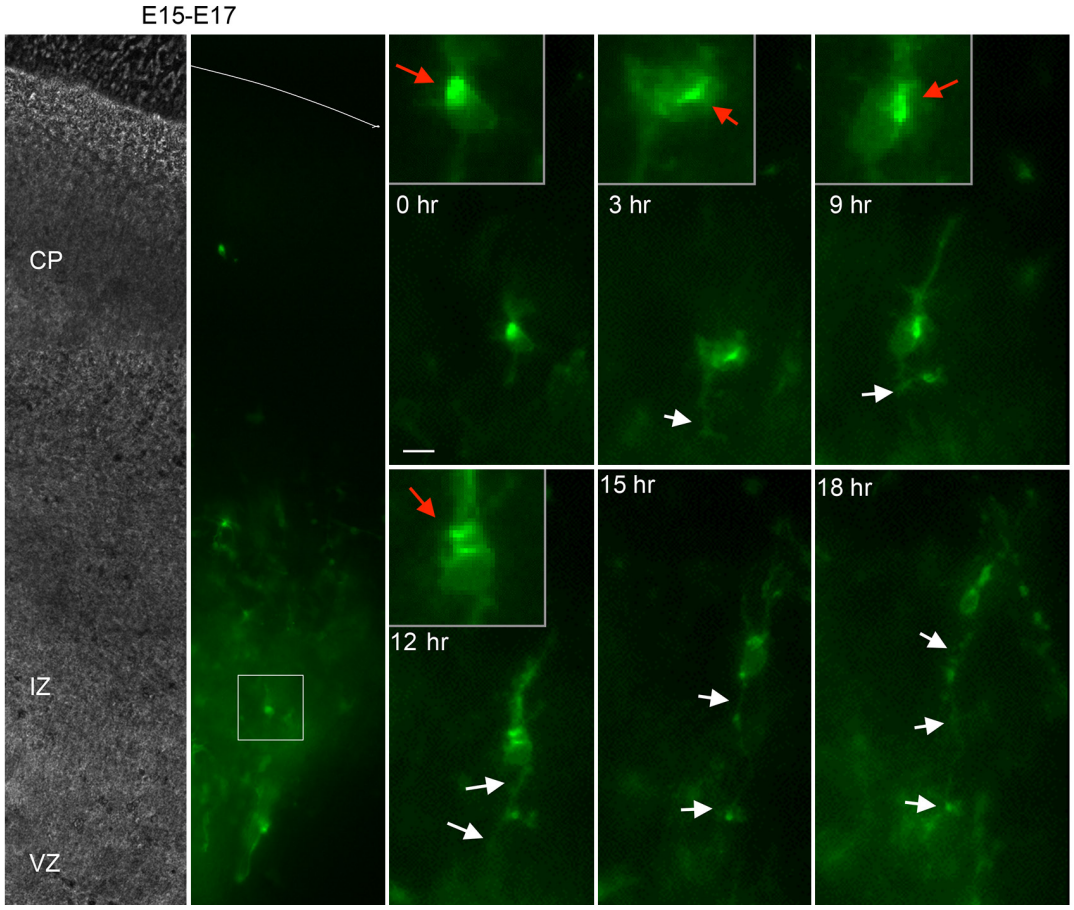
The term polarity is used in a biological context to describe asymmetry. In neurons, this polarity reflects their complex morphology with typically an axon and several dendrites. Although neurons come in many shapes and sizes, in general they maintain these two domains, which are important for neuronal functioning. The formation of these domains is the result of polarized differences of membrane delivery, actin dynamics, and microtubule stability. However, it is not well understood how their position is defined. One possibility is that external cues select where the axon and dendrites will grow, following a stochastic model. However, our data support the role of an intracellular organization behind the axon selection: the position of the centrosome and Golgi apparatus predict from where in the cell body the axon elongation takes place.

In the developing mammalian cortex, the first sign of axon outgrowth is evident in neuronal

cells in the lower intermediate zone (IZ) that exhibit multipolar morphology. The multipolar neuron stage is a transitional one, occurring after newborn bipolar neurons ascend from the ventricular zone (VZ) to the IZ, and before the more mature bipolar neurons migrate out of the IZ and into the cortical plate (CP). Early electron microscopic studies showed that the centrosome is generally located at the origin of the extending axon, which projects tangentially or towards the VZ in multipolar neurons of the IZ. However, in more mature neurons, which are already located in the CP, the centrosome was found in proximity to the apical/leading process or future apical dendrite, which is oriented towards the cortex surface. This initial observation already suggested that the centrosome is dynamic during neuronal differentiation in the developing cortex. Indeed, live imaging of multipolar cells in the IZ demonstrated that the centrosome or Golgi apparatus translocates towards the site of axon formation before or at the time of initial axon emergence (Fig. 2).

In summary, neuronal polarization is a complex process, which determines the morphological and eventually functional orientation of a neuron to achieve the fidelity of neuronal connectivity. A crucial initial step in this tightly regulated process is the axon selection. Centrosome, Golgi apparatus and the associated intracellular organization of microtubules and filamentous actin may function to define the position of axon formation. The external environment, which governs the final axon trajectory, could also act as a regulator of centrosome and Golgi positioning prior to axon extension. Thus, we can conclude that axon selection is regulated by intrinsic mecha-

Figure 2. Rotation of polarized cytoplasm precedes the elongation of the axon. Time-lapse analysis of a cell in the IZ (white box), which expresses farnesylated E-GFP confirm the inversion of the polarized cytoplasm (red arrows, inset in 0hr-12hr) toward the VZ prior the elongation of the axon (white arrows). Scale bar: 10µm.



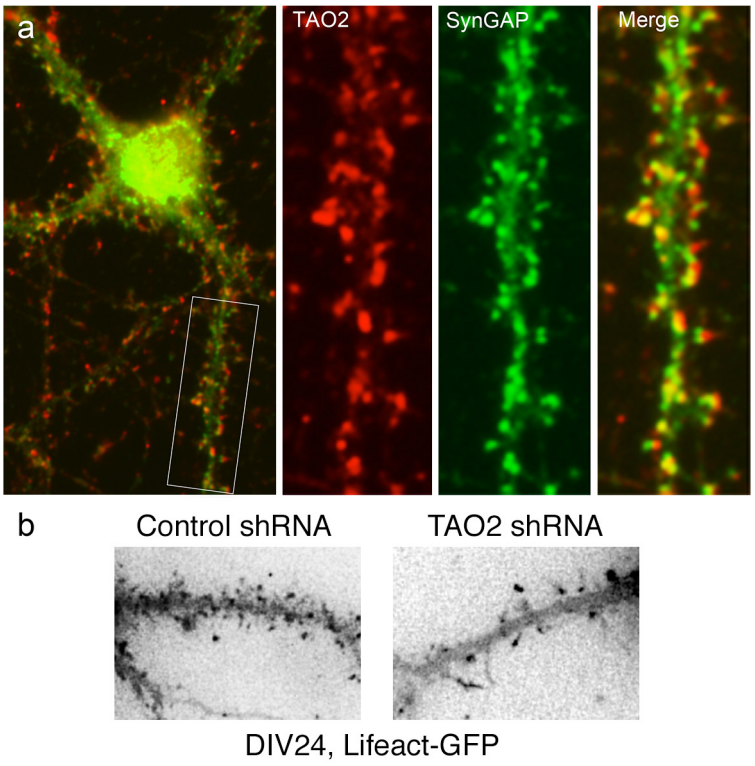


Figure 3. TAO2 affects spine formation. a) TAO2 accumulates in spines of cultured neurons, and localizes with postsynaptic marker SynGAP. b) Knockdown of TAO2 results in dendritic spine defects *in vitro* (this is a static image from live imaging of dendritic spines.

nisms that are influenced by extracellular cues. We do not have a complete understanding of the cellular events and molecular pathways that regulate centrosome and Golgi motility in multipolar cells in the developing cortex. However, it is conceivable that the perturbation of this system will have pathological consequences associated with cortical circuit malformation.

3. The role of Autism Spectrum Disorder susceptibility gene TAO2 in neuronal development.

Autism spectrum disorders (ASDs) are neurodevelopmental disorders in which individuals have disrupted social communication and repetitive stereotyped behaviors, which lead to life-long difficulties. Approximately 1% of individuals in Asia, North America and in Europe have an ASD, which demonstrates the need to better understand these disorders, and find effective treatments to improve quality of life. In this regard, one of the key discoveries in recent years is that a person's genetic blueprint plays a very important role in risk for ASDs. This means that there are genetic risk factors for ASD, and understanding how these genes cause abnormal brain development will help us to better understand the origins of ASDs to develop better treatments.

Recently, a novel recurrent copy number variation (CNV) micro deletion of chromosome 16p11.2 has been identified that carries substantial susceptibility to ASDs. While there are ~30 genes in this interval, the expression of one gene named TAO2 is of particular interest because it has been identified by us that affects basal dendrite formation and axon elongation in pyramidal neurons from the neocortex. This suggests the exciting possibility that TAO2 regulates brain connectivity. This study (Calderon de Anda et al., Nat. Neurosci., 2012) highlights that TAO2 is expressed in newborn neurons and co-localizes with the actin cytoskeleton, suggesting it might also regulate several aspects of neuronal differentiation. Accordingly, live imaging of cultured cortico-hippocampal neurons revealed loss of TAO2 results in initial decreased filopodia density but increased motility, which results in less dendritic spines compared to control cells later in development (Fig. 3). This suggests that TAO2 regulates spine stability and may impact synapse formation. Additionally, TAO2 mutant (-/-) mouse brains are disrupted with a reduced cortex size compared with control littermates. We also examined whether TAO2 -/- mice displayed abnormal behaviors. Our initial behavioral testing revealed TAO2 -/- mice have increased locomotor activity in the open field and decreased habituation, suggesting increased anxiety. TAO2 -/- mice also display impaired working memory and reduced preference for

social stimuli in the novel object recognition test. Together, these studies will advance our knowledge of a signaling axis relevant for 16p11.2 syndromes, with the potential to provide insight into future therapeutic directions.

Support

ERA-NET NEURON (The role of TAO2 in spine formation and Autism Spectrum Disorders).

Selected Publications

Rudenko, A., Seo, J., Hu, J., Su, S.C., Calderon de Anda, F., Durak, O., Ericsson, M., Carlén, M., and Tsai, L.-H. (2015). Loss of cyclin-dependent kinase 5 from parvalbumin interneurons leads to hyperinhibition, decreased anxiety, and memory impairment. J. Neurosci. 35, 2372-2383.

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Calderon de Anda, F., Pollarolo G., Da Silva J.S., Camoletto P., Feiguin F. and Dotti C.G. (2005) Centrosome localization determines neuronal polarity. Nature 436, 704-708.

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Neuronal Patterning and Connectivity

(established in February 2011)

Peter Soba

Proper neuronal development and maintenance of functional circuits are the basis for nervous system function in the entire animal kingdom. Neurons typically form stereotyped dendrite fields and connect to the right partners to create a functional network. However, the basic molecular and functional mechanisms regulating dendrite growth, receptive field formation and connectivity are still very incompletely understood. Moreover, defects in dendrite development and network formation are strongly linked to neurodevelopmental disorders like Autism Spectrum Disorders (ASD) or schizophrenia. Our laboratory is using *Drosophila melanogaster* as a simple and efficient model organism that offers powerful genetic tools to elucidate these fundamental mechanisms in a defined circuit.

In our projects we are working on the larval peripheral nervous system (PNS), which is well suited to study dendrite and circuit formation and their function *in vivo*. These well characterized sensory neurons feature stereotyped dendritic trees and axon projections and can be classified according to their dendrite complexity and function. This system allows us to live image dendrite development *in vivo* and manipulate gene function in specific neuronal subtypes (Fig. 1). For our studies we utilize genetic, cell biological, physiological and behavioral readouts to characterize molecular mechanisms regulating circuit development and function in the PNS.

Currently we are focusing on class IV da (C4da) neurons, which feature complex sensory dendrites and are the primary nociceptive sensors in Drosophila larvae. We are using C4da neurons to understand how dendrites are growing and maintained and how the nociceptive sensory network is established to mediate appropriate behavior.

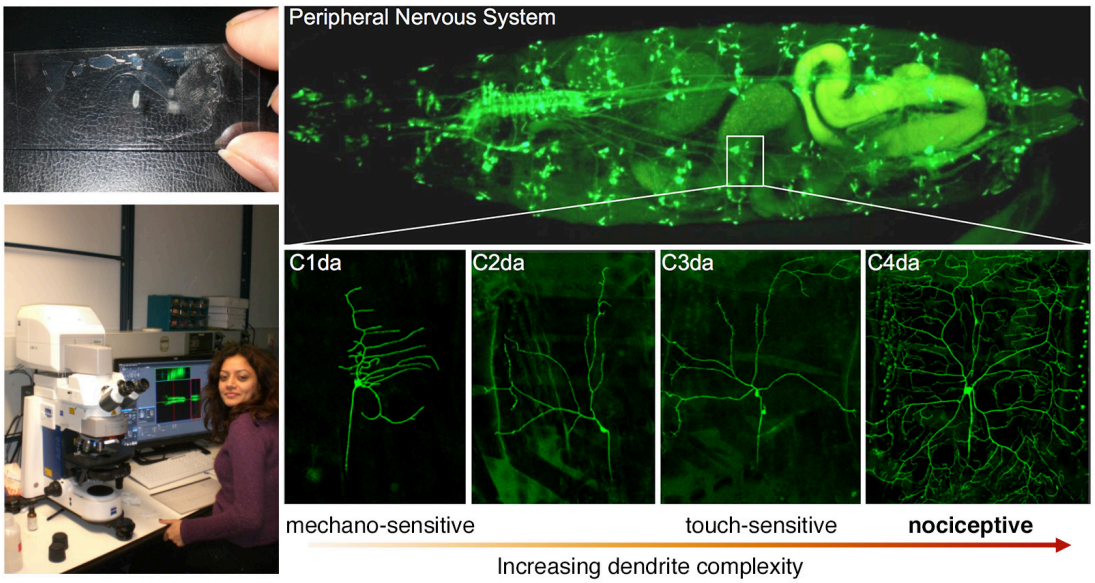


Figure 1. Organization and *in vivo* imaging of the peripheral nervous system in Drosophila larvae.
Living Drosophila larvae can be mounted and their PNS structures visualized by using specific transgenic fluorescent markers and confocal microscopy. Four classes of sensory neurons (C1da-C4da) can be identified by their increasing dendrite complexity and specific functions.

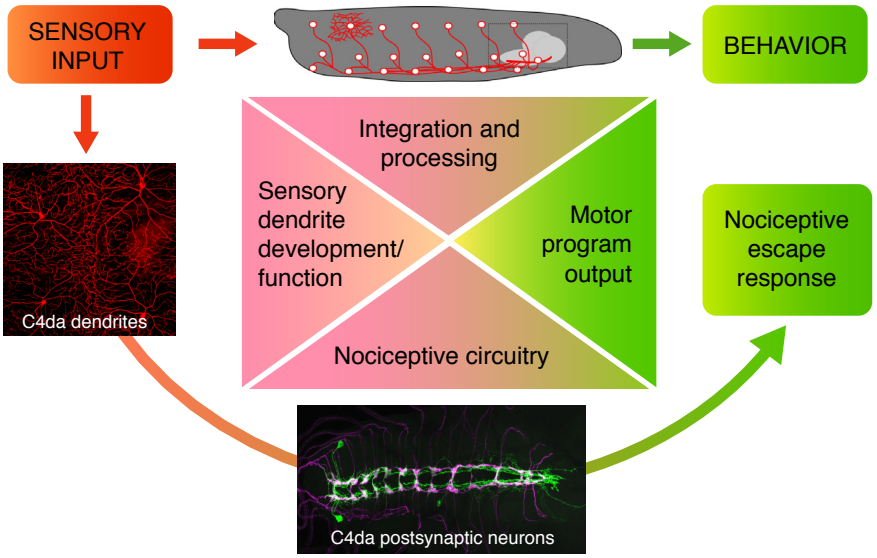


Figure 2. The nociceptive sensory network in Drosophila larvae. Nociceptive stimuli (noxious heat, mechanical touch, UV light) are detected by C4da neurons with their sensory dendrites. The sensory information is then conveyed and processed by the nociceptive network and results in the activation of a motor program, typically a nociceptive escape response. We are studying the development and function of these circuit components at different levels to get insight into the molecular nature of network formation and processing.

Circuit formation and function of the nociceptive sensory network

Meike Petersen, Bettina Spitzweck, Chun Hu, Nina Hoyer

For all animals, sensing noxious stimuli and responding with an appropriate nociceptive response is essential for identifying and avoiding potentially harmful environments and predators. This requires a functional neuronal network that reliably detects and conveys nociceptive stimuli and translates it into stereotyped behavioral responses. In *Drosophila* larvae, C4da neurons are the primary nociceptors detecting different noxious stimuli including heat, harsh mechanical touch and bright light. Very little is however known about the downstream network integrating and conveying the proper behavioral responses. In our work we identified distinct populations of 2nd order neurons and characterized their connectivity with C4da neurons at the light microscopic and ultrastructural level. We have used optogenetic approaches and *in vivo* Calcium imaging to show that they are physiologically activated and both necessary and sufficient to elicit C4da neuron dependent nociceptive behavioral responses. Our findings give insight into a complex nociceptive network required to efficiently avoid noxious stimuli. We are now continuing to elucidate this network further and have started to get molecular insight into its assembly and function.

The Ret receptor and regulation of dendrite growth and adhesion

Nina Hoyer, Chun Hu, Meike Petersen

Neurons develop highly stereotyped receptive fields by coordinated growth of their dendrites. Cell surface cues play a major role in this process, but to date very few dendrite specific signals have been identified. We have used *in vivo* RNAi screening in C4da neurons and identified the conserved receptor tyrosine kinase Ret, an important axon guidance receptor, as a regulator of dendrite development (Soba et al., 2015). In our studies we have shown that Ret interacts with integrins to regulate dendrite adhesion via the small GTPase Rac1. In addition, Ret is required for dendrite stability and normal F-actin distribution suggesting it also has an essential role in maintaining dendrites. Our work has therefore uncovered novel functions for the Ret receptor as a regulator in dendrite patterning and adhesion. We have followed up on these findings and performed microarray analysis comparing Ret mutant and wildtype C4da neurons. Using this approach we have identified and characterized additional downstream components which are involved in Ret signaling (Fig. 3). Our current focus is the identification of candidate ligands that mediate Ret receptor dependent dendrite growth.

Tao kinase as a bidirectional regulator of sensory dendrite plasticity and function
Chun Hu, Lin Cheng, Nina Hoyer

Dendrites need to exhibit the appropriate level of plasticity required for receptive field establishment, maintenance and neuronal network refinement and function. Plastic changes of dendrites are largely governed by cytoskeletal remodeling, which also determines the proper localization and function of ion channels. How dendrite stability, turnover and dynamics are regulated by molecular signals is not fully understood. C4da neurons exhibit tight regulation of dendrite plasticity during larval development and their nociceptive function depends on the proper localization and tethering of mechanosensory channels.

In collaboration with the Calderon lab we have identified Tao, a highly conserved Ser/Thr-kinase implicated in ASD, as a regulator of plastic dendrite growth in our system. Down-regulation of Tao by RNAi or loss of function mutation results in dendritic overgrowth and abnormally increased dendrite occupancy of sensory fields (Fig. 4 B,D). Conversely, increasing Tao activity by overexpression resulted in reduced dendrite growth and incomplete sensory field coverage. Tao regulates cytoskeletal components, in particular microtubule and actin dynamics, although the precise mechanism of its action is unknown. We have studied the impact of Tao on dendrite growth and dynamics and have characterized the Tao dependent changes in F-actin and microtubule dynamics (Fig. 4 A). Interestingly, Tao induced change in dendritic structure and plasticity has severe functional and behavioral consequences: in behavioral assays that allow assessment of larval nociception we found that Tao deregulation impairs sensory neuron function dramatically (Fig. 4 C). We are currently investigating the localization and functionality of the mechanosensitive channels expressed in C4da neurons to understand the functional changes induced by Tao deregulation.

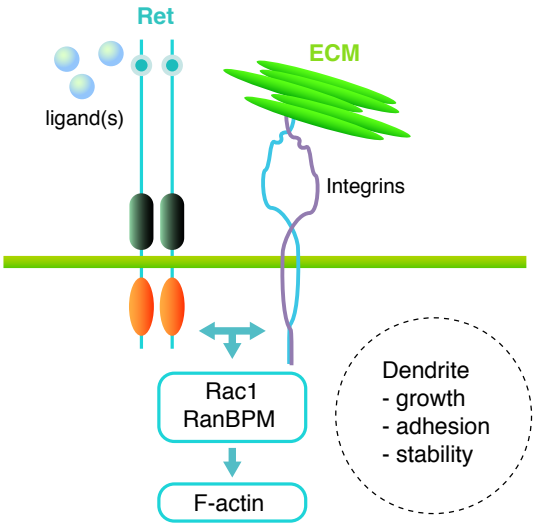
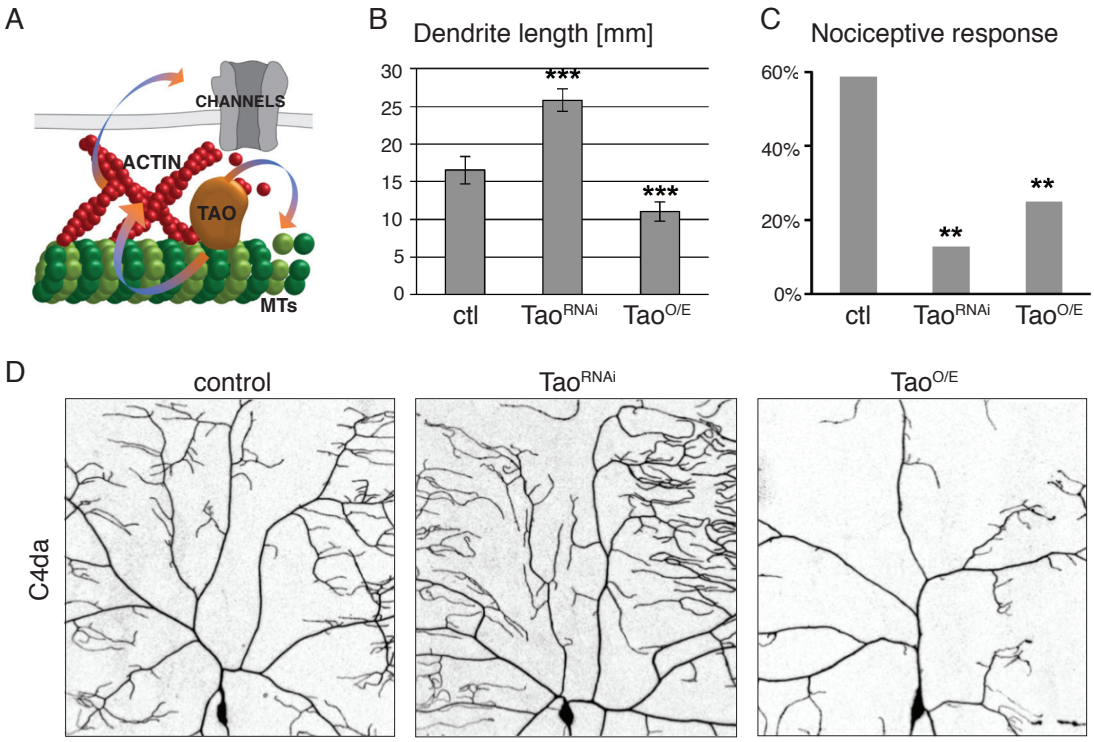


Figure 3. Model of Ret receptor function in dendrite development.
Ret is a receptor tyrosine kinase that is required for dendrite adhesion to the extracellular matrix (ECM). It functionally and biochemically interacts with integrins to mediate ECM adhesion, which requires intracellular Rac1 signaling. Together with additional components of the intracellular signaling machinery Ret also affects F-actin distribution in dendrites which is required for their growth and maintenance.

Future perspectives

Over the past years we have established the tools and expertise to study the development and function of the *Drosophila* nociceptive circuit *in vivo*. This allows us to get novel insight into the formation and maintenance of a specific network, which is of fundamental importance for our understanding of brain function. In our future studies we are particularly interested in investigating how and where the integration of different sensory modalities (e.g. touch vs. nociceptive touch) converges within the network and how changes in individual circuits affect behavior. In addition, we are now in a position to uncover molecular signals that are required for the specificity of synaptic connections. We will continue to explore this system using our ability to screen in *Drosophila* for new genes involved in these processes. Our studies therefore aim to advance our knowledge of how circuits form specifically at the molecular and functional level, which will ultimately contribute to our understanding of the underlying basis of neurodevelopmental disorders.

Figure 4. Tao kinase regulates cytoskeletal dynamics, dendrite plasticity and nociceptive function of C4da neurons.
A model of Tao kinase function is shown in (A). Tao can bind and regulate microtubule (MT) and F-actin growth and disassembly, which particularly affects mechanosensitive channel function in C4da neurons. (B,D) Downregulation of Tao by RNAi results in increased dendrite growth, while overexpression reduces dendrite complexity. (C) Tao down or up-regulation in C4da neurons impairs mechano-nociceptive behavior suggesting that maintaining balanced Tao signaling in sensory dendrites is essential for normal C4da dendrite plasticity and behavior.



Support

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Selected Publications

Soba, P.*, Han, C., Zheng, Y., Perea, D., Miguel-Aliaga, I., Jan, L.Y., Jan, Y.N.* (2015) The Ret receptor regulates sensory neuron dendrite growth and integrin mediated adhesion. eLife in press. **co-corresponding authors*

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Neuronal Translational Control

(established in May 2010)

Kent Duncan

We study how translational control contributes to cell-specific functions *in vivo*, with emphasis on the nervous system. Much of what we currently know about translational control is derived from studies in biochemical systems, yeast or cell culture. Comparatively little is known about how regulated translation serves cell-specific functions *in vivo* and how alterations to these cell-specific regulatory functions contribute to human disease. To gain insight into these areas, we study two classes of translational regulatory proteins: Non-canonical translation factors and RNA-binding proteins.

We seek to answer the following questions:

- How does 'non-canonical' translation contribute to organismal biology?
- What is the role of RNA-binding proteins in long-term memory consolidation?
- How does altered RNA-binding protein function cause neurodegenerative disease?

We use a multi-level, interdisciplinary approach that combines genetic, biochemical, and genomic methods and integrates *in vitro* and *in vivo* approaches. We work with both *Drosophila melanogaster* and mouse as model organisms, taking advantage of powerful genetic approaches available in each system for studying development, neurobiology, and for modeling aspects of human diseases.

A common goal of our projects is to identify specific mRNAs regulated by the factors we study in behaviorally relevant cellular populations. For this purpose we have established at ZMNH cutting edge methods for studying translational control on a genome-wide scale. In addition to classic methods like the polysome-microarray approach (Schleich, 2014), we are now also competent with newer technologies that offer important advantages: Ribosome 'footprint' profiling and TRAP.

1. Non-canonical translation factor function in vivo

Eukaryotic translation involves many essential factors that promote different steps of the 'canonical' inititation pathway for most cellular mRNAs in all cells. By contrast, little is known about *in vivo* functions of related 'non-canonical translation factors' (Fig. 1). These proteins interact physically with ribosomes and have biochemical activities that could support translation initiation via non-canonical mechanisms. However, prior to our work, nothing was known about the biological functions or molecular targets of these proteins *in vivo* in multicellular organisms. We set out to determine these functions using a reverse genetic approach in *Drosophila.*

1a. The DENR-MCT-1 complex promotes reinitiation downstream of uORFs to control tissue growth.

Using a combined in *vivo/in vitro* approach with Aurelio Teleman's lab at the DKFZ, we showed that the DENR-MCT-1 complex selectively

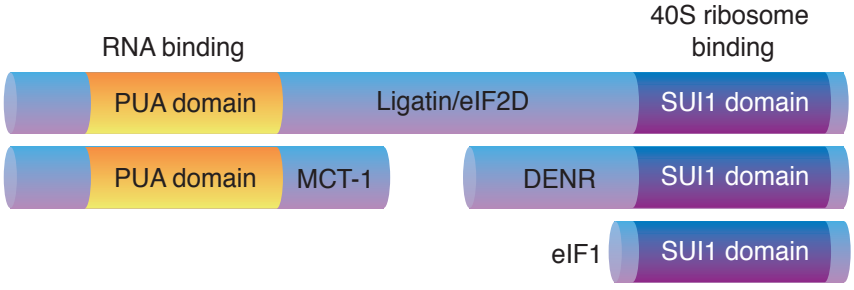

Figure 1. Non-canonical translation factor domains. Ligatin/eIF2D and DENR are related to canonical translation factor eIF1 which plays a crucial role in start site selection.

promotes translation reinitiation downstream of upstream Open Reading Frames (uORFs) to promote tissue growth. First, we identified specific developmental defects in DENR knockout flies that highlighted a role in proliferating cells. We then turned to cell culture and our polysome-microarray approach to identify mRNAs whose translation was sensitive to DENR. Detailed analysis of translational reporters from these mRNAs enabled us to determine the cis-elements that were necessary and sufficient to confer regulation by DENR: uORFs with strong consensus initiation sites. We then went back to the fly to show that misregulation of mRNAs of this class could explain the *in vivo* phenotypes. Collectively, our work has defined a new mode of translational regulation which seems to be particularly important in proliferating cells to enable normal tissue growth (Schleich et al., 2014).

Interestingly, a *de novo* mutation in DENR has been identified in a patient with autism spectrum disorder. Accordingly, our future goals will include determining whether DENR function is conserved in mammals and examining the molecular basis for potential connections to human disease.

1b. eIF2D/Ligatin is important for normal locomotion behavior and synaptic transmission.

We have also analyzed for the first time *in vivo* functions of the DENR ortholog Ligatin/eIF2D in animals. This non-canonical translation factor caught our attention, since primary culture studies suggested a possible role in neurons. We generated Ligatin-KO flies and found that they are viable, fertile, and have no gross developmental or morphological defects, but display striking deficits in locomotory behavior. Importantly, we can fully rescue larval locomotion phenotypes by overexpressing a Ligatin transgene in neurons in the Ligatin-KO background. Moreover, Ligatin expression in glutamatergic neurons, but not other neuronal populations tested (e.g. sensory neurons) was sufficient for full behavioral rescue (Fig. 2). We find no evidence of altered synaptic morphology in Ligatin KO larvae, but clear functional deficits in synaptic transmission at neuromuscular junctions (not shown). Our aim now is to identify mRNAs whose translation is modulated by Ligatin in motor neurons and to determine the mechanism by which Ligatin modulates their translation. A longer term goal will be to understand how regulation of these mRNAs supports synaptic transmission and normal behavior.

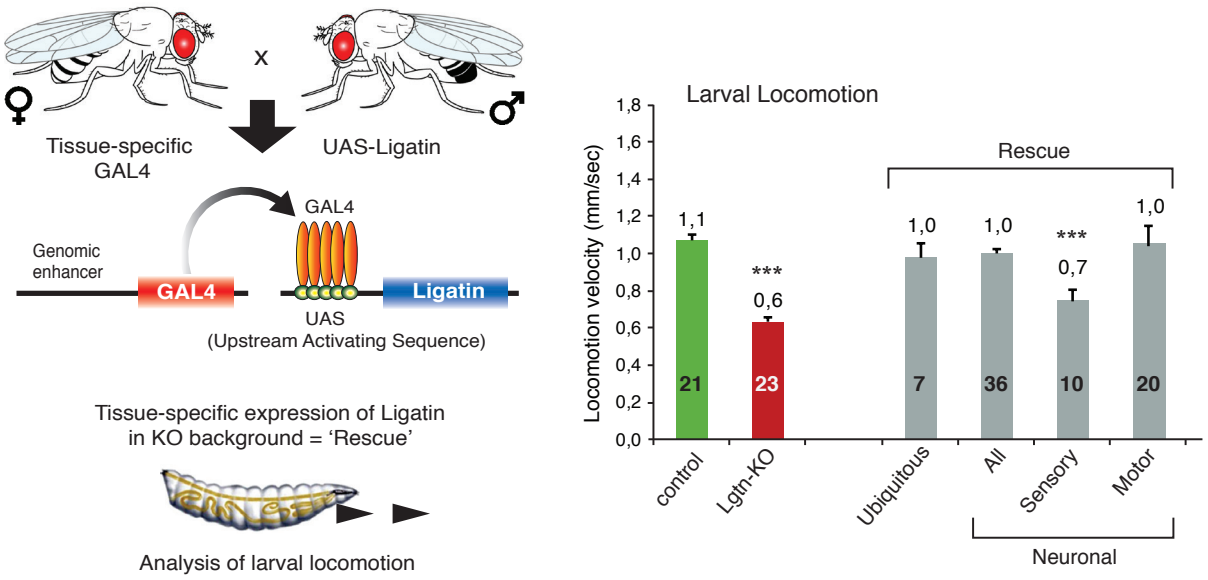

Figure 2. Behavioral rescue assays.
Ligatin expression in motor neurons is sufficient to rescue Ligatin-KO locomotion deficits. Control Gal4 and UAS lines alone (not shown) behave like KO.

2. RNA-binding protein function in memory consolidation

The ability to form long-lasting memories is a fundamental property of complex nervous systems and the devastation of Alzheimer's disease provides a vivid illustration of its importance. Translational control is believed to play a critical role in long-term memory formation and maintenance, but precise molecular mechanisms supporting memory remain to be defined. To gain insight into these mechanisms, we are investigating the role of the RNA-binding protein, Pum2, in mammalian memory consolidation. The *Drosophila* Pum2 ortholog, Pumilio, is a translational repressor identified in a screen for genes selectively affecting long-term memory. However, it has remained unclear whether Pum2 contributes to long-term memory consolidation *in vivo* in mammals.

Together with the ZMNH Transgenic Service Unit, we generated the first Pum2 conditional knockout mice. We crossed these mice to a forebrain-specific Cre line (Fig. 3) and analyzed behavior with Fabio Morellini in the Behavioral Biology Unit. This revealed striking effects on long-term memory consolidation when Pum2 is missing in forebrain principal neurons (Fig. 4). Our major goals now are to understand the underlying molecular and physiological basis for altered memory. Our hypothesis is that altered translation of specific mRNAs in specific cells in memory-relevant brain regions underlies the phenotype and we will address this with our established methods for studying translation. We anticipate that our characterization of Pum2's role *in vivo* will significantly advance understanding of how translational control contributes to persistent stability of long-term memory.

3. Altered RNA-binding protein function as a cause of neurodegenerative disease

TDP-43 is an RNA-binding protein implicated in etiology of several neurodegenerative diseases, including amyotrophic lateral sclerosis (ALS), the most common motor neuron disease, and frontotemporal lobar degeneration (FTLD). In diseased cells, TDP-43 frequently redistributes from nucleus to cytoplasm and forms inclusions. Additionally, numerous TDP-43 patient mutations have been identified. Model organism studies have shown that misregulated TDP-43 causes motor deficits and motor neuron degeneration, and these effects require TDP-43's RNA-binding ability. Nevertheless, how TDP-43 contributes to disease remains unclear.

TDP-43's relocalization from the nucleus to the cytoplasm in disease-affected neurons raises a fundamental, unanswered question: is disease due to loss of nuclear function, gain of cytoplasmic function, or both? We have found that TDP-43 protein associates with cytoplasmic

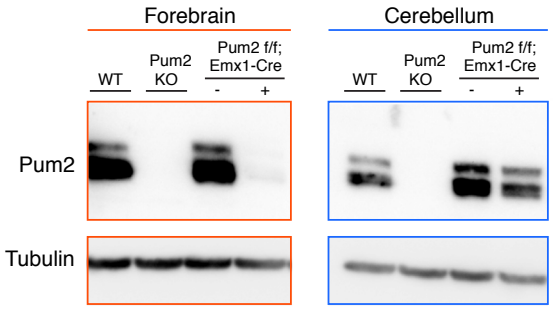

Figure 3. Forebrain-specific deletion of Pum2.
Immunoblot analysis of brain tissue reveals forebrain-specific elimination of Pum2 protein in *Pum2*$^{flox/flox;}$ *Emx1-Cre* mice. Lysates from complete knockout mice ('Pum2-KO') serve as specificity controls.

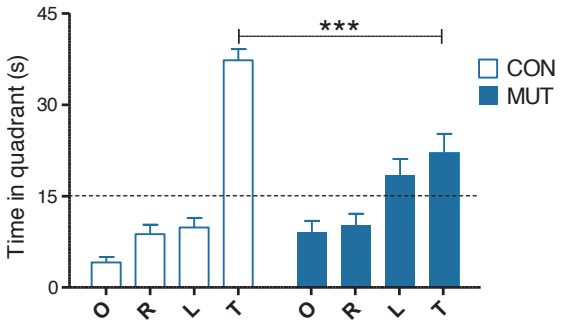

Figure 4 Impaired memory consolidation in Pum2-fbKO mice.
Mice lacking Pum2 in forebrain principle neurons display significantly reduced memory performance in the water maze relative to *Cre*- littermate controls. Both genotypes show equivalently robust learning.

polyribosomes and therefore hypothesize that it promotes disease in the cytoplasm by directly affecting translation.

3a. Does altered TDP-43 expression directly affect translation?

To determine whether TDP-43 regulates translation, we first examined the impact of altered TDP-43 expression on general translation in motor neuron-like cells. Neither TDP-43 knockdown nor expression of human TDP-43 or specific mutant variants of hTDP43 affected general translation. To investigate possible effects on translation of specific mRNAs genome-wide with high resolution we are now performing 'ribosome footprint profiling'. This method features deep sequencing of ribosome-protected fragments and essentially reveals the position of all ribosomes on all cellular mRNAs simultaneously. Using this sensitive approach we will profile our motor neuron-like cell models expressing WT TDP-43 or patient mutation variants. Subsequently, we will validate our results in primary neuronal cultures.

3b. Is ALS caused by mutant TDP-43 different from ALS caused by mutant SOD1?

Mutations in SOD1 were the first identified genetic cause of ALS and the basis for the most commonly used mouse model. Unfortunately, pre-clinical developments with this model have translated poorly to the clinic. A possible explanation is that ALS-SOD represents a special form of the disease with a distinct etiology. To explore this possibility, we are currently performing a controlled *in vivo* study in collaboration with Manuel Friese's group. We first established optimized 'translating ribosome affinity purification' (TRAP) of mRNAs from $ChAT^{+}$ neurons from spinal cords of 'chat bacTRAP' mice. We have now crossed these mice to established mouse models of ALS and will use TRAP with deep sequencing to identify mRNAs with altered ribosome association in spinal motor neurons *in vivo* as disease develops. Using both ALS-SOD and ALS-TDP mice will enable a systematic comparison of these models.

As for other projects in the lab, we anticipate that our combined *in vitro/in vivo* approach will provide significant insight into TDP-43's potential role in translational control and how it causes neurodegenerative disease.

Support

Our work during the reported period was supported by the Fritz Thyssen Stiftung, the Else Kröner Fresenius Stiftung, the Hans und Ilse Breuer Stiftung, and the Federal State of Hamburg.

Selected Publications

Schleich, S., Strassburger, K., Janiesch, P.C., Koledachkina, T., Miller, K.K., Haneke, K., Cheng, Y., Kuechler, K., Stoecklin, G., Duncan, K.E.*, Teleman, A.A.* (2014). DENR-MCT-1 promotes translation reinitiation downstream of uORFs to control tissue growth. Nature 512, 208-12. * *co-corresponding authors*

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Experimental Neuropediatrics

(established in 2009, since 2014 guest group)

Dirk Isbrandt *(2009-2013)*
Axel Neu *(since 2014)*

The ENP team is affiliated with both the Center for Molecular Neurobiology (ZMNH) and the Center for Obstetrics and Pediatrics at the University Medical Center Hamburg-Eppendorf. In October 2013, Dirk Isbrandt accepted the position of a joint professorship for Experimental Neurophysiology at the University of Cologne and the German Center for Neurodegenerative Diseases (DZNE) in Bonn. As of 2014, the ENP team has been headed by Dr. Axel Neu, Department of Pediatrics, UKE. To foster translational research and synergies between basic science and experimental clinical research, the ENP team is hosted in and supported by the ZMNH.

The major goal of our research is to understand the pathophysiological mechanisms of ion channel diseases (channelopathies) using transgenic mouse lines to investigate the physiological and pathophysiological changes at molecular, cellular, and systemic levels, as well as to develop treatment strategies. In another line of research, we generated and phenotypically characterized two mouse models for creatine deficiency disorders.

Our team has a broad range of scientific and methodological expertise that includes molecular and cellular biology, *in vitro* electrophysiology, *in vivo* electrophysiology, and behavioral neuroscience, allowing us to implement a multi-level experimental strategy.

Pathophysiology of ion channelopathies

In collaboration with the transgenic facility of the ZMNH, we generated conditional transgenic or knock-in mouse lines to analyze the systemic effects of ion channel dysfunction in complex excitable organs, such as the brain and heart, *in vivo*.

Kv7 channels in brain development

Using mouse lines in which the activity of Kv7/KCNQ channels (mediating the M current) or HCN channels (mediating I_h) is under control of the Tet-Off system, we are able to study the electrophysiological and behavioral consequences of the development-dependent inactivation of these subthreshold-activating ion channels with respect to their importance to learning, plasticity, and behavioral performance. The developing nervous system is especially vulnerable during critical developmental time windows, when insults may be more likely to produce long-term consequences including neurological diseases, such as epilepsy. We tested a pharmacological intervention timed to a critical neonatal period, which prevents pathology in mice with dominant-negative Kv7.2 subunits, which are linked to neonatal epileptic encephalopathy in humans. Neonatal treatment with the loop diuretic bumetanide normalized *in vivo* cortical network activity and mutant-specific alterations in spike train autocorrelation structure and bursting, preventing hippocampal structural damage and restoring wild-type behavior (Le et al., in revision). Our findings suggest prophylactically safe interventions targeted to key developmental windows may be an effective strategy for protecting at-risk patients against disease pathology.

HCN channels in brain development

The HCN/h channels mediate I(h), and are important determinants of the biophysical properties of neurons. Changes in expression patterns, subcellular localization, or biophysical characteristics of HCN channels have been associated with neurological dysfunctions ranging from motor learning deficits to diseases such as epilepsy. Recently, de novo mutations in the HCN1 gene in human patients have been linked to epileptic encephalopathy with concomitant neurological abnormalities, including autistic features, ADHD, absence of language, behavioral disturbances, ataxia, and delay of motor development. Our team generated HCN/h channel-deficient

mice in which we functionally suppressed I(h) in different developmental stages. The mice developed phenotypes that were dependent on the age of onset of I(h) suppression, and that resembled comorbidities observed in human patients with different de novo mutations in the HCN1 gene. HCN-DN expression under the control of either the EMX1 or CaMKII alpha promoters resulted in prenatal or peri-/postnatal ablation of I(h) in forebrain projection neurons. EMX1 promoter-mediated early prenatal ablation of the HCN/h current caused severe morphological abnormalities in the developing brain. Brain volume and cortex thickness were strongly reduced in HCN-DN-expressing mice. In contrast, CaMKII alpha promoter-driven early postnatal suppression of HCN channel-activity did not affect brain morphology, but resulted in behavioral abnormalities. HCN-DN mice displayed delayed somatosensory development with respect to sensorimotor reflexes, cognitive deficits in working memory and spatial learning and memory, as well as hyperactivity. Post-weaning onset of HCN-DN expression resulted in slight learning and memory deficits, but not in hyperactivity. Our results suggest distinct roles of HCN/h-channel activity during pre- and postnatal development of the central nervous system of the mouse. The different age-dependent developmental phenotypes observed in our I(h)-deficient mice may provide a model for investigating the range and variability of neurological dysfunctions associated with HCN1 mutations in human patients.

HCN channels in the heart

To study the physiological and pathophysiological roles of HCN channels in cardiac pacemaking, we generated mice with heart-specific and inducible expression of dominant-negative HCN4 mutations that abolish the cAMP-dependent regulation or pore function of HCN channels. Our data demonstrate that I(f) determines basal and maximal heart rates, and is critical for impulse conduction in the AV node (Alig et al., 2009, Mesirca et al. 2014).

Pathophysiology of creatine deficiency disorders

For many years, our group has studied the pathophysiological consequences of disturbed energy metabolism caused by disorders of creatine metabolism, which are a group of recently identified, severely disabling diseases that affect creatine synthesis or transport. The first neurological symptoms in affected patients usually appear in early childhood and include developmental arrest, mental retardation, ataxia, and epilepsy. To be able to study GAMT and AGAT deficiencies, two creatine synthesis defects, in a systematic manner, we generated knockout mouse models by targeted gene deletion for both diseases. The generation of AGAT knockout mice enabled us for the first time to study the effects of systemic creatine (Cr) deficiency in the absence of the accumulation of other guanidino compounds (Choe et al., 2013b).

Whereas AGAT deficiency had strong adverse effects on body size, fertility, and muscle morphology (Nabuurs et al., 2013), it improved glucose tolerance and conferred resistance against diet-induced obesity (Choe et al., 2013b). Cr deficiency resulted in the activation of AMP-activated protein kinase (AMPK), a key sensor and regulator of energy homeostasis, suggesting a mechanism mediating positive metabolic effects. AMPK activation in metabolically relevant tissues such as brain, skeletal muscle, adipose tissue, and liver was dependent on intracellular energy depletion and was fully reversible upon oral Cr supplementation (Choe et al., 2013b).

We further phenotyped the AGAT mouse model and discovered tissue-specific leptin dependence for AMPK activation through intracellular energy depletion (Choe et al., 2013b; Stockebrand et al., 2013).

Moreover, AGAT not only catalyzes the synthesis of the Cr precursor guanidinoacetate but, surprisingly, also controls the body content of homoarginine, which, independent of Cr, determines stroke volumes in an experimental stroke model.

This finding revealed a novel approach to Cr metabolism contributing to neuroprotection (Choe et al., 2013a).

Selected Publications

Choe, C.-U., Nabuurs, C., Stockebrand, M.C., Neu, A., Nunes, P., Morellini, F., Sauter, K., Schillemeit, S., Hermans-Borgmeyer, I., Marescau, B., et al. (2013a). L-arginine:glycine amidinotransferase deficiency protects from metabolic syndrome. Hum. Mol. Genet. 22, 110–123.

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Developmental Neurophysiology

(established in October 2008,
since October 2013 guest group)

Ileana Hanganu-Opatz

Following universal rules of living, the brain operates perpetually and periodically. These two main attributes of brain activity became obvious even after the first attempt of capturing it, since 1929 Hans Berger noted that "the electroencephalogram represents a continuous curve with continuous oscillations". Today it is generally accepted that brain rhythms, which emerge within local and large-scale networks and have different frequencies, not only tightly correlate with the behavioral/conscious state but also support information processing. These network oscillations encode sensory perception and gating as well as mnemonic and executive abilities at adult age.

The research group Developmental Neurophysiology has been established at the end of 2008 at ZMNH and was funded by the Emmy Noether-Program of the DFG (2009-2014) and by the BMBF (2008-2013). Our main research aim is to elucidate the role of network oscillations for the development of local and long-range communication in the brain in relationship with the emergence of cognitive behavior and multisensory perception. To this end, we developed during the last years an innovative methodological approach that combines opto- and electrophysiology *in vivo* with immunohistochemistry, imaging and behavioral assessment.

The following main topics are currently being investigated:

1. Development of neuronal networks accounting for cognitive processing;
2. Uni- and multisensory processing and ontogeny;
3. Dysfunction of neuronal networks and their early oscillations under pathological conditions (e.g. neuropsychiatric disorders, perinatal hypoxia-ischemia);

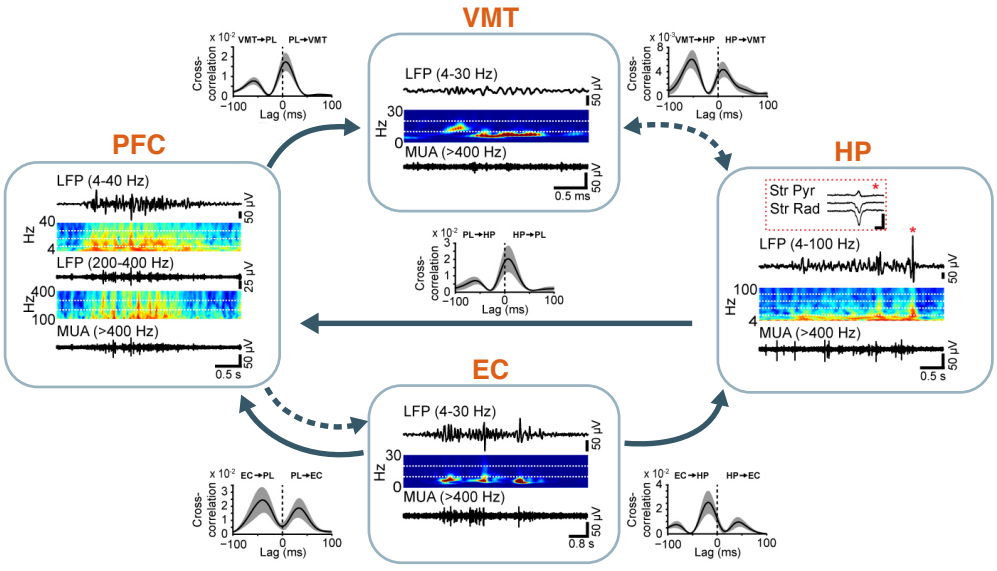

Figure 1. Network interactions within prefrontal-hippocampal networks under physiological conditions.
Directed interactions between PFC, HP, VMT and EC assessed by synchrony and causality analysis of discontinuous activity patterns. The characteristic nested gamma spindle bursts in PFC and theta bursts in hippocampal CA1 area, VMT and EC are exemplified together with the corresponding wavelet spectra. The hippocampal theta bursts are accompanied by sharp-wave (red asterisk, inset). Amplitude cross-correlation plots of network oscillations for pairs of brain areas reveal the directionality of interactions. Time lags correspond to either mono- (10-20 ms) or polysynaptic (30-50 ms) interactions. Modified from Brockmann et al. (2011) and Hartung et al. *(under review)*.

1. Development of neuronal networks accounting for cognitive processing

In contrast to oscillatory rhythms in the adult brain, during the first postnatal week the network activity of brain areas critically involved in cognitive processing [e.g. prefrontal cortex (PFC), hippocampus (HP), medial and lateral entorhinal cortex (EC) and ventral midline thalamus (VMT)] is discontinuous, spindle-shape field oscillations alternating with long periods of network "silence". The neonatal PFC starts to generate theta-gamma oscillations few days after birth. Their emergence is driven by discontinuous theta bursts in the HP that phase-locked the neuronal firing via monosynaptic pathways (Brockmann et al., 2011; Cichon et al., 2014) (Fig. 1). In the absence of monosynaptic reciprocal communication, the question arises, whether indirect feedback interactions control the early drive from HP to PFC. While at adulthood both EC and VMT have been proposed to interface the prefrontal-hippocampal coupling, we recently demonstrated that these areas have different contributions to the neonatal long-range communication. Discontinuous theta bursts in the EC push the activation of PFC and HP via monosynaptic projections, whereas theta-band entrainment in the VMT is controlled by prefrontal inputs and further relayed to HP (Fig. 1). The directed long-range communication during neonatal development is strongly modulated by subcortical regions (Janiesch et al., 2011) as well as early environmental stressors, , such as maternal separation and seems to be critical for the emergence of cognitive abilities, such as recognition memory (Kruger et al., 2012).

Complex synaptic interactions are the basis of oscillatory rhythms in neonatal prefrontal-hippocampal networks. Selective immunotoxic lesion as well as simultaneous extracellular and patch-clamp recordings *in vivo* from morphologically- and neurochemically-characterized neurons revealed that oscillatory theta activity mainly results from long-range coupling of pyramidal neurons, whereas gamma activity emerges within local networks and requires glutamatergic drive on prelimbic interneurons (Bitzenhofer and Hanganu-Opatz, 2014; Bitzenhofer et al., *in press*). To prove these correlative findings, we recently initiated the investigation of cellular mechanisms of network coupling by manipulation of distinct neuronal populations in neonatal networks using novel optogenetic tools. Our preliminary data showed that selective activation of prefrontal pyramidal neurons that have been embryonically transfected with the double mutant ChR2ET/TC (Berndt et al., 2011) by cell- and layer-specific *in utero* electroporation (IUE) facilitates the emergence of theta oscillations within prefrontal-hippocampal networks towards the end of the first postnatal week.

2. Uni- and multisensory processing and ontogeny

Most environmental events provide inputs to multiple senses that need to be integrated into a unified percept. Beside hierarchically higher-order brain regions, the primary sensory cortices, traditionally regarded as sensory-specific, have been recently identified as processing and integration site of these cross-modal inputs (Hanganu-Opatz et al., *in press*).

Our investigations in pigmented rats with good visual acuity showed that visual-tactile cross-modal stimuli modulate the neuronal firing of cortical neurons and to shape the power and phase of oscillatory network activity. Direct cortico-

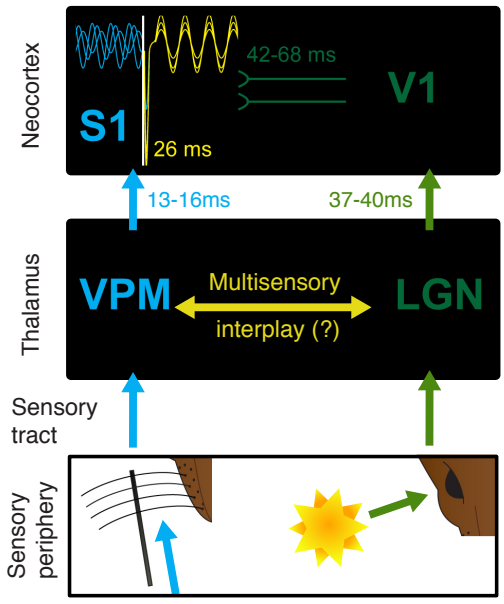

Figure 2. Schematic diagram of the mechanisms and anatomical substrate of visual-somatosensory interplay (yellow) at neocortical and subcortical level.

cortical connectivity and feed-forward projections from thalamic nuclei represent possible anatomical substrates of efficient multisensory processing at the cortical level (Sieben et al., 2013) (Fig. 2). While the multisensory abilities are indispensable for the daily life, their emergence is a progressive and protracted process that continues well after the development of individual senses. We identified neonatal unimodal experience during defined developmental stages as necessary for setting up the neuronal networks of multisensory processing.

3. Dysfunction of neuronal networks and their early oscillations under pathological conditions (e.g. neuropsychiatric disorders, perinatal hypoxia-ischemia)

The long-lasting burden of major neuropsychiatric disorders results from disruption of cognitive performance in daily life as result of abnormal coupling between PFC and HP. While it has been hypothesized that this impairment emerges long before the first clinical symptoms, technical and ethical limitations of non-invasive investigations in high-risk infants precluded the elucidation of ontogenetic mechanisms underlying the pathophysiology of disease. Understanding the complex interactions governing the formation and refinement of neonatal prefrontal-hippocampal networks under physiological conditions served as basis for the assessment of their dysfunction in major neuropsychiatric disorders, such as schizophrenia. Investigating mice models of genetic-environmental aetiology of disease, we showed that the de-coupling of prefrontal-hippocampal networks during early development is a potential mechanism underlying adult circuit dysfunction and poorer cognitive performance in schizophrenia.

Due to improved outcome of human infants experiencing an hypoxic-ischemic episode, cognitive dysfunctions have become prominent. Using an animal model of hypoxic-ischemic encephalopathy, we provided first experimental evidence that mnemonic deficits at adulthood result from decreased coupling synchrony within prefrontal-hippocampal networks at neonatal age (Brockmann et al., 2013).

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Selected Publications

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Bitzenhofer, S.H., Sieben, K., Siebert, K., Spehr, M., Hanganu-Opatz, I.L. (2015) Oscillatory activity in developing prefrontal networks results from theta-gamma modulated synaptic inputs. Cell Reports, *in press*.

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Development and Maintenance of the Nervous System

(established in March 2008)

Edgar Kramer

Cell surface proteins of neurons have a multitude of functions during development and maintenance of the nervous system. During development cell surface proteins allow to communicate with the surrounding cells and the extracellular matrix for proper proliferation, migration, differentiation and contact formation in the complex network. But also in the mature and aging nervous system they are needed for electrical activity, neuronal communication, survival and even regeneration. Alterations in cell surface protein signaling have been implicated in the pathogenesis of neurodegenerative disorders such as motoneuron diseases, Parkinson's disease (PD) and Alzheimer's disease but also in diseases such as depression, attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. There are many cross-talks of different cell surface proteins on neuronal membranes which even can be different concerning their localization in axons, dendrites, synapses and other specialized membrane structures. In addition they are connected with the intraneuronal processes by a large amount of signaling and regulatory pathways. So far our knowledge about neuronal cell surface protein interaction, signaling and their physiological function is still limited.

My research group focuses on investigating the cross-talk and function of the glial cell line-derived neurotrophic factor (GDNF) receptors, such as the receptor tyrosine kinase Ret, the neural cell adhesion molecule (NCAM), integrins, N-cadherins, and syndecan 3 in the midbrain dopaminergic (DA) system altered in PD patients and drug addicts and motoneurons innervating the skeletal muscles. We study their signaling mechanisms on a molecular and cellular level as well as in intact animals. Therefore, we use diverse experimental approaches such as molecular biological techniques, cell culture, mouse genetics, histology, as well as behavioral and physiological experiments.

To enhance the analysis of the midbrain dopaminergic and the peripheral nervous system we also developed unique tools for genetic manipulation and *in vivo* and *in vitro* imaging and quantification.

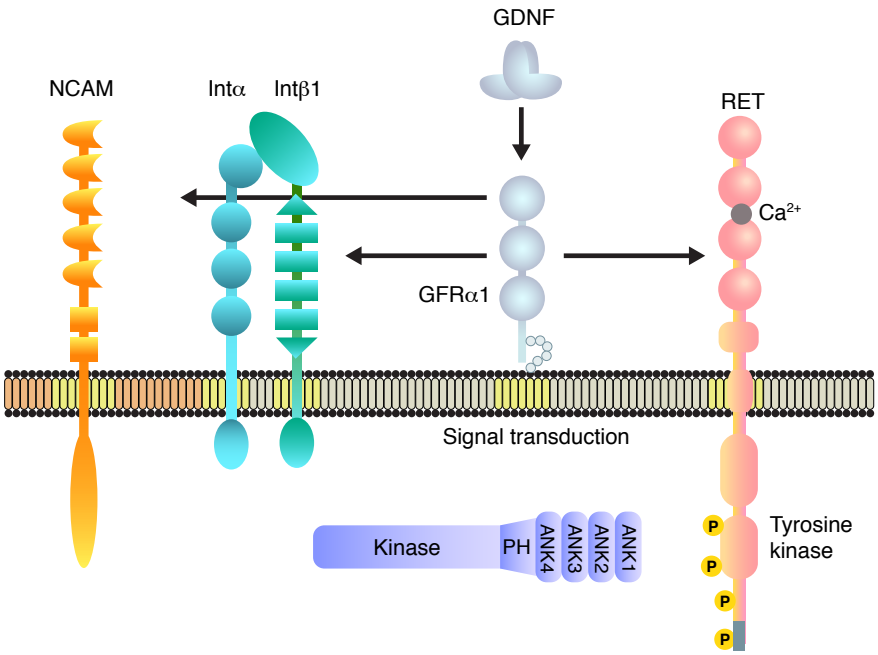

Figure 1. Glial cell line-derived neurotrophic factor (GDNF) is one out of four family members that can activate the canonical GDNF receptor Ret, a receptor tyrosine kinase, after binding to the high affinity GDNF co-receptor GFR α1. Besides Ret, GDNF has been suggested to be also able to stimulate alternative receptors such as the neuronal cell adhesion molecule (NCAM) and heterodimeric integrin complexes with Int β1. The integrin-linked kinase (ILK) might be involved to mediate GDNF events downstream of integrin β1 and the Ret receptor.

Functional specification of the different GDNF receptors in the dopaminergic system
Yen-Yen Chen, Bettina Spitzweck, Julia Lüdemann, Franziska Bursch, Richa Das, Miriam Ruf, Fenja Stolle, Merit Wildung, Ina Geedicke

The DA system in the brain is essential for mental and physical health since it controls many basic processes including movement, memory, motivation and emotion. GDNF has been shown to have many important functions in the DA system such as triggering survival, differentiation, dopamine production, protection from toxic insults and regeneration. Since the canonical GDNF receptor Ret is not mediating all GDNF function, we started to dissect in the mouse the critical *in vivo* functions of at least two alternative GDNF receptors during dopaminergic system development, adulthood, and aging namely the neural cell adhesion molecule (NCAM) and integrin β1. While we could show, that Ret is only essential to maintain substantia nigra (SN) DA neurons but not ventral tegmental (VTA) dopaminergic neurons, NCAM seems to be required during development of both DA neurons, and integrin β1 is important during development of the SN dopaminergic neurons and for maintenance of both DA cell populations. In addition, we found integrin-linked kinase (ILK) to mediate also a maintenance function for SN and VTA DA neurons most likely as a downstream signaling molecule below integrin β1 and Ret. This suggests a unique survival function for Ret, NCAM, integrins and ILK with respect to the time point and subgroup of midbrain dopaminergic neurons.

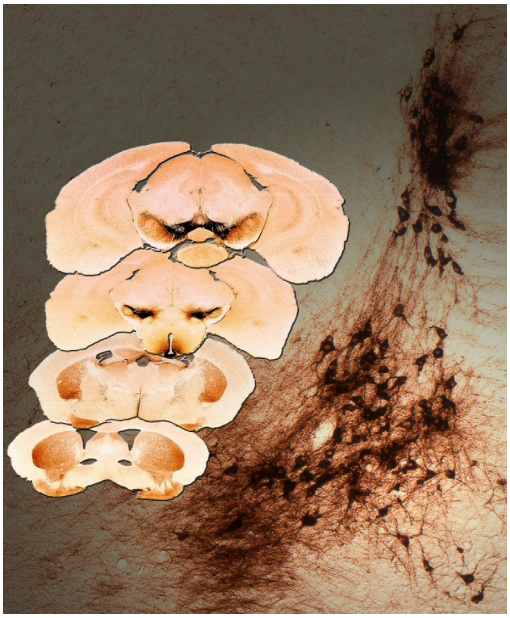

Figure 2. To visualize and quantify in coronal mouse brain sections midbrain dopaminergic neurons in the substantia nigra and the ventral tegmental area and their innervation in the striatum they were stained immunohistochemically with antibodies against the rate limiting enzyme of dopamine synthesis, tyrosine hydroxylase.

An efficient and versatile system for visualization and genetic modification of dopaminergic neurons in transgenic mice
Helia Aboutelabi, Karsten Tillack, Sneha Nemani, Fan Yan, Gustav Schneider

We generated tetracycline-dependent transactivator (tTA) and reverse tetracycline-dependent transactivator (tTA) mouse lines under control of the tyrosine hydroxylase promoter, TH-tTA and TH-rtTA, to visualize and genetically modify DA neurons. In combination with a tetracycline-responsive luciferase construct or Cre-activated mCherry expressing adeno-associated viruses (AAV-LSL-mCherry) we visualized the DA system in living mice progressively over time. TH-tTA/AAV-LSL-mCherry mice allowed us also to unbiasedly determine the absolute number of labeled dopaminergic neurons when using a glass brain-ultramicroscopy approach. Additionally, RGB labeling of single DA neurons was achieved by injecting AAVs expressing three different fluorescent colors. These experiments establish TH-tTA mice as a powerful tool to generate and monitor mouse models for DA system diseases.

Despite the positive effect of GDNF and its receptor Ret in different PD animal models on maintenance, protection and regeneration of DA neurons, clinical trials on PD patients with Ret ligands are inconclusive. In addition, recently the biological activity of Ret ligands in PD patients with α-synuclein accumulation was questioned since viral overexpression of α-synuclein in rats

resulted in Nurr-1 dependent down-regulation of Ret in DA neurons and rendered them unresponsive to GDNF. Crossing our TH-tTA mice with tetracycline-responsive Cre mice to delete the Ret receptor postnatally in DA neurons confirmed the important maintenance function of Ret in these neurons. Here we developed a more physiological α-synuclein transgenic PD mouse model with a slow progressive DA neuron degeneration and still unaltered Ret protein levels. Additional deletion of the Ret receptor in these α-synuclein PD mice resulted in a more severe DA neuron degeneration and even protein inclusions. These data support the idea of an *in vivo* neuroprotective function of GDNF/Ret signaling even in α-synuclein accumulating DA neurons and they underpin the importance to continue with clinical PD trials using Ret activators.

Parkin cooperates with GDNF/Ret signaling in dopaminergic neurons

Prakash Nidadavolu, Praveen Meka, Behnam Mohammadi, Mahmoud Bassal, Anil Annamneedi, Srinivas Kumar Ponna

Parkin and the GDNF receptor tyrosine kinase Ret have both been independently linked to DA neuron degeneration underlying PD.

In the present study, we demonstrate the genetic cross-talk of parkin and Ret in two different mouse models. Mice which have lost parkin and Ret show an accelerated dopaminergic cell and axonal loss compared to no alterations in parkin- and a moderate degeneration in Ret-deficient mice. Increased expression of parkin protects the dopaminergic system of aged Ret-deficient

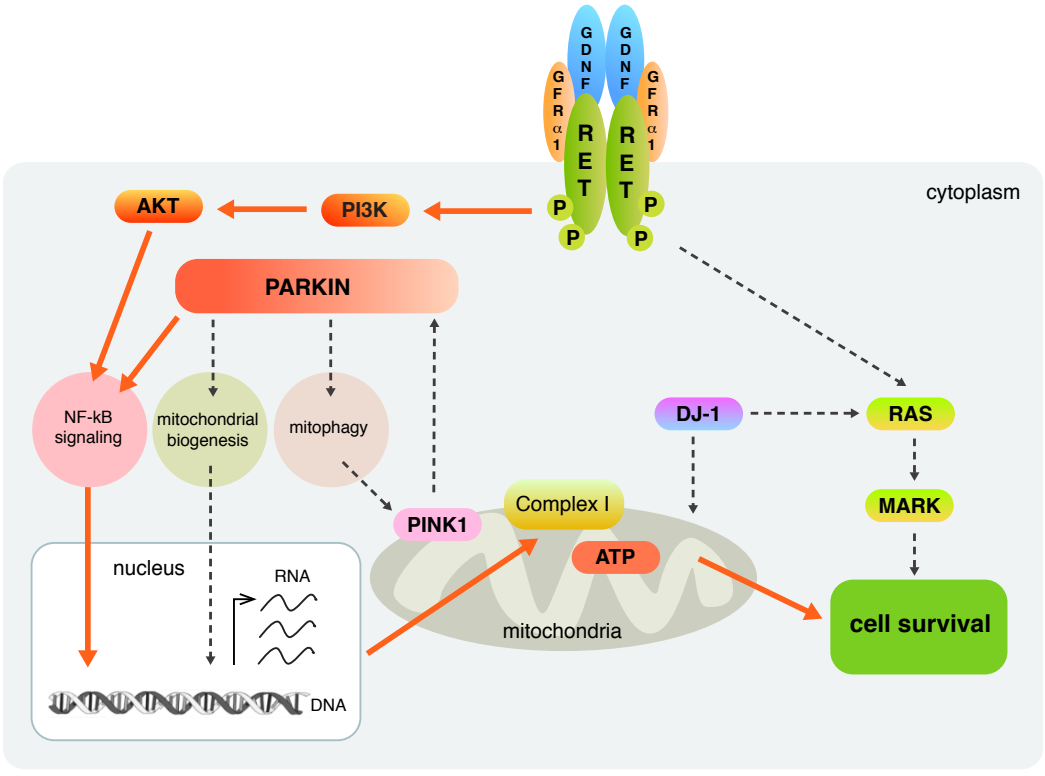

Figure 3. Converging cascades of Ret and parkin signaling to ensure mitochondrial integrity and substantia nigra dopaminergic neuron maintenance. Red arrows shows the new found activation of the NF-κB pathway through Ret via PI3K and Akt leading to stimulation of ATP synthesis through the mitochondrial complex I which enhances cell survival.

mice. Both the down-regulation of parkin and Ret leads to impaired mitochondrial function and morphology. We also show that parkin and GDNF/Ret can substitute for each other to ensure proper mitochondrial function by converging signaling cascades activating the nuclear factor 'kappa-light-chain-enhancer' of activated B-cells (NF-κB). Ret activates NF-κB through the phosphoinositid-3-kinase (PI3K) pathway. Taken together these observations reveal an essential *in vivo* survival function of parkin in close cross-talk with the Ret signaling cascade, converging on mitochondrial integrity control to properly maintain SNpc DA neurons and their innervation in the striatum.

In addition we have found further interactions between parkin and Ret signaling which we currently study in more detail. This confirms the tight interaction of parkin and Ret and their combined function at multiple sites in the cell.
The cross-talk of parkin and Ret enhances our understanding of the interplay in the protein network altered in PD and highlights new therapeutic targets and strategies to treat PD.

Visualization and genetic modifications of motoneurons and peripheral nerves
Melanie Richter

In motor neurons, Ret and its ligand GDNF can affect axon outgrowth, muscle innervation, survival and the identity of different motor neuron pools. We could show that Ret is also involved in axon guidance of motoneurons innervating the flexor muscles in the hindlimb. We helped to develop staining and analyzing techniques to visualize defects in motoneuron axons and peripheral nerves in 3D using ultramicroscopy. This technique helps to study axonal processes involved during axon injury, degeneration but also regeneration and might therefore help to develop novel therapies.

Future perspectives

Since funding of my research group at the ZMNH is only granted till beginning of 2016, we are now focusing on finishing up the projects and looking for new perspectives how and where to go on with our work. We would like to continue to study cell surface proteins in the dopaminergic system and in motoneurons and their function in disease related processes in more details. In addition we would like to explore the potentials of our new imaging tools.

Support

2010-2014 DFG Forschergruppe FOR885 Neuronal Protein Turnover DFG Kramer, FKZ KR3529/4-1
2010-2012 Landesexzellenz Cluster Neurodapt
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Selected Publications

Meka DP, Müller-Rischart AK, Nidadavolu P, Mohammadi B, Motori E, Ponna SK, Aboutalebi H, Bassal M, Annamneedi A, Finckh B, Miesbauer M, Rotermund N, Lohr C, Tatzelt J, Winklhofer KF, Kramer ER. (2015) Parkin cooperates with GDNF/Ret signaling to prevent dopaminergic neuron degeneration J.Clinical Invest. 125(5): *in press*

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Synaptic Protein Networks

(2001 – 2011)

Hans-Christian Kornau

Brain function largely relies on the connections between neurons through chemical synapses. Their number and strength is altered in a developmental and use-dependent manner. We are trying to get insight into the molecular processes underlying these changes. Dendritic spines, small protrusions from the dendritic shaft, contain the postsynaptic specialization of excitatory synapses with complex protein machineries that translate synaptic activity patterns into cellular responses. Starting from neurotransmitters receptors we investigate protein-protein interactions mediating synaptic signaling. We reconstitute signaling pathways of interest in heterologous cell systems and analyze the function of endogenous proteins in primary neuronal cultures. Recently, we examined two independent G-protein-mediated pathways triggered by γ-aminobutyric acid (GABA) or L-glutamate. We believe that insight into synaptic signal transduction will help us understand how synaptic connectivity is regulated and may offer new opportunities for targeted pharmacotherapeutic approaches.

Composition of $GABA_B$ receptor complexes

Tudor Bartoi, Janina Sülflow, Andrea Zaisser

$GABA_B$ receptors mediate metabotropic effects at both inhibitory and excitatory synapses of the central nervous system. They rely on a heterodimeric assembly of the two seven-transmembrane domain proteins $GABA_{B1}$ and $GABA_{B2}$. N-terminal isoforms of the ligand-binding subunit $GABA_{B1}$ underlie $GABA_B$ receptor subtypes that convey separate functions at pre- and postsynaptic sites and are thought to contain a differential set of associated proteins. We generated two lines of transgenic mice that express $GABA_{B1}$ subunits containing tandem affinity purification (TAP) tags (Bartoi et al., 2010). These additional subunits were incorporated into endogenous $GABA_B$ receptors, did not change their properties and allowed a straightforward purification of $GABA_B$ receptor subtypes from brain extracts. Mass spectrometry of the purified receptor complexes identified novel components including K channel tetramerization domain-containing protein 12 (KCTD12). Subsequent analyses revealed that KCTD12 interacts with the $GABA_B$ receptor via the $GABA_{B2}$ subunit and that it can augment the axonal plasma membrane expression of $GABA_{B2}$ in transfected neurons (Bartoi et al., 2010). Parallel work by others identified KCTD12 and additional KCTD family members as components of $GABA_B$ receptor complexes and showed that functional properties of the receptor are altered in a KCTD subtype-dependent manner (Schwenk et al. (2010) Nature 465, 231-235). Thus, the mice expressing TAP-tagged $GABA_{B1}$ allow elucidating components of native $GABA_B$ receptors.

Arf6 activation during long-term synaptic depression

Ralf Scholz, Janina Sülflow

AMPA-type glutamate receptor channels mediate fast excitatory neurotransmission in the brain. Their number in the postsynaptic membrane determines the strength of a synapse. Select synaptic activity patterns can lead to long-term potentiation or depression of the synaptic strength. Transport of AMPA receptors into or out of the postsynaptic specialization—either laterally within the membrane or by vesicular processes—has been identified as an underlying cellular mechanism. An important open question is how synaptic activity patterns are translated into alterations of AMPA receptor transport.

We identified an interaction between the principal AMPA receptor subunit GluA2 and BRAG2, a synapse-enriched guanine nucleotide exchange factor for the small GTPase Arf6 (Scholz et al., 2010). GTP-bound Arf6 promotes membrane lipid modifications at the plasma membrane that alter vesicular transport. The interaction between GluA2 and BRAG2 allowed the AMPA receptor to activate Arf6 upon ligand binding. However,

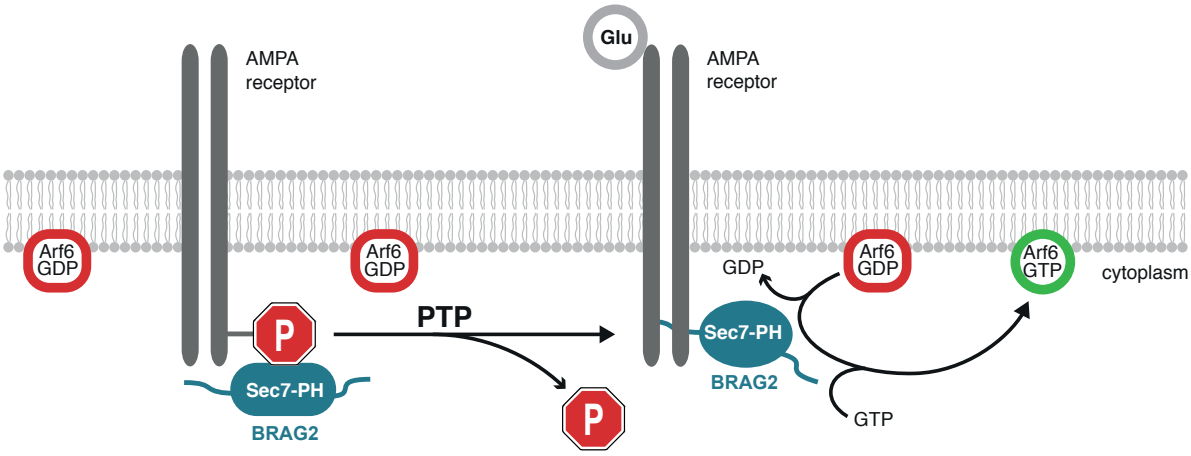

Figure 1. Model for the regulation of BRAG2-mediated Arf6 activation by the AMPA receptor subunit GluA2 (Scholz et al., 2010). Phosphorylation of tyrosine 876 in GluA2 prevents signaling between AMPA receptors and the guanine nucleotide exchange factor BRAG2. Tyrosine dephosphorylation and glutamate binding allow AMPA receptors to stimulate BRAG2-dependent activation of the small GTPase Arf6. Glu, L-glutamate. P, phosphate group. PTP, Protein tyrosine phosphatase. Sec7-PH, tandem of a Sec7 domain catalyzing GDP/GTP exchange on Arf GTPases and a pleckstrin homology domain.

the GluA2-BRAG2 signaling was blocked by phosphorylation of a specific tyrosine residue (Y876) that is part of the BRAG2 binding site in GluA2 (Fig. 1).

Activation of metabotropic glutamate receptors (mGluRs) in primary neuronal cultures reduced phosphorylation at Y876 in GluA2 and stimulated Arf6. Knockdown of BRAG2 prevented not only the mGluR effect on Arf6, but also an mGluR-induced loss of GluA2 from the cell surface. In collaboration with the group of Dr. Georg Köhr we then evaluated whether BRAG2 was involved in long-term depression (LTD) in the mouse hippocampus. Viral constructs targeting BRAG2 were injected into the hippocampal CA1 region of three-week-old mice and LTD of synapses between CA3 and CA1 neurons was assessed two weeks later. LTD could be induced in uninfected and control-infected CA1 neurons, but not in CA1 neurons lacking BRAG2. The loss of BRAG2 prevented LTD induced through mGluRs, but also LTD induced through NMDA-type glutamate receptors, suggesting that BRAG2-mediated Arf6 activation is critical for different forms of LTD (Scholz et al., 2010). Two additional members of the BRAG protein family accumulate at synapses and it will be interesting to get insight into their function and regulation.

Support

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Selected Publications

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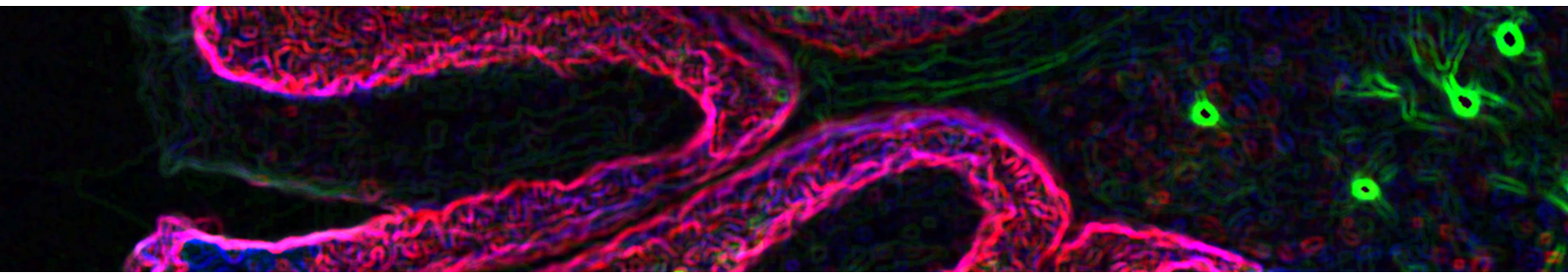
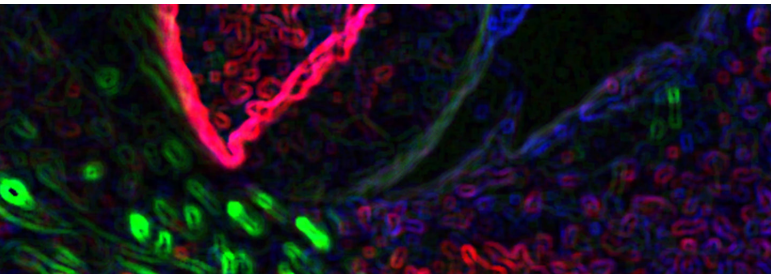
Ralf Scholz*
Technicians:
Janina Sülflow*
Andrea Zaisser*
Secretary: Renate Erb

* during part of the reported period





Research Reports of the ZMNH Service Groups

Bioanalytics

Sabine Hoffmeister-Ullerich

The service group Bioanalytics, former DNA-sequencing facility, was established in October 1995. Automated DNA-sequencing started with an ABI Prism 373 DNA sequencer which was replaced in succeeding steps by an ABI Prism 377 and a refurnished 3100 Avant running with four capillaries of 50 cm length. This was then finally upgraded in 2010 to the 3130 DNA analyzer which is running under Windows 7 since the beginning of 2014 up to now. Routinely the chain-termination method developed by Sanger and coworkers is performed using fluorescently labeled dideoxynucleotides (Big Dye). The ABI Genetic Analyzer enables a reading-length of about 700 - 1000 bases with a run time of 2 hours. From January 2010 until January 2015 approximately 40,000 sequence analyzes were handled. We also perform fragment analysis runs with the ABI 3130; TCR rearrangements for instance have been analyzed successfully (Yousef et al., 2012). Starting from 2009 our service group is also responsible for the two RT-PCR instruments, 7900 HT from Life technologies. We offer support in any respect of the usage of the instruments and, moreover, during the last 4 years together with the ZMNH SG Transgenic Mouse Facility we also developed several assays which are applicable for genotyping of genetically altered mice. Three of these assays are based on High Resolution Melting which was established by our group for use with our instruments. These assays are performed on demand.

Publications

Elakkary, S., Hoffmeister-Ullerich, S., Schulze, C., Seif, E., Sheta, A., Hering, S., Edelmann, J., and Augustin, C. (2014). Genetic polymorphisms of twelve X-STRs of the investigator Argus X-12 kit and additional six X-STR centromere region loci in an Egyptian population sample. Forensic Sci. Int. Genet. 11, 26-30.

Yousef, S., Planas, R., Chakroun, K., Hoffmeister-Ullerich, S., Binder, T.M.C., Eiermann, T.H., Martin, R., and Sospedra, M. (2012). TCR bias and HLA cross-restriction are strategies of human brain-infiltrating JC virus-specific CD4+ T cells during viral infection. J. Immunol. 189, 3618-3630.

Structure of the Group

Group leader: Sabine Hoffmeister-Ullerich
Technician: Marion Däumigen-Kullmann

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Morphology and Electron Microscopy

Michaela Schweizer

Our facility covers a large spectrum of LM and EM techniques with a major focus on sample preparation and characterisation of genetically engineered animals, including immuno-localisation of proteins, ultrastructural analysis, and data processing.

We advice interested scientists on morphological questions and teach and train researchers in the application of microscopy techniques. Finally, our facility introduces and establishes new techniques and guarantees efficient use of the respective equipment.

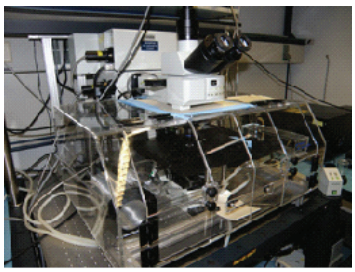
Offered services

- Performance of light- and electron microscopical investigations
- Advice and practical instruction in the application of histochemical techniques
- Instruction of researchers in operation of microscopes and accessories
- Introduction of useful new (immuno-) histochemical techniques and/or equipment

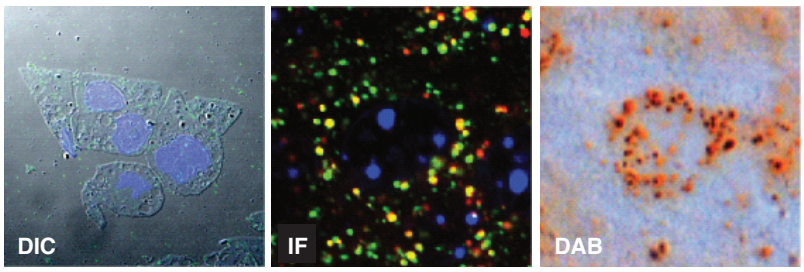
Techniques

- Morphological studies of many kinds of tissues with light-, confocal laser scanning-, or transmission electron microscopy
- Patho-histological analysis of the whole body of transgenic mice
- Histo- (cyto) chemical staining procedures
- Immunohisto- (cyto) chemistry
- Pre- and postembedded immunogold labelling techniques
- Correlated light-and electron microscopy (CLEM)

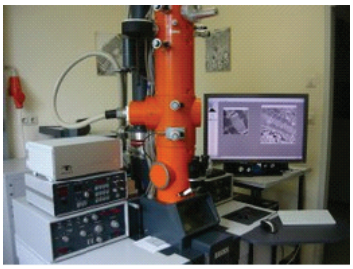
Using our equipment (LM, CLSM and TEM) and different protocols, we cover the whole range in light- to electron microscopical resolution. The localisation of lysosomal proteins like LAMP and Cathepsin D with DIC, fluorescent markers (IF), DAB and pre- or postembedding immunogold (IG) are shown using different imaging modalities.



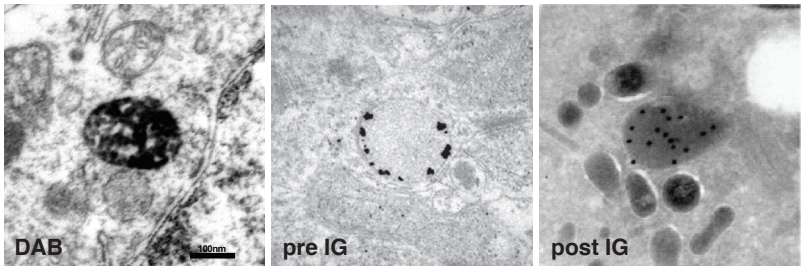
Scanning Confocal Microscope



mm – 0.2μm



Transmission Electron Microscope



100μm – 0.2 nm

We prepare cell and tissue samples for scientific histological and (immuno-) histochemical light and fluorescence microscopy. All preparation steps, (including fixation, sectioning with vibratome, cryotome or microtome, staining, mounting etc.) are performed by the group. The Morphology Unit has at its disposal both conventional and fluorescence microscopes (Zeiss Axiophot), as well as two confocal scanning laser microscopes in inverted (Leica SP2) and in upright configuration (Olympus Fluoview 1000).

We process cells and tissues for conventional transmission electron microscopy (Zeiss 902) and offer immunolocalisation of gene products applying pre- and postembedding protocols. We take care to preserve both antigenicity and structural integrity. All results are documented in high resolution digital images.

Selected Publications

Pirone, A., Kurt, S., Zuccotti, A., Rüttiger, L., Pilz, P., Brown, D.H., Franz, C., Schweizer, M., Rust, M.B., Rübsamen, R., Friauf, E., Knipper, M., and Engel, J. (2014). α2δ3 is essential for normal structure and function of auditory nerve synapses and is a novel candidate for auditory processing disorders. J. Neurosci. 34, 434-445.

Schweizer, M., Markmann, S., Braulke, T., and Kollmann, K. (2013). Ultrastructural analysis of neuronal and non-neuronal lysosomal storage in mucolipidosis type II knock-in mice. Ultrastruct. Pathol. 37, 366-372.

Marschner, K., Kollmann, K., Schweizer, M., Braulke, T., and Pohl, S. (2011). A key enzyme in the biogenesis of lysosomes is a protease that regulates cholesterol metabolism. Science 333, 87–90.

Weinert, S., Jabs, S., Supanchart, C., Schweizer, M., Gimber, N., Richter, M., Rademann, J., Stauber, T., Kornak, U., and Jentsch, T.J. (2010). Lysosomal Pathology and Osteopetrosis upon Loss of H+-Driven Lysosomal Cl- Accumulation. Science 328, 1401-1403.

Wartosch, L., Fuhrmann, J.C., Schweizer, M., Stauber, T., and Jentsch, T.J. (2009). Lysosomal degradation of endocytosed proteins depends on the chloride transport protein ClC-7. FASEB J. 23, 4056-4068.

Structure of the Group

Group leader: Michaela Schweizer
Technicians:
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Coworker: Susanne Fehr*

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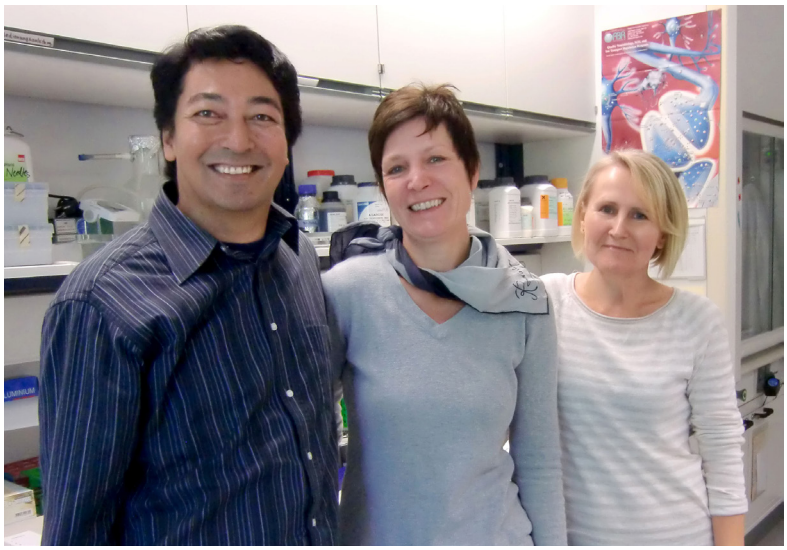

Systems Biology

Christian Schulze

The systems biology group supports researchers in the analysis and the interpretation of high-dimensional experimental data (genotyping, gene expression analysis, gene regulation, fluorescence-activated cell sorting). Here, extraction of statistically significant information is a crucial step in the description of the study subjects/ systems and the starting point for the generation of hypotheses aiming at an advanced understanding of systems behaviour. Another topic of the group has been the functional characterization of molecular interactions using a surface plasmon resonance (SPR) biosensor (Biacore 3000).

Following the establishment of the Institute for Synaptic Physiology, the group is now also actively working at the interface between data generation (two-photon microscopy, instrument control) and subsequent processing (image analysis). The newly developed add-on tool (FHImager) extends the range of applications of the standard operating system, making it more flexible and enabling a higher throughput.

Selected Publications

Rissiek, A., Schulze, C., Bacher, U., Schieferdecker, A., Thiele, B., Jacholkowski, A., Flammiger, A., Horn, C., Haag, F., Tiegs, G., Zirlik, K., Trepel, M., Tolosa, E., and Binder, M. (2014). Multidimensional scaling analysis identifies pathological and prognostically relevant profiles of circulating T-cells in chronic lymphocytic leukemia. Int. J. Cancer 135, 2370-2379.

Stürner, K.H., Borgmeyer, U., Schulze, C., Pless, O., and Martin, R. (2014). A multiple sclerosisassociated variant of CBLB links genetic risk with type I IFN function. J. Immunol. 193, 4439-4447.

Jäger, J., Schulze, C., Rösner, S., and Martin, R. (2013). IL7RA haplotype-associated alterations in cellular immune function and gene expression patterns in multiple sclerosis. Genes Immun. 14, 453-461.

Werner, S., Frey, S., Riethdorf, S., Schulze, C., Alawi, M., Kling, L., Vafaizadeh, V., Sauter, G., Terracciano, L., Schumacher, U., Pantel, K., and Assmann, V. (2013). Dual roles of the transcription factor grainyhead-like 2 (GRHL2) in breast cancer. J. Biol. Chem. 288, 22993-23008.

Sawcer, S., Hellenthal, G., Pirinen, M., Spencer, C.C.A., Patsopoulos, N.A., et al . (2011). Genetic risk and a primary role for cell-mediated immune mechanisms in multiple sclerosis. Nature 476, 214-219.

Structure of the Group

Group leader: Christian Schulze

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Transgenic Mouse Facility

Irm Hermans-Borgmeyer

The transgenic mouse facility supports scientists of the ZMNH and the UKE in all aspects of transgenic mouse production.

In 2012 new laboratory space was provided and two injection set ups, both equipped with Femto Jets and one with Laser and Piezo are available.

In the last years there was a shift from Pronucleus-injection and ES cell targeting experiments towards an increasing number of injections of ES cells provided by the IKMC and gene editing using designer nucleases.

Techniques:

- Pronuclear injection of DNA fragments and BACs, PACs
- Pronuclear/cytoplasmatic injection of RNA and RNA/DNA
- Injection of ES cells into blastocysts or eight cell stage embryos
- Cryopreservation of sperm and IVF
- Cryopreservation of embryos
- ES cell targeting and culture including C57-derived ES cells
- Embryo transfer of complex mouse lines
- Isolation and purification of DNA fragments for pronuclear injection
- Template preparation and in vitro transcription for injection of nucleases
- Genotyping via Southern blot analysis and PCR

Various colonies of mouse lines of general interest (driver and reporter lines) are maintained and some additional lines are cryopreserved and are thawed on demand.

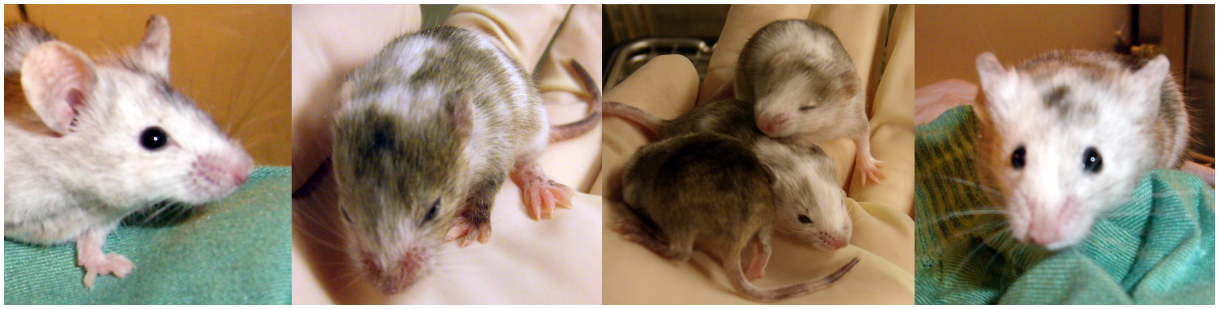
The collaboration with research group in the ZMNH and in the UKE resulted in 15 publications (see chapter Publications by ZMNH Scientists and Collaborators).

We offer training courses for animal care takers and interested scientists.

I.H.-B. is a member of the "Kommission für Tierversuche" according to § 15 of the "Tierschutzgesetz" and the "Tierschutzausschuss" of the UKE.

Selected Publications

Keller, J., Catala-Lehnen, P., Huebner, A.K., Jeschke, A., Heckt, T., Lueth, A., Krause, M., Koehne, T., Albers, J., Schulze, J., Schilling, S., Haberland, M., Denninger, H., Neven, M., Hermans-Borgmeyer, I., Streichert, T., Breer, S., Barvencik, F., Levkau, B., Rathkolb, B., Wolf, E., Calzada-Wack, J., Neff, F., Gailus-Durner, V., Fuchs, H., Angelis, M.H. de, Klutmann, S., Tsourdi, E., Hofbauer, L.C., Kleuser, B., Chun,



J., Schinke, T., and Amling, M. (2014). Calcitonin controls bone formation by inhibiting the release of sphingosine 1-phosphate from osteoclasts. Nat. Commun. 5, 5215.

Kumar, D., Freese, M., Drexler, D., Hermans-Borgmeyer, I., Marquardt, A., and Boehm, U. (2014). Murine Arcuate Nucleus Kisspeptin Neurons Communicate with GnRH Neurons In Utero. J. Neurosci. 34, 3756-3766.

Choe, C.-u., Nabuurs, C., Stockebrand, M.C., Neu, A., Nunes, P., Morellini, F., Sauter, K., Schillemeit, S., Hermans-Borgmeyer, I., Marescau, B., Heerschap, A., and Isbrandt, D. (2013). L-arginine:glycine amidinotransferase deficiency protects from metabolic syndrome. Hum. Mol. Genet. 22, 110-123.

Küspert, M., Weider, M., Müller, J., Hermans-Borgmeyer, I., Meijer, D., and Wegner, M. (2012). Desert hedgehog links transcription factor Sox10 to perineurial development. J. Neurosci. 32, 5472–5480.

Shin, J.D., Bossenz, M., Chung, Y., Ma, H., Byron, M., Taniguchi-Ishagaki, N., Zhu, X., Jiao, B., Hall, L.L., Green, M.R., Jones, S.N., Hermans-Borgmeyer, I., Lawrence, J.B., and Bach, I. (2010). Maternal Rnf12/RLIM is required for imprinted X-chromosome inactivation in mice. Nature 467, 977-981.

Structure of the Group

Group leader: I. Hermans-Borgmeyer
Technicians:
Sarah Homann
Peggy Putthoff *(since January 2014)*

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IT Service and Development

Hans-Martin Ziethen

The IT Service Group is responsible for maintaining the ZMNH intranet, internet and e-mail and for providing support to the center's around 900 network clients. Additionally, among our responsibilities we count data storage and protection and the operation of the central servers. Another part of our expertise is the integration and adaptation of the Open Source technology and the development of customized applications.

IT Infrastructure and Service

During the reported period, we have permanently enhanced our IT infrastructure. Due to the rapid increase in storage demand, computing power and rack space, a new server room had to be built. The new server room has been designed with the following requirements in mind: highest energy efficiency, highest reliability, maximum expandability and scalability. The server cooling supply is dimensioned in such a way that a thermal load of at least 20 to 25 kW can be discharged. The cold isle containment of the racks and the design of the liquid cooling packages allow us to run in the free cooling mode for about 95% of the year. To meet the dynamic demand for network services, scientific applications and data storage, a VMware cluster has been set up. The cluster contains a storage array of about 80 TB capacity, which can easily be extended to 360 TB. To accomplish the backup of such large amounts of data, our tape libraries have been upgraded to LTO6 and Backup-to-disk has been introduced. Our network has been completely redesigned to support Virtual Local Area Networks (VLANs) and a lot of security features like the 802.1x authentication. This measure significantly improves our network's performance and security. Moreover, most areas of the center have been equipped with WLAN.

Software Development

Apart from the enhancement and maintenance of the IT infrastructure, we are also active in the field of software development. This includes the development of tools and programs for the analysis, visualization and conversion of neurobiological data, the optimization and redesign of cluster algorithms and the application of mathematical algorithms to answer scientific questions. During the reported period we have developed several smaller tools, but we have also created a larger software application to predict peptide immunogenicity. The implemented algorithms combine the bioinformatics power of MHC binding prediction tools, pattern recognition algorithms and graphic structural modulation tools. At present, we are working on a software platform for automated cluster analysis of flow cytometry data.

Services We Offer

- Engineering of special server and hardware configurations
- Conceptual design, planning and implementation of network and server infrastructures
- Development of software in the field of scientific computing, numerical mathematics, image processing and web applications
- Programming in Java, C/C++, PHP, Perl, MATLAB, ImageJ and GNU R
- Procurement of hard- and software equipment
- Web design and development

Structure of the Group

Group leader: Hans-Martin Ziethen
IT specialists: Siegfried Koloschin
Stephan Rattai
MD students: Jan Meier (until 2013)
Apprentices:
Laura Glau *(mathematical technical software developer, until 2011)*
Patrick Glomb *(specialist systems, 2011)*
Kim Köpke *(specialist systems, until 2014)*
Lorentz Wellmer *(specialist systems, since 2014)*

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ZMNH Kollegium and WIKO

The Scientists' Conference ("Wissenschaftlerkonferenz", WIKO) of the ZMNH is the assembly of the scientific staff of the Center, including technical assistants, students, postdoctoral fellows and professors. The aim of the WIKO is to involve the scientific staff in internal decisions regarding the Center. To this aim, the WIKO meets at least every six months to discuss issues of general interest for the ZMNH. Every two years the WIKO elects one representative in the ZMNH council ("ZMNH Kollegium"). In taking his/her decisions, the representative is supported by a standing committee that meets before and after each meeting of the Council. The standing committee is generally composed by one member from each institute, one member from the research groups, one member from the service groups and one member of the technical assistants. The members of the standing committee are elected by the WIKO every two years. In this way, the scientific staff is democratically represented in the ZMNH Council. Within the Council, the WIKO representative has a vote and his/her opinions and suggestions count for final decisions taken by the Council. A recent example of how the scientific staff can influence the structure of the Center is the fact that the ZMNH PhD program was entirely initiated and organized by doctoral and postdoctoral fellows. Also the Ombudsperson for the ZMNH PhD program is elected during the plenary meeting of the WIKO. Finally, in addition to organizing plenary meetings, the WIKO is actively involved in the scientific organization of the yearly retreat of the ZMNH.

Representatives: Uwe Borgmeyer *(till 2014)*
Fabio Morellini *(since 2014)*
Deputy Representatives: Martin Kruse *(2009)*
Fabio Morellini *(2010-2013)*
Alexander Drakew *(since 2014)*
Standing committee: Uwe Borgmeyer, Achim Dahlmann, Torben Hausrat, Irm Hermans-Borgmeyer , Nina Hoyer, Benjamin Schattling, Simon Wiegert

ZMNH PhD Program

In 2013 a doctoral training program was established at the ZMNH with the aim to ensure that the graduate students gain a broad knowledge and key competencies and to assure the quality of dissertations. The program is designed to lead to the award of a doctoral degree in conformity with the regulations of the UKE or the MIN Faculty (Faculty of Mathematics, Informatics and Natural Sciences) of the Universität Hamburg. It is mandatory for all graduate students at the ZMNH if not being enrolled in any of the other programs offered in Hamburg.

A thesis committee consisting of a main supervisor and two mentors is monitoring the progress of the dissertation. Ombudspersons and two student representatives of the ZMNH PhD students are elected for the ZMNH PhD Program by the WIKO (Scientists' Conference) for a one year period.

To introduce the graduate students to putative external mentors a very successful "Meet the Mentors" presentation was organized in 2014. Scientists from various institutes of the UKE, the Biology/Biochemistry Department of the Universität Hamburg, the Heinrich Pette Institute and the Bernhard Nocht Institute for Tropical Medicine presented their research topics and are willing to support the PhD students as mentors.

In 2014 the first six graduate students presented their progress report to the mentors. The students as well as mentors and supervisors appreciated that the discussions were extremely fruitful and some of the students asked to give the next progress report already after six months.

In addition to the support and supervision of PhD students' thesis research, the attendance of the ZMNH-Seminars and of the lectures and research methods courses of the ZMNH-based Graduate Program in Molecular Biology (ASMB) is offered. Moreover, the PhD students may join the interdisciplinary, research methods and academic key skill courses of other PhD programs at the Faculty of Medicine, the MIN Faculty as well as the Career Center of the Universiät Hamburg.

Ombudsperson: Sabine Fleischer
(deputy: Irm Hermans-Borgmeyer)
Student representatives:
Urban Maier (2013-2015)
Elena Katic (2014-2015)
Chun Hu (2013-2014)

ZMNH-based ASMB Graduate Program in Molecular Biology

The ASMB (Aufbaustudium Molekularbiologie) was founded in 1986 by Professor Dr. G. Koch at the UKE and was then permanently established at the ZMNH to promote in a multi-disciplinary approach the skills for scientific thinking and working. Thus, it may represent the first graduate school at a German university. The ASMB presents molecular biology within a broader context of the basic sciences and biomedicine. Fundamental and clinical aspects are explored and integrated with relevant areas of other disciplines.

The ASMB is of particular value to those who plan a career in academic biomedical research or industry. It harnesses the high quality expertise existing within the biomedical sciences at the University of Hamburg.

The program is taught at the ZMNH in collaboration with the Faculty of Medicine. It is:

- Interdisciplinary
- Focused on research and
- Oriented towards practical aspects.

Students are expected to have a graduation in a physiological, biological or other natural science, or a medical qualification.

Academic content
The ASMB is a four-semester course and is taught entirely in English. In parallel to lectures, seminars and practical courses students have to perform a project study which can be done as part of a PhD/MD thesis or independent of that.

At the beginning of the first semester the students present in a short talk their research project. Lectures and seminars impart background and techniques in molecular biology dealing primarily with nucleic acids. The second semester focuses on cell biology and proteomics. At the end of the second and beginning of the third semester students are requested to give a progress report about their project study. The third semester covering neurobiology and immunology is taught in collaboration with the Department of Immunology, UKE and the Bernhard Nocht Institute for Tropical Medicine. Topics are presented primarily as "Fresh from the bench" lectures which give students the opportunity to discuss ongoing research projects with the lecturer and to develop ideas how to address scientific problems. In the fourth semester, mechanisms of inherited diseases are discussed. At the end of each semester two practical courses held in groups of not more than four students have to be successfully passed. At the end of the fourth semester students present the results of their project study and write a report in the style of a "letter to Nature". Successful students are awarded a certificate.

Representative of the ASMB:
Prof. Dietmar Kuhl *(since 2008)*

Lecturers from the ZMNH: Directors of the ZMNH institutes and co-workers

Heads of the ZMNH junior research groups and of the ZMNH service groups

Lecturers from other institutions
(regularly or sporadically):

Department of Immunology, UKE and Bernhard Nocht Institute for Tropical Medicine Hamburg:
Prof. Bernhard Fleischer,
PD Dr. Thomas Jacobs,
Prof. Friedrich Nolte
Dr. Anke Osterloh,
PD Dr. Eva Tolosa,
Prof. Klaus-Peter Wandinger

Department of Clinical Chemistry, UKE:
PD Dr. Friedrich Buck,
Dr. Benjamin Otto,
Prof. Thomas Streichert

Department of Experimental Pharmacology and Toxicology, UKE:
Prof. Thomas Eschenhagen,
Prof. Arne Hansen,
PD Dr. Torsten Christ

Department of Human Genetics, UKE:
PD Dr. Hans-Jürgen Kreienkamp

Department of Osteology and Biomechanics, UKE:
Prof. Thorsten Schinke,
Dr. Jean-Pierre David

Center for Oncology, Bone Marrow Transplantation Unit, UKE:
Prof. Boris Fehse,
Dr. Kerstin Cornils

Heinrich Pette Institute:
Prof. Adam Grundhoff

Central Services and Administration

Scientific Workshop

Torsten Renz and Fritz Kutschera

The scientific workshop has been of central importance for supporting and accelerating research at the ZMNH. Innovative scientific research often requires the use of specific equipment and instruments that are either not commercially available or not suited for the specific research purpose. To be able to develop and manufacture these instruments/devices and to meet the high quality and versatility demands, the scientific workshop is equipped with state-of-the-art mechanic precision devices. Our expertise acquired over many years allows the processing and use of almost any raw material, such as plastics, acryl, epoxy resin, wood, and metals. If no devices or instruments are available for a specific experiment, we often design, construct, manufacture and test new devices that are tailored to the needs specified by the scientists. Among these instruments are, for example, amplifiers, setup for running distance measurement, deep freezer for embryos, data loggers, pressure regulators, specific filling level indicators, gas sensor control devices, custom-made chambers for microscopic examination, step-down units for electrophysiological setups, or impulse generators, to name only a few.

The daily work of scientists in the fields of electrophysiology, molecular and cell biology is often made easier by our expertise and dedication to details that do make a difference. Examples here include the manufacturing or adaptation of specimen holders, electrical and mechanical adapters, special power supplies, electrophysiological measurement station, stereotactic equipment, optical devices, electrophoresis gel combs, etc. The workshop helps scientists to assemble and test scientific equipment, such as electrophysiological instruments which usually consist of several devices, or to eliminate interference and noise.

A wide range of behavioral experiments conducted in the ZMNH, mainly with mice, is made possible by the construction of test arenas and test devices (such as open field arenas, test chambers, mobile open field cabin, behavior setup for Drosophila, water maze components, whisker stimulation device) that are uniquely tailored to the experimental requirements. It is the ideal combination of scientific creativity and technical know-how that helps to develop and implement innovative experimental approaches. The close proximity of the laboratories to the workshop ensures effective communication and collaboration with the scientists. This smooth exchange of information and ideas is indispensable to the daily work of researchers and has resulted in numerous scientific publications over the last years.

The most important fields of work include:

- Development and construction of scientific instruments
- Configuration or adaptation of instruments and devices for specific scientific and experimental purposes
- Assembly of components for experimental setups, troubleshooting of mechanical or electronic systems
- Providing advice to scientists and administration of the ZMNH and planning in collaboration with them modifications of the structure of the building
- Advice, preparation and order processing of custom-made products according to models or drawings. Products made of metal, glass and plastic in high quantities and precision
- Overseeing an extensive range of equipment/systems and the building's infrastructure (except of the IT network)
- Coordination of the maintenance or repair of equipment/systems with the subsidiaries of the University Medical Center Eppendorf (KME/KFE) and coordination or conduct of important safety checks

Structure of the Group

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Technician: Fritz Kutschera

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ZMNH Library

Heiko Pump

The ZMNH library is a reference library with a special focus on molecular neurosciences. It comprises more than one thousand books. Access to e-journals and databases of the Hamburg University Library System is available via the campus network that offers numerous licensed journals in full text. The librarian's main task is to supply scientists with specialist literature and information.

The barrier-free library keeps five workplaces with computers including internet access. More information about the loan services, library regulations and contact details of the librarian Mr. Heiko Pump may be found on the ZMNH library's homepage:
http://www.zmnh.uni-hamburg.de/zmnh/library/library.html

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ZMNH Administration

Managing director: Katja Husen

Personnel manager: Rolf Maronde

Financial manager and coworkers:
Uwe Csizmadia
Herma Dörnbrack
Heike Pehlke

ZMNH Secretary: Eva-Maria Suciu

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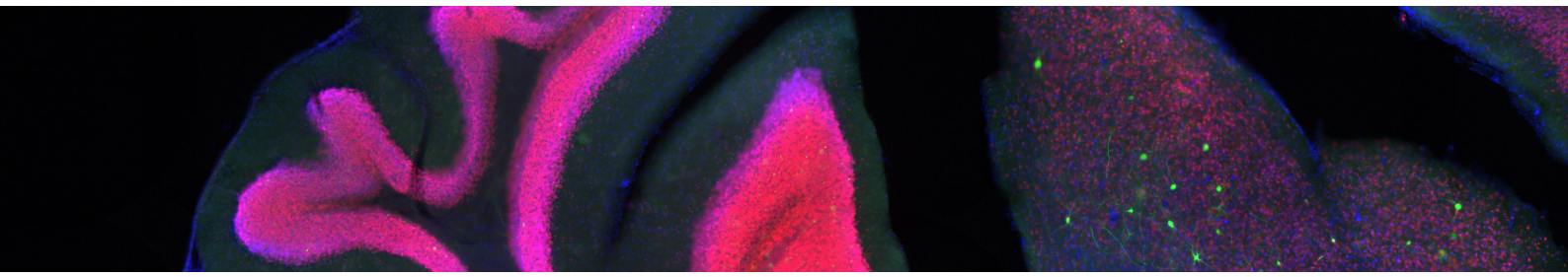

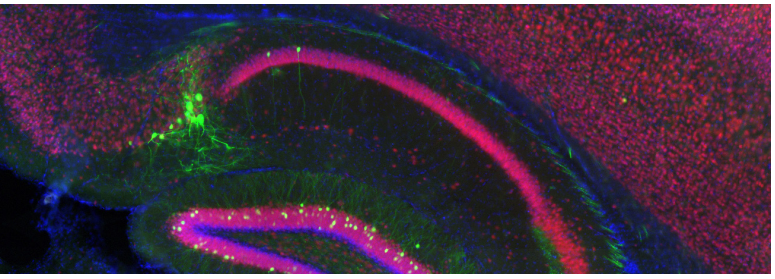

Publications by ZMNH Scientists and Collaborators

Institutes

Neuroimmunology and Multiple Sclerosis

Director: Manuel Friese *(since April 2014)*
Dietmar Kuhl *(provisional, May 2011 until March 2014)*
Roland Martin *(2006 until April 2011)*

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(established in October 2011)

Director: Thomas Oertner

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Structural Neurobiology

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Director: Michael Frotscher

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Molecular Neurogenetics

(established in February 2010)

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(2002 - 2010 Head of the ZMNH Research Group Protein Trafficking and Synapse Formation)

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Guest scientist group Jürgen R. Schwarz

(established in 2006)

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Molecular and Cellular Cognition

(established in October 2008)

Director: Dietmar Kuhl

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Biosynthesis of Neural Structures

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Director: Olaf Pongs *(1991 until September 2011)*

Provisional Director: Dietmar Kuhl
(October 2011 until December 2014)

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Emeritus Group Cell Biochemistry and Clinical Neurobiology

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Junior Research Groups

Behavioral Biology

(established in October 2013)

Head: Fabio Morellini

Hochgäfe, K., Sydow, A., Matenia, D., Cadinu, D., Könen, S., Petrova, O., Pickhardt, M., Goll, P., Morellini, F., Mandelkow, E., Mandelkow., E.M. (2015). Preventive methylene blue treatment preserves cognition in mice expressing full-length pro-aggregant human Tau. Acta Neuropathol. *(in press)*.

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Choe, C.-u., Nabuurs, C., Stockebrand, M.C., Neu, A., Nunes, P., Morellini, F., Sauter, K., Schillemeit, S., Hermans-Borgmeyer, I., Marescau, B., Heerschap, A., and Isbrandt, D. (2013). L-arginine:glycine amidinotransferase deficiency protects from metabolic syndrome. Hum. Mol. Genet. 22, 110-123.

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Neuronal Development

(established in July 2012)

Head: Froylan Calderon de Anda

Rudenko, A., Seo, J., Hu, J., Su, S.C., Calderon de Anda, F., Durak, O., Ericsson, M., Carlén, M., and Tsai, L.-H. (2015). Loss of cyclin-dependent kinase 5 from parvalbumin interneurons leads to hyperinhibition, decreased anxiety, and memory impairment. J. Neurosci. 35, 2372-2383.

Durak, O.*, Calderon de Anda, F.*, Singh, K.K., Leussis, M.P., Petryshen, T.L., Sklar, P., Tsai, L.H. (2014). Ankyrin-G regulates neurogenesis and Wnt signaling by altering the subcellular localization of ß-catenin. Mol. Psychiatry, 13 May 2014 **equal contribution*

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Neuronal Patterning and Connectivity

(established in February 2011)

Head: Peter Soba

Jiang, N., Soba, P,, Parker, E., Kim, C.C., Parrish, J.Z. (2014). The microRNA bantam regulates a developmental transition in epithelial cells that restricts sensory dendrite growth. Development 141, 2657-2668.

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Neuronal Translational Control

(established in May 2010)

Head: Kent Duncan

Schleich, S., Strassburger, K., Janiesch, P.C., Koledachkina, T., Miller, K.K., Haneke, K., Cheng, Y.-S., Küchler, K., Stoecklin, G., Duncan, K.E., and Teleman, A.A. (2014). DENR-MCT-1 promotes translation re-initiation downstream of uORFs to control tissue growth. Nature 512, 208-212.

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Experimental Neuropediatrics

(established in 2009, since 2014 guest group)

Head: Dirk Isbrandt *(2009-2013)*
Axel Neu *(since 2014)*

Mesirca, P., Alig, J., Torrente, A.G., Müller, J.C., Marger, L., Rollin, A., Marquilly, C., Vincent, A., Dubel, S., Bidaud, I., Fernandez, A., Seniuk, A., Engeland, B., Singh, J., Miquerol, L., Ehmke, H., Eschenhagen, T., Nargeot, J., Wickman, K., Isbrandt, D., and Mangoni, M.E. (2014). Cardiac arrhythmia induced by genetic silencing of 'funny' (f) channels is rescued by GIRK4 inactivation. Nat Commun 5, 4664.

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Developmental Neurophysiology

(established in October 2008, since Oct. 2013 guest group)

Head: Ileana Hanganu-Opatz

Andreou, C., Nolte, G., Leicht, G., Polomac, N., Hanganu-Opatz, I.L., Lambert, M., Engel, A.K., Mulert, C. (2015) Increased resting-state gamma-band connectivity in first-episode schizophrenia. Schizophrenia Bull Aug 28. pii: sbu121.

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Hanganu-Opatz, I.L., Rowland, B., Bieler, M., Sieben, K. Unraveling Cross-modal Development in Animals: Neural Substrate, Functional Coding and Behavioral Readout. Multisensory Res, *in press.*

Andreou, C., Faber, P.L., Leicht, G., Schoettle, D., Polomac, N., Hanganu-Opatz, I.L., Lehmann, D., and Mulert, C. (2014). Resting-state connectivity in the prodromal phase of schizophrenia: Insights from EEG microstates. Schizophr. Res. 152, 513-520.

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Brockmann, M.D., Kukovic, M., Schönfeld, M., Sedlacik, J., and Hanganu-Opatz, I.L. (2013). Hypoxia-Ischemia Disrupts Directed Interactions within Neonatal Prefrontal-Hippocampal Networks. PLoS ONE 8, e83074.

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Development and Maintenance of the Nervous System

(established in March 2008)

Head: Edgar Kramer

Meka DP, Müller-Rischart AK, Nidadavolu P, Mohammadi B, Motori E, Ponna SK, Aboutalebi H, Bassal M, Annamneedi A, Finckh B, Miesbauer M, Rotermund N, Lohr C, Tatzelt J, Winklhofer KF, Kramer ER. (2015) Parkin cooperates with GDNF/Ret signaling to prevent dopaminergic neuron degeneration J.Clinical Invest. 125(5): *in press*

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Synaptic Protein Networks

(2001 - 2011)

Head: Hans-Christian Kornau

Bartoi, T., Rigbolt, K. T. G., Du, D., Köhr, G., Blagoev, B., and Kornau, H.-C. (2010). $GABA_B$ receptor constituents revealed by tandem affinity purification from transgenic mice. J. Biol. Chem. 285, 20625–20633.

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Scientific Service Groups

Bioanalytics

Head: Sabine Hoffmeister-Ullerich

Elakkary, S., Hoffmeister-Ullerich, S., Schulze, C., Seif, E., Sheta, A., Hering, S., Edelmann, J., and Augustin, C. (2014). Genetic polymorphism of twelve X-STRs of the investigator Argus X-12 kit and additional six X-STR centromere region loci in an Egyptian population sample. Forensic Sci. Int. Genet. 11, 26-30.

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Morphology

Head: Michaela Schweizer

Damme, M., Brandenstein, L., Fehr, S., Jankowiak, W., Bartsch, U., Schweizer, M., Hermans-Borgmeyer, I., and Storch, S. (2014). Gene disruption of Mfsd8 in mice provides the first animal model for CLN7 disease. Neurobiol. Dis. 65, 12-24.

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Systems Biology

Head: Christian Schulze

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Transgenic Mouse Facility

Head: Irm Hermans-Borgmeyer

Damme, M., Brandenstein, L., Fehr, S., Jankowiak, W., Bartsch, U., Schweizer, M., Hermans-Borgmeyer, I., and Storch, S. (2014). Gene disruption of Mfsd8 in mice provides the first animal model for CLN7 disease. Neurobiol. Dis. 65, 12-24

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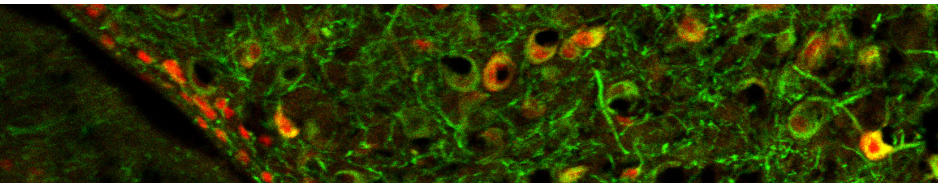


Theses and Dissertations

Theses and Dissertations

ZMNH Institutes

Neuroimmunology and Multiple Sclerosis

Director: Manuel Friese *(since April 2014)*
Dietmar Kuhl *(provisional, May 2011 until March 2014)*
Roland Martin *(2006 until April 2011)*

PhD Theses

Piedavent, Melanie (2013) Funktionelle Relevanz der genetischen Varianten von CD226 für die Pathogenese der Multiplen Sklerose. Fachbereich Biologie, Universität Hamburg

Schattling, Benjamin (2013) Mechanismen der axonalen Degeneration im Verlauf einer chronischen Entzündung des zentralen Nervensystems. Fachbereich Biologie, Universität Hamburg

Willing, Anne (2013) Phänotypische und funktionelle Charakterisierung IL-17 produzierender CD8+ T-Zellen in der Multiplen Sklerose. Fachbereich Biologie, Universität Hamburg

Yousef, Sara (2012) The role of CD4+ T cells in the pathogenesis of progressive multifocal leukoencephalopathy. Fachbereich Biologie, Universität Hamburg

Abramowski, Pierre (2012) Anti-inflammatory mechanisms of the alkyl-lysophospholipid edelfosine in the murine experimental autoimmune encephalomyelitis and in human cells. Fachbereich Biologie, Universität Hamburg

Jäger, Jan Christian (2012) Analyse der funktionellen Relevanz unterschiedlicher Interleukin-7 Rezeptor Haplotypen für die Ätiologie und Pathogenese der Multiplen Sklerose. Fachbereich Biologie, Universität Hamburg

Tillack, Kati (2011) The role of polymorphonuclear neutrophils in inflammatory conditions. Fakultät III – Prozesswissenschaften, Technische Universität Berlin

Steinbach, Karin (2011) Role of autoimmune inflammation and impaired neuroregeneration in the pathogenesis of experimental autoimmune encephalomyelitis. Fachbereich Biologie, Universität Hamburg

Brucklacher-Waldert, Verena (2010) Phenotypical and functional characterisation of Th17 cells in multiple sclerosis. Fachbereich Biologie, Universität Tübingen

Medical Doctoral Theses

Mohme, Malte (2014) Funktionelle Rolle des HLA-DR15 Haplotyps in der antologen T-Zell-Proliferation bei Multipler Sklerose. Universität Hamburg

Aly, Lilian Marlene (2013) Characterization of JC virus-specific CD4+ T cell epitopes in healthy individuals. Universität Hamburg

Gebauer, Nina (2013) Entwicklung eines Schulungsprogramms: Immuntherapien bei Multipler Sklerose (MS). Universität Hamburg

Nägele, Matthias (2013) Neutrophils in multiple sclerosis are characterized by a primed phenotype. Universität Hamburg

Lintze, Friederike (2013) Untersuchungen zur Heterogenität der Multiplen Sklerose: ein MRT-basierter Algorithmus mit OCT-Korrelation. Universität Hamburg

Erikli, Nilgün (2013) Verlaufsformen und Therapie der Multiplen Sklerose in Hamburg, eine zentrumsbasierte Erhebung. Universität Hamburg

Fischer, Korbinian (2013) Entwicklung und Evaluation eines Schulungsprogramms für neudiagnostizierte Multiple Sklerose-Patienten zu Diagnose, Prognose und Frühtherapie. Universität Hamburg

Krüger, Sunhild Schulamith (2013) Neuroendokrine und immunologische Faktoren der Depression bei Multipler Sklerose. Universität Hamburg

Quynh-Nhu Nguyen, Franziska (2013) Patienteninformation und Risikowahrnehmung zur Prognose und Therapie bei Multipler Sklerose: Evaluation eines OLAP-Instruments zur Prognose und Untersuchung zur Risikowahrnehmung bei Natalizumab. Universität Hamburg

Götze, Nele (2012) Pilotstudie zum Einsatz von Akzelerometrie mittels actibelt zum Mobilitätsmonitoring bei Patienten mit Multipler Sklerose. Universität Hamburg

Hajilou, Sahar (2012). Spezielle Verlaufsformen der Multiplen Sklerose in Hamburg, eine zentrumsbasierte Erhebung. Universität Hamburg

Mina, Ghoncheh (2012) Klassische Konditionierung mit Mitoxantron als Therapieansatz bei MS. Universität Hamburg

Neumann, Johannes (2012) Phänotyp. Charakterisierung des Immunzellfilrates in der experimentellen autoimmunen Enzephalomyelitis. Universität Hamburg

Böhm, Julia (2011) Wichtigkeit körperlicher Funktionen bei MS und Validierung der Coping-Self-Efficacy Scale. Universität Hamburg

Schömig, Sara (2011) Prognostische Bedeutung des Dex-CRH Test bei MS. Universität Hamburg

Stückrath, Eva-Maria Irma Gerda (2011) Rehabilitation bei Multipler Sklerose: Eine Bestandsaufnahme der MS. Gibt es krankheitsspezifische Konzepte und Standards? Universität Hamburg

Böhm, Julia (2010) Patientenselbstbewertung neurologischer Beeinträchtigungen bei Multipler Sklerose: Welche körperlichen Funktionen sind die wertvollsten?. Universität Hamburg

Schömig, Sara Maria (2010 Prognostische Bedeutung des Dexamethason-CRH-Suppressionstests bei Multipler Sklerose. Universität Hamburg

Alpen, Amelie (2009). Quantitative Verfahren zur Bestimmung des Gehvermögens bei Patienten mit Multipler Sklerose. Universität Hamburg

Hartmann, Sten (2009) Zytokine und Nervenwachstumsfaktoren unter 8-wöchigem Fitnesstraining. Universität Hamburg

Marquardt, Peter (2009) Erfassung von Ungewissheiten bei chronischen Krankheiten: Vergleich zweier Versionen des QUiCC-Fragebogens (Quality of Uncertainty in Chronic Conditions) angewandt bei Multiple Sklerose Patienten. Universität Hamburg

Nawrath, Lars (2009) Multiple sclerosis related Fatigue and the hypothalamic-pituitary-adrenal axis. Universität Hamburg

Schäffler, Nina (2009). Metanalyse von diagnost. Tests bei MS und Entwicklung eines evidenzbasierten Instruments „MS Verdacht was nun?“. Universität Hamburg

Solf, Kathrin (2009). Responsivität des HALEMS für Veränderungen. Universität Hamburg

Diploma Theses

Fischer, Anja (2011).Dysfunction in glucocorticoid regulation as a biomarker of multiple sclerosis-associated major depressive disorder. Fachbereich Psychologie, Universität Kiel.

Chakroun, Karima (2009). Neuroprotektive Eigenschaften von Hydroxytyrosol. Fachbereich Biologie, Universität Hamburg

Master Theses

Eggert, Britta Kristin (2012) Analysis of DNAM-1 Regulation in Human Lymphocytes. Faculty of Health and Medical Sciences, University of Copenhagen.

Synaptic Physiology
(established in October 2011)

Director: Thomas Oertner

PhD Theses

Udwari, Daniel (2014) A photoactivated adenylyl cyclase as an optogenetic tool to manipulate neuronal signaling and synaptic plasticity. Fachbereich Biologie, Universität Hamburg

Structural Neurobiology
(established in May 2011)

Director: Michael Frotscher

PhD Theses

Tippmann, Anja (2014) Die Rolle des Spine Apparates als Kalzium-Speicher während der synaptischen Transmission – Kombination von Zwei-Photonen Kalzium-Imaging mit Glutamat-Uncaging an individuellen Synapsen in organotypischen Schnittkulturen. Fachbereich Biologie, Universität Hamburg

Master Theses

Radziejewski, Johanna (2013) Role for Reelin in the positioning of dopaminergic neurons in the mesencephalon. Fachbereich Biologie, Universität Bremen

Molecular Neurogenetics
(established in February 2010)

Director: Matthias Kneussel
(2002 - 2010 Head of the ZMNH Research Group Protein Trafficking and Synapse Formation)

PhD Theses

Rathgeber, Louisa (2013) Analysis of activity-induced changes in the subcellular distribution of the postsynaptic scaffold protein gephyrin in cultured hippocampal neurons from Mus

musculus (Linnaeus, 1754). Fachbereich Biologie, Universität Hamburg

Dorthe Labonté (2012) Untersuchung der Funktion von TRIM3 in Mikrotubuli-assoziierten Transportprozessen im Nervensystem von Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Lee, Han Kyu (2011) Analysis oft he adaptor proteins, gephyrin and GRIP1, in KIF5-driven neuronal transport in Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Hausrat, Torben Johann (2010) Untersuchung der Funktion von Radixin bei der synaptischen und extrasynaptischen Lokalisation von GABAA Rezeptoren im Nervensystem von Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Heisler, Frank (2009). Untersuchung des Proteins Muskelin im Nervensystem von Mus musculus. Fachbereich Biologie, Universität Hamburg.

Schapitz, Inga (2009). Mikrotubuli-assoziierter Transport von postsynaptischen NLG1 in Rattus norvegicus (Berkenhout, 1769) und Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg.

Guest scientist group Jürgen R. Schwarz
(*established in 2006)*

Dinu, Crenguta Elena (2010) Erg K+ channels in mouse (Mus musculus (Linnaeus, 1758)) gonadotropes. Fachbereich Biologie, Universität Hamburg

Niculescu, Dragos (2010) Erg K+ current in immature Purkinje neurons of the mouse (Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Molecular and Cellular Cognition
(established in October 2008)

Director: Dietmar Kuhl

PhD Theses

Binkle, Lars (2014) Untersuchungen zur Rolle von Arc/Arg3.1 in synaptischer Plastizität und endosomaler Sortierung. Fachbereich Biologie, Universität Hamburg

Gruhlich, Jerome (2014) Untersuchungen zur Arc/Arg3.1-Expression nach N-Methyl-D-Aspartat-induzierter Langzeitdepression. Fachbereich Biologie, Universität Hamburg

Marquarding, Tiemo (2014) The role of Arc/Arg3.1 in functional and structural neuronal plasticity. Fachbereich Biologie, Chemie, Pharmazie, FU Berlin

Mensching. Daniel (2014) Investigation of activity dependent Arl5b mediated signaling in synaptic plasticity. Fachbereich Biologie, Universität Hamburg

Oetjen, Sandra (2014) Characterization of interactions and trafficking of the Neuronal Ceroid Lipofuscinosis protein CLN3. Fachbereich Biologie, Universität Hamburg

Ditzen, Doreen (2013) Funktionelle Analyse des Transports der Arg3.1/Arc-mRNA und der Regulation der Translation. Fachbereich Biologie, Chemie, Pharmazie, FU Berlin

Gutzmann, Jakob (2013) Characterization of Tmem128 – An activity regulated ER protein, interacting with the immediate early gene Arc/Arg3.1. Fachbereich Biologie, Chemie, Pharmazie, FU Berlin

Theden, Florian (2013) Etablierung eines Mausmodells zur Identifizierung Tinnitus-spezifischer Aktivierungsmuster nach Schalltrauma. Fachbereich Biologie, Universität Hamburg

Medical Doctoral Theses

Kläschen, Hanne (2013) The role of Arc/Arg3.1 in protein synthesis dependent and independent forms of synaptic plasticity. Universität Hamburg

Diploma Theses

Binkle, Lars (2010) Strukturelle und funktionelle Analysen des aktivitätsregulierten Gen 3.1. Fachbereich Biologie, Chemie, Pharmazie, FU Berlin

Master Theses

Herzet, Angie Mientje (2014) Analyse der funktionellen Rolle von Arg3.1/Arc im AMPA-Rezeptor-Trafficking in primären Neuronen der Maus. Fachbereich Biologie, Universität Hamburg

Rozewitz, Monika (2014) Charakterisierung der subzellulären Lokalisation und der Interaktionen des neuronalen Rezeptors SorLA. Fachbereich Biologie, Universität Hamburg

Bluhm, Björn (2013) Untersuchung zur intrazellulären Zielsteuerung des Amyloid-Precursor-Protein

bindenden Rezeptors SorCS1. Fachbereich Biologie, Universität Hamburg

Bachelor Theses

Himat, Zadat (2014) Biochemischer Nachweis neu synthetisierter Proteine durch Click-Chemie in hippocampalen Hirnschnitten von Arc/Arg3.1-Wildtyp- und Knockout-Mäusen. Department Biotechnologie, Hochschule für Angewandte Wissenschaften Hamburg

Biosynthesis of Neural Structures

(established in 1995, since 2011 Emeritus Group)

Head: Melitta Schachner Camartin

PhD Theses

Djogo, Nevena (2013). Functional interplay between extracellular matrix molecules and their cell surface receptors in regeneration of the murine central nervous system. Fachbereich Biologie, Universität Hamburg

Hoffmann, Kathrin (2013). Funktionelle Rolle des Prion Proteins bei der Regulation von Zelladhäsionsmolekül-assoziierten Transportsystemen unter physiologischen und pathophysiologischen Bedingungen. Fachbereich Biologie, Universität Hamburg

Lutz, David (2013). Functional characterization of novel proteolytic fragments of the cell adhesion molecule L1. Fachbereich Biologie, Universität Hamburg

Theis, Thomas (2013). Functional consequences of the interaction between the intracellular domain of the neural cell adhesion molecule NCAM and the transient receptor potential canonical (TRPC) channels. Fachbereich Biologie, Universität Hamburg

Knepper, Michael (2011) Klonierung, rekombinante Expression und Charakterisierung Kohlenhydrat-bindender Antikörper. Fachbereich Chemie, Universität Hamburg

Bian, Shan (2010) Effects of carbohydrate sulfotransferases CHST11 and CHST14 in the proliferation, differentiation and migration of neural stem cells in Mus musculus (Linnaeus, 1758). Fakultät für Biologie, Albert-Ludwigs-Universität Freiburg im Breisgau

Mishra, Bibhudatta (2010) Identification of novel polysialic acid interacting partners and functional relevance of their interaction for peripheral nerve regeneration after injury in Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Brandewiede, Jörg (2009) Ethological analysis of three mouse strains: senescence-accelerated P-8 mice, constitutive NCAM-deficient mice, and conditional NCAM-deficient mice. Fachbereich Biologie, Universität Münster

Cui, Yifang (2009) Functional effects of transplanted embryonic stem cell-derived neural aggregates overexpressing the neural cell adhesion molecule L1 in the MPTP model of Parkinson's disease and in a spinal cord injury model in Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Fellini, Laetitia (2009) Learning and memory processes in mice: A behavioral, molecular and pharmacological study in wild-type and transgenic animals. Fakultät für Biologie/Chemie, Universität Bremen

Figge, Carina (2009) Die Rolle Zytoskelett-assoziierter Proteine bei der L1-vermittelten Neuritogenese und dem Neuritenwachstum. Fachbereich Chemie, Universität Hamburg

Köhlitz, Isabel (2009) Rekombinante Expression, Reinigung und Charakterisierung der neuralen Zellerkennungsmoleküle P0 und L1. Mathematisch-Naturwissenschaftliche Fakultät, Ernst-Moritz-Arndt-Universität Greifswald

Lee, Hyun-Joon (2009) Alteration of the H-reflex after compression spinal cord injury in mice (Mus musculus, Linné 1758). Fachbereich Biologie, Universität Hamburg

Li, Shen (2009) The neural cell adhesion molecule associates with and signals through p21-activated kinase 1 to regulate neuronal growth cone morphology in mice (Mus musculus Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Mehanna, Ali (2009) Regeneration in peripheral and central nervous systems after injury and application of glycomimetics - Study in Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Novak, Daniel (2009) Untersuchungen zur Interaktion zwischen dem neuralen Zelladhäsionsmolekül NCAM und dem multiple PDZ-Domänen-enthaltenden Protein MUPP1 im Nervensystem der Maus. Fachbereich Biologie, Universität Hamburg

Ramser, Elisa (2009) Unraveling the interactions of 14-3-3 with the neuronal proteins L1 and alpha

II spectrin. Naturwissenschaftliche Fakultät, Universität Hannover

Schmid, Janinne-Sylvie (2009) Morphologische und funktionelle Analyse heterozygot L1 defizienter Mäuse (Mus musculus, Linné 1758). Fachbereich Biologie, Universität Hamburg

Tian, Nan (2009) CHL1 organizes ankyrin-B / ßII spectrin based cytoskeleton in developing neurons (Mus musculus L., 1758). Fachbereich Biologie, Universität Hamburg

Wang, Shiwei (2009) Synapsin I released via exosomes is an oligomannose bearing glycoprotein and an oligomannose binding lectin that promotes neurite outgrowth in Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg.

Xiao, Meifang (2009) Neural cell adhesion molecule NCAM modulates dopamine-related behavior by regulating dopamine D2 receptor internalization in mice (Mus musculus Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg.

Xu, Jinchong (2009) Murine neural stem cells engineered to express the neural adhesion molecule L1 under the control of the human GFAP promoter promote functional recovery after transplantation in a mouse spinal cord injury model in Mus musculus (Linneaus, 1758). Fachbereich Biologie, Universität Hamburg.

Medical Doctoral Theses

Bruhn, Sandra (2012) Identifizierung und funktionelle Charakterisierung von Glykomimetika für das Tn-Antigen. Universität Hamburg

Henze, Mervin (2012) Influence of brief electrical stimulation on peripheral nerve regeneration in heterozygous trkB deficient mice. Universität Hamburg

Lebsack, Helena (2012) Impact of T, B and NK lymphocyte deletion on the motor recovery after spinal cord compression in mice. Universität Hamburg

Laczynska, Ewa Helena (2011) Stereological analysis of the motor cortex and the hippocampus of dermatan-4O-sulfotransferase1 (chondroitin sulfotransferase 14) knockout mice. Universität Hamburg

Eberhardt, Kirsten Alexandra (2010) The influence of reduced expression of the TrkB receptor on peripheral nerve regeneration in mice. Universität Hamburg,

Fey, Andreas Raphael (2010) Single-frame motion analysis after sciatic nerve crush reveals late recovery in C57BL/6 mice and deficits in NCAM-deficient mice. Universität Hamburg

Wolters, Gerrit (2010) Untersuchungen neuer Funktionen der intrazellulären Domäne des Zelladhäsionsmoleküls L1 im Gehirn von Mus musculus (Linnaeus, 1758). Universität Hamburg

Acar, Ayse (2009). Stereological analyses of neurons and glial cells in the lesioned and unlesioned spinal cord of wild-type and CHL1-deficient mice. Universität Hamburg.

Horn, Lena (2009). Impacts of conditional ablation of the cell adhesion molecule CHL1, the close homologue of L1, on gross-anatomical variables and defined cell populations in forebrain regions of the mouse. Universität Hamburg.

Stein, Ian Belle (2009) Long-term effects of chronic unpredictable mild stress on cell adhesion molecules NCAM and L1 in the regulation of behaviour in C57BL/6J mice. Universität Hamburg

Siering, Janina (2009) Morphologische Untersuchungen des Kleinhirns und des visuellen Kortex im Hinblick auf die Hauptzellpopulationen in der erwachsenen CHL1-defizienten Maus. Universität Hamburg

Diploma Theses

Bostelmann, Daniela (2010) Klonierung und rekombinante Expression eines Kohlenhydrat-Antikörpers zur Identifizierung von Blutgruppen H-Typ-2-Antigen tragenden Proteinen im Mausgehirn. Hochschule für Angewandte Wissenschaften Hamburg

Sering, Janina (2010) Produktion eines anti-idiotypischenAntikörpers zur Identifizierung neuer HNK-1 Rezeptoren. Hochschule für Angewandte Wissenschaften Hamburg

Neural Signal Transduction

Director: Olaf Pongs *(1991until September 2011)*

Provisional Director: Dietmar Kuhl
(October 2011 until December 2014)

PhD Theses

Hermainski, Joanna (2012) Untersuchung zur Funktion des neuronalen Calciumsensors-1 an genetisch veränderten Mauslinien (Mus musculus(Linneaeus,1758). Fachbereich Biol-

ogie, Universität Hamburg

Prokofyev, Alexander V. (2012) Structural and functional investigation of the phospholipid modulation of KcsA K+ channel (K+ channel of Streptomyces lividans). Fachbereich Biologie, Universität Hamburg

Wu,Yu (2012) Ion channel TRPM4 activity and cardiac conduction disease. Fachbereich Chemie, Universität Hamburg

Mayer, Christian (2010) Signalwege von Galanin-like Peptid- und Kiss Neuronen bei der Integration von Metabolismus und Reproduktion. Fachbereich Biologie, Universität Hamburg

Sachse, Gregor (2010) Untersuchungen zur Regulation des Blutdrucks durch Ca2+-abhängige Kaliumkanäle großer Leitfähigkeit in der Maus (Mus musculus, LINNAEUS 1758). Fachbereich Biologie, Universität Hamburg

Velisetty, Phanindra (2010) Inactivation gating of potassium channels. Fachbereich Biologie, Universität Hamburg

Wen, Shuping (2010) Genetic labeling and functional characterization of GnRH target cells in the house mouse (Mus musculus (Linnaeus, 1758). Fachbereich Biologie, Universität Hamburg

Hornig, Sönke (2009) Inhibition spannungsabhängiger Kaliumkanäle aus Rattus norvegicus (John Berkenhout, 1769) durch einen allosterischen Effektor. Fachbereich Biologie, Universität Hamburg

Hubo, Simone (2009) Autoregulation von FoxP2: Identifizierung und Funktion von FoxP2 Bindungssequenzen im distalen FOXP2 Promotor. Fachbereich Chemie, Universität Hamburg

Kruse, Martin (2009) Regulation von kardialer KCNQ1- und TRPM4b-Ionenkanalaktivität. Fachbereich Chemie, Universität Hamburg

Ogrodowzcyk, Christoph (2009) Untersuchungen zur Rolle der Ionenkanal-Genexpression während der Aktivierung humaner T-Zellen. Fachbereich Biologie, Universität Hamburg

Stockebrand, Malte (2009) Interaktionspartner des Neuronalen Calcium-Sensors-1 (NCS-1) in der Maus (Mus musculus). Fachbereich Chemie, Universität Hamburg

Diploma Theses

Luther, Denise (2010) Charakterisierung eines durch einen Serotonin-Rezeptor aktivierbaren spannungsabhängigen Kaliumkanals und des zugehörigen Signalwegs durch elektrophysiologische Untersuchungen an primären Kardiomyozyten der maus (Mus musculus , Linneaus 1758). Fachbereich Biologie, Universität Hamburg

Bachelor Theses

Freese, Maria (2011) Untersuchungen zur Entstehung von Kisspeptinneuronen in weiblichen Mäuseembryos. Fachbereich Biologie, Universität Hamburg

Emeritus Group Cell Biochemistry and Clinical Neurobiology

(1985–2005 Institute for Cell Biochemistry and Clinical Neurobiology, since 2005 Emeritus Group)

Head: Dietmar Richter *(Founding Director of the ZMNH)*

Schütt, Janin (2009). Das Fragile X Syndrom: Molekulare Veränderungen der postsynaptischen Dichte in der Maus (Mus musculus L.). Fachbereich Biologie, Universität Hamburg

ZMNH Research Groups

Neuronal Translational Control

(established in May 2010)

Head: Kent Duncan

PhD Thesis

Miller, Katharine (2014) TDP-43 and Translational Regulation in Amyotrophic Lateral Sclerosis and Related Neurodegenerative Diseases. Fachbereich Biologie, Universität Hamburg

Experimental Neuropediatrics

(established in 2009, since 2014 guest group)

Head: Dirk Isbrandt *(2009-2013)*
Axel Neu *(since 2014)*

PhD Theses

Milkereit, Daniel (2013) Charakterisierung und pharmakologische Behandlung der M-Strom-defizienten Maus (Mus musculus, Linnaeus 1758)KCNQ2Nmf134 als Modell neonataler Epilepsien Fachbereich Biologie, Universität Hamburg

Alig, Jaqueline (2009) Rolle der cAMP-Sensitivität der HCN-Kanäle für die Herzfrequenzregulation in der adulten Maus (Mus musculus, Linnaeus 1758). Fachbereich Biologie, Universität Hamburg

Le, Quyen (2009). Untersuchungen der physiologischen Rolle von Kv7.2-Kanälen und der pathophysiologischen Mechanismen von Kv7.2-Kanaldefizienz im Gehirn der Maus (Mus musculus), Linnaeus 1758). Fachbereich Biologie, Universität Hamburg

Master Theses

Merseburg, Andrea (2011) Phenotypic characterization and pharmacological treatment of transgenic mice with conditional suppression of HCN channel activity in forebrain neurons. Fachbereich Biotechnologie, Hochschule Lausitz

Hinsch, Robin (2013) Entwicklung der neuronalen Netzwerkaktivität während der Hirnreifung der neonatalen Maus. Fachbereiche Chemie, Biologie und Medizin (Molecular Life Sciences), Universität Hamburg

Diploma Theses

Schlusche, Anna (2012) Morphologische Charakterisierung zweier H-Strom defizienter Mauslinien. Fachbereich Humanbiologie, Universität Marburg

Bachelor Theses

Szeremeta, Jannis (2013) Etablierung eines NO-Biotin-Switch-Assays zur Detektion der endogenen Protein-S-Nitrosylierung im Vorderhirngewebe kreatindefizienter Mäuse. Fachbereich Chemie, Universität Hamburg

Eichler, Ronny (2009). Pharmacological treatment of Kv7/M-current-deficient mice. Fachbereich Biotechnologie, Hochschule Lausitz

Developmental Neurophysiology

(established in October 2008, since Oct. 2013 guest group)

Head: Ileana Hanganu-Opatz

PhD Theses

Brockmann, Marco David (2013) Functional development of prefrontal-hippocampal networks under physiological conditions and after hypoxic-ischemic injury in the rat in vivo. Fachbereich Biologie, Universität Hamburg

Cichon, Nicole (2014) Netzwerkaktivität während der Entwicklung des Präfrontalen Kortex in der Ratte. Fachbereich Biologie, Universität Hamburg

Sieben, Kay (2014) Entwicklung multisensorischer Prozessierung im primären somatosensorischen Kortex der Ratte. Fachbereich Biologie, Universität Hamburg

Medical Doctoral Theses

Krüger, Hanna-Sophie (2013) Konsequenzen der frühen Läsion cortikaler und subcortikaler Kerne auf das Verhalten neugeborener und juveniler Ratten. Fachbereich Medizin, Universität Hamburg

Master Theses

Bitzenhofer , Sebastian (2013) Contribution of glutamatergic and GABAergic neurons to network oscillations in the prefrontal cortex of neonatal rat in vivo. Fachbereich Biologie, Universität Hamburg

Development and Maintenance of the Nervous System

(established in March 2008)

Head: Edgar Kramer

PhD Theses

Meka, V.V. Durga Praveen (2014) Parkin cooperates with GDNF/Ret signaling to prevent dopaminergic neurodegeneration in mice. Fachbereich Biologie, Universität Hamburg

Tillack, Karsten (2013) New approaches to genetically modify and visualize dopaminergic neurons in mice. Fachbereich Prozesswissenschaften, Technische Universität Berlin

Master Theses

Lüdemann, Julia Katrin (2014) Funktion der GDNF-Rezeptoren in dopaminergen Neuronen. Fachbereich Molecular Life Science, Universität zu Lübeck

Bursch, Franziska (2014) Funktion von NCAM in dopaminergen Neuronen. Fachbereich Molecular Life Sciences, Universität Hamburg

Das, Richa (2014) Functional specification of the alternative GDNF receptors in the dopaminergic system in vivo. Fachbereich Ingenieurwissenschaften, Martin-Luther-Universität Halle-Wittenberg

Ponna, Srinivas Kumar (2013) Effect of transgenic overexpression of human parkin on the degenerated nigrostriatal system of the aged Ret deficient mice. Fachbereich Ingenieurwissenschaften, Martin-Luther-Universität Halle-Wittenberg

Annamneedi, Anil (2012) Characterization of parkin overexpressing mice and their rescuing effect on the dopaminergic neurodegeneration phenotype of Ret deficient mice. Fachbereich Ingenieurwissenschaften, Martin-Luther-Universität Halle-Wittenberg

Yang, Fan (2012) Attempt to trace midbrain dopaminergic neurons. Fachbereich Molecular Biology, Universität Lund, Schweden

Bachelor Theses

Ruf, Miriam (2014) Characterization of a new rabbit monoclonal antibody against the receptor tyrosine kinase Ret for immunocytochemistry, immunohistochemistry for electron microscopy and for studying internalization of GDNF. Fachbereich Medical and Life Sciences, Hochschule Furtwangen University

Stolle, Fenja (2013) Aufreinigung und funktionelle Charakterisierung eines monoklonalen Kaninchenantikörpers gegen die Rezeptortyrosinkinase Ret. Fachbereich Biotechnologie, Hochschule Emden/Leer

Wildung, Merit (2013) Characterization of a new rabbit monoclonal antibody against the receptor tyrosine kinase Ret for Western blot, immunohistochemistry and immunocytochemistry. Fachbereich Biotechnologie, Hochschule Emden/Leer

Geedicke, Ina (2012) Histologische Untersuchung von Integrin β1 Knock-out Mäusen im dopaminergen System, Fachbereich Biotechnologie, Hochschule für Angewandte Wissenschaften Hamburg

Schneider, Gustav (2010) Funktioneller Test von induzierbaren genetischen Systemen in mäusen zur Darstellung von dopaminergen Neuronen. Fachbereich Biologie, Universität Hamburg

Synaptic Protein Networks

(2001 - 2011)

Head: Hans-Christian Kornau

PhD Theses

Scholz, Ralf (2010) Ein AMPA-Rezeptor-BRAG2-Komplex aktiviert Arf6 bei synaptischer Langzeitdepression in Rattus norvegicus (Berkenhout, 1769). Fachbereich Biologie, Universität Hamburg

Diploma Theses

Myllynen, Laura Johanna (2009). Analysis of SPAR proteins in neurons of rodents. Fachbereich Biologie, Universität Hamburg

Awards and Distinctions

Member of FENS-Kavli Network of Excellence 2014

Ileana L. Hanganu-Opatz, Developmental Neurophysiology

Jacob-Henle-Medaille der Medizinischen Fakultät der Georg-August-Universität Göttingen 2013

Michael Frotscher, Director of the ZMNH Institute for Structural Neurobiology

Wissenschaftspreis für Klinische Forschung der GlaxoSmithKline Stiftung 2013

Manuel Friese, Head of the ZMNH Research Group Neuroimmunology

Friedrich Linneweh Prize awarded by the German Society of Pediatrics and Adolescent Medicine 2013

Walid Fazeli, ZMNH Research Group Experimental Neuropediatrics

Dr.-Martini-Preis 2013

Chi-un Choe, ZMNH Research Group Experimental Neuropediatrics

Gebhard Koch-Promotionspreis für Zellbiochemie und Neurobiologie 2013

Benjamin Schattling, ZMNH Institute for Neuroimmunology and Clinical Multiple Sclerosis Research

Gebhard Koch-Promotionspreis für Zellbiochemie und Neurobiologie 2012

Pierre Abramowski, ZMNH Institute for Neuroimmunology and Clinical Multiple Sclerosis Research

Member of the National Academy of Sciences Leopoldina 2012

Melitta Schachner Camartin, Head of the ZMNH Emeritus Group and of the former ZMNH Institute Biosynthesis of Neural Structures

Fellow of the American Association for the Advancement of Science 2011

Michael Frotscher, Director of the ZMNH Institute for Structural Neurobiology

DFG Heisenberg Fellowship 2011

Hans-Christian Kornau, ZMNH Research Group Synaptic Protein Networks

Else Kröner Memorial Stipend from the Else Kröner-Fresenius-Stiftung 2011

Chi-un Choe, ZMNH Research Group Experimental Neuropediatrics

Gebhard Koch-Promotionspreis für Zellbiochemie und Neurobiologie 2010

Frank Heisler, ZMNH Institute for Molecular Neurogenetics

Heinrich Netheler-Promotionspreis für Molekularbiologie 2010

Ralf Scholz, ZMNH Research Group Synaptic Protein Networks

Short-Term Fellowship of the Chica and Heinz Schaller Foundation 2010

Hans-Christian Kornau, ZMNH Research Group Synaptic Protein Networks

InformatiCup of the German Informatics Society 2010

Laura Glau and Tom Kirchner, ZMNH IT Service Group

DFG Heisenberg Professorship 2009

Dirk Isbrandt, ZMNH Research Group Experimental Neuropediatrics

SRU (SRU Biosystems, Woburn, MA, USA) Grant Award 2009

Gabriele Loers, ZMNH Institute for Biosynthesis of Neural Structures together with Dr. Ralf Fliegert, Department of Biochemistry and Molecular Cell Biology, UKE

ZMNH Research Funding in the Framework of Coordinated Programmes

Start-up funding by the Hamburg Ministry of Science and Research (Behörde für Wissenschaft und Forschung der Freien und Hansestadt Hamburg)

Project: **"Molecular mechanisms of neuronal circuit modification: tuning synapses and networks for plasticity"**
Speaker: Matthias Kneussel, ZMNH, UKE
Funding period: 2014 – 2017
Participating scientists from the ZMNH:
Froylan Calderon de Anda, Research Group Neuronal Development
Kent Duncan, Research Group Neuronal Translational Control
Manuel Friese, Institute for Neuroimmunology and Multiple Sclerosis
Michael Frotscher, Institute for Structural Neurobiology
Christine Gee, Institute for Synaptic Physiology
Ileana Hanganu-Opatz, Research Group Developmental Neurophysiology
Fabio Morellini, Research Group Behavioral Biology
Thomas Oertner, Institute for Synaptic Physiology
Ora Ohana, Institute for Molecular and Cellular Cognition
Matthias Kneussel, Institute for Molecular Neurogenetics
Dietmar Kuhl, Institute for Molecular and Cellular Cognition
Thomas Oertner, Institute for Synaptic Physiology
Wolfgang Wagner, Institute for Molecular Neurogenetics

Priority Program SPP 1757 funded by the German Research Foundation (DFG)

Project: **"Functional specializations of neuroglia as critical determinants of brain activity"**
Coordinators: Christine R. Rose, University of Düsseldorf, Frank Kirchhoff, University of Saarland
Funding period: 2014 – 2017
Participating scientists from the ZMNH:
Bianka Brunne, Institute for Structural Neurobiology
Michael Frotscher, Institute for Structural Neurobiology

ERA-Net NEURON JTC2013 "European Research Projects on Mental Disorders" funded by the European Commission

Project: **"The role of TAO2 in brain connectivity and autism spectrum disorders"**
Coordinator: Froylan Calderon de Anda, ZMNH, UKE
Funding period: 2014 - 2017
Participating scientist from the ZMNH:
Froylan Calderon de Anda, Research Group Neuronal Development

Priority Program SPP 1665 funded by the German Research Foundation (DFG)

Project: **"Resolving and manipulating neuronal networks in the mammalian brain"**
Speaker: Ileana Hanganu-Opatz, ZMNH and Department of Neuroanatomy, UKE
Funding period: 2013 - 2019
Participating scientists from the ZMNH:
Ileana Hanganu-Opatz, Research Group Developmental Neurophysiology
Thomas Oertner, Institute for Synaptic Physiology

GRK 1459 funded by the DFG

Project: **"Sorting and interactions between proteins of subcellular compartments"**
Speaker: Thomas Braulke, Department of Paediatrics, UKE
Funding period: 2008 - 2017
Participating scientist from the ZMNH: Matthias Kneussel, Institute for Molecular Neurogenetics

Collaborative Research Centre SFB 936 funded by the DFG

Project: **"Multi-Site Communication in the Brain"**
Speaker: Andreas K. Engel, Department of Neurophysiology and Pathophysiology, UKE
Funding period: 2011 –2015
Participating scientists from the ZMNH:
Ileana Hanganu-Opatz, Research Group Developmental Neurophysiology
Dirk Isbrandt, Research Group Experimental Neuropediatrics
Fabio Morellini, Research Group Behavioral Biology
Dietmar Kuhl, Institute for Molecular and Cellular Cognition

Biopharma NEU2 consortium funded by the German Federal Ministry of Education and Research (BMBF) and a group of industry partners

Project: **"ASIC 1 inibitors for treatment of Multiple Sclerosis"**
Speaker: Timm Jessen, Bionamics GmbH
Applicant and donee: Merck KGaA, Evotec AG
Funding period: 2010 - 2015
Participating scientist from the ZMNH: Manuel Friese, Institute for Neuroimmunology and Multiple Sclerosis

Project : **"MRI and clinical platforms and validation study SABA"**
Applicants and donees: Roland Martin and Christoph Heesen, ZMNH, UKE
Funding period: 2009 - 2015
Participating scientists from the ZMNH: Roland Martin, Christoph Heesen, Institute for Neuroimmunology and Multiple Sclerosis

Project: **"Identification of small molecule inhibitors for CD25"**
Applicant and donee: Roland Martin, ZMNH, UKE
Funding period: 2010 - 2011
Participating scientist from the ZMNH: Roland Martin, Institute for Neuroimmunology and Multiple Sclerosis

Project: **"Treatment of Multiple Sclerosis with the monoclonal antibody BT-061"**
Applicant and donee: Biotest AG
Funding period: 2010 - 2015
Participating scientist from the ZMNH: Roland Martin, Institute for Neuroimmunology and Multiple Sclerosis

Project: **"Relapse escalation treatment trial in Optic Neuritis (RESCON)"**
Applicant and donee: Christoph Heesen, ZMNH, UKE
Funding period: 2012 - 2015
Participating scientist from the ZMNH: Christoph Heesen, Institute for Neuroimmunology and Multiple Sclerosis

Project: **"Connectivity Platform: New approaches for the analysis of networks and their function in Multiple Sclerosis"**
Applicants and donees: Christoph Heesen and Stefan Gold, ZMNH, UKE; Andreas Engel, Dept. of Neurophysiology and Pathophysiology, UKE
Funding period: 2012 - 2015
Participating scientists from the ZMNH: Christoph Heesen, Stefan Gold, Institute for Neuroimmunology and Multiple Sclerosis

Project: **"Nanodeliver: Optimization and clinical testing of a tolerance-inducing drug candidate for Multiple Sclerosis"**

Applicants and donees: Johannes Herkel, I. Department of Internal Medicine, UKE; Christoph Heesen, ZMNH, UKE
Funding period: 2013 - 2015
Participating scientist from the ZMNH: Christoph Heesen, Institute for Neuroimmunology and Multiple Sclerosis

Project: **"Identification of a small molecule inhibitor for ion channel TRPM4"**
Applicant and donee: Manuel Friese, ZMNH, UKE
Funding period: 2014 - 2016
Participating scientist from the ZMNH: Manuel Friese, Institute for Neuroimmunology and Multiple Sclerosis

Project: **"Evaluation of miRNAs and Metabolites – Discovery of Biomarkers for Neurodegeneration in Multiple Sclerosis"**
Applicanst and donees: Manuel Friese, ZMNH, UKE; Ole Pless, Fraunhofer Institute IME SP; Nikolaus Schauer, Metabolomic Discoveries GmbH
Funding period: 2014 - 2017
Participating scientist from the ZMNH: Manuel Friese, Institute for Neuroimmunology and Multiple Sclerosis

Collaborative research project funded by the German-Israeli Foundation for Scientific Research and Development (GIF)

Project: **"Synaptopodin, calcium stores and neuronal plasticity"**
Applicants: Menahem Segal, Weizmann Institute of Science, Rehovot, Israel
Michael Frotscher, ZMNH, UKE
Funding period: 2012 –2015
Participating scientist from the ZMNH: Michael Frotscher, Institute for Structural Neurobiology

Priority Programme SPP 1392 funded by the DFG

Project: **"Integrative analysis of olfaction"**
Speaker: Giovanni Galizia, Department of Biology, Universität Konstanz
Funding period: since 2009
Participating scientist from the ZMNH: Ulrich Boehm *(since 06/2012 at the Universitätsklinikum des Saarlandes, Homburg)*

International Collaboration in Education and Research with India funded by the BMBF

Project: **"Untersuchungen des therapeutischen Potentials von PSA-Mimetika in Zellkultur- und Mausmodellen von Verletzungen und Erkrankungen des zentralen Nervensystems"**
Funding period: 2011 - 2013
Participating scientist from the ZMNH: Melitta Schachner, Institute for Biosynthesis of Neural Structures

Research Unit 885 funded by the DFG

Project: **"Neuronal protein turnover"**
Speaker: Markus Glatzel, Department of Neuropathology, UKE
Matthias Kneussel, ZMNH, UKE
Funding period: 2009 - 2013
Participating scientists from the ZMNH: Matthias Kneussel, Institute for Molecular Neurogenetics
Edgar Kramer, Research Group Development and Maintenance of the Nervous System
Dietmar Kuhl, Institute for Molecular and Cellular Cognition
Olaf Pongs, Institute for Neural Signal Transduction

German-Israeli Project Cooperation, 11th Call funded by the DFG

Project: **"Structure and function of Kv7 potassium channel proteins: from X-ray crystal and MNR structures to human disease"**

Applicants: Bernard Attali, Department of Physiology and Pharmacology, Tel Aviv University, Israel
Olaf Pongs, ZMNH, UKE *(since 10/2011 at the Universität des Saarlandes, Homburg)*
Funding period: 2008 - 2012
Participating scientist from the ZMNH:
Olaf Pongs, Institute for Neural Signal Transduction

Research Unit 604 funded by the DFG

Project: **"Signaling pathways in the healthy and diseased heart"**

Speaker: Thomas Eschenhagen, Department of Experimental Pharmacology and Toxicology, UKE
Funding period: 2005 - 2012
Participating scientists from the ZMNH:
Olaf Pongs, Institute for Neural Signal Transduction
Dirk Isbrandt, Research Group Experimental Neuropediatrics

Hamburg Excellence Initiative 2009 funded by the Hamburg Ministry of Science and Research

Project: **"neuroadapt! Learning, memory, plasticity and related disorders - from molecules to behaviour"**

Speaker: Christian Büchel, Department of Systems Neuroscience, UKE
Funding period: 2009 - 2010
Participating scientists from the ZMNH:
Ileana Hanganu-Opatz, Research Group Developmental Neurophysiology
Dirk Isbrandt, Research Group Experimental Neuropediatrics
Matthias Kneussel, Institute for Molecular Neurogenetics
Edgar Kramer, Research Group Development and Maintenance of the Nervous System
Dietmar Kuhl, Institute for Molecular and Cellular Cognition

Project **"Nanotechnology in Medicine"**

Speaker: Horst Weller, Department of Physical Chemistry, University of Hamburg
Funding period: 2009 - 2010
Participating scientist from the ZMNH:
Melitta Schachner, Institute for Biosynthesis of Neural Structures

German-Polish Research Projects in Neuroscience funded by the BMBF and the Polish Ministry of Education and Research

Project **"Combinatorial therapeutic approaches targeting recognition molecules, neurotrophins and locomotor exercise for spinal cord repair"**

Funding period: 2007 - 2010
Participating scientist from the ZMNH:
Melitta Schachner, Institute for Biosynthesis of Neural Structures

Collaborative Research Centre SFB 470 funded by the DFG

Project: **"Glycostructures in Biological Systems – Synthesis and Function"**

Speaker: Joachim Thiem, Department of Chemistry, University of Hamburg
Funding period: 1997 – 2009
Participating scientists from the ZMNH:
Melitta Schachner and Dr. Ralf Kleene, Institute for Biosynth

Scientific Events

ZMNH Symposia and Conferences

10-13/05/14 34th Blankenese Conference
"Brain Complexity: From Synaptic Dynamics to Connectomics"

Wolf Singer, Frankfurt
"The dynamic brain: The role of temporal coordination in normal and disturbed cognitive functions"

Winfried Denk, Munich
"Towards a cellular-level connectome of the whole mouse brain"

Nahum Sonenberg, Montreal
"Translational control in ASD and FXS syndrome"

Eric Klann, New York
"Translational control in synaptic function, behavior, and neurodevelopmental disorders"

Kelsey Martin, Los Angeles
"Neuron-wide distribution of mRNAs combines with local translation to spatially restrict gene expression during synapse formation and synaptic plasticity"

Jernej Ule, London
"hiCLIP identifies the STAU1-target long-range RNA structures"

Peter Scheiffele, Basel
"Deconvolving molecular diversity and logic of polymorphic synaptic adhesion molecules"

Froylan Calderon de Anda, Hamburg
"Newly born neurons re-enter the cell cycle and acquire the fate of intermediate progenitors in response to calcium influx"

Frank, Bradke, Bonn
"Systemic administration of epothilone B promotes axon regeneration and functional recovery after spinal cord injury"

Carlos Dotti, Madrid
"Survival and plasticity in the aging brain"

Orly Reiner, Rehovot
"Unorthodox activities of components of the complement pathway in regulation of radial neuronal migration"

Herwig Baier, Munich
"Retinal ganglion cell diversity creates distinct visual processing channels that are tailored to behavioral output"

Madeline Lancaster, Vienna
"Developmental regulation of brain size in cerebral organoids"

Elly Nedivi, Boston
"In vivo imaging of coordinated excitatory and inhibitory synaptic dynamics on pyramidal cell dendrites"

Christian Rosenmund, Berlin
"Regulation of neurotransmitter release by *vesicular glutamate transporters"*

Rustem Khazipov, Marseille
"Early activity patterns in the developing sensory cortex"

Marie Carlen, Stockholm
"Cortical parvalbumin interneurons – connectivity and in vivo function"

Ileana Hanganu-Opatz, Hamburg
"Learning to remember: The ontogeny of cognitive processing within prefrontal-hippocampal networks"

George Dragoi, Boston
"Internal representation of spatial information by hippocampal cellular assemblies"

Marlene Bartos, Freiburg
"Truncated Disrupted in Schizophrenia 1 impairs fast-spiking interneurons and gamma oscillations"

Jochen Roeper, Frankfurt
"From simplicity to complexity – the emerging diversity of the dopamine midbrain system"

Peter Soba, Hamburg
"The receptor tyrosine kinase Ret: A novel regulator of dendrite morphogenesis and sensory neuron function"

Edgar Kramer, Hamburg
"Neurotrophic modulation of the dopaminergic system"

Johannes Gräff, Lausanne
"Learning to forget: Using epigenetic memory aids to attenuate remote fear memories"

Klaus-Arnim Nave, Göttingen
"Myelination and oligodendroglial support of axonal energy metabolism"

Christian Klämbt, Münster
"Glial specific gene functions affecting neuronal network function in Drosophila"

Cagla Ergoglu, Durham
"Control of synaptic connectivity by astrocytes"

Alfonso Araque, Minneapolis
"Tripartite synapses: Astrocyte regulation of synaptic transmission and plasticity"

Gero Miesenböck, Oxford
"Light Sleep"

Jürgen Haag, Munich
"A directional tuning map of Drosophila elementary motion detectors"

Chair: Wolfgang Meyerhof, Potsdam and Dietmar Richter
Organizers: Froylan Calderon de Anda, Kent Duncan, Michael Frotscher, Ileana Hangan-Opatz. Edgar Kramer and Peter Soba

10/03/14 Mini-Symposium *"Advances in Neural Plasticity"*

Ali Ertürk, Genentech, San Francisco, USA
"Sculpting the nervous system by local apoptosis and neuroinflammation"

Sally Marik, The Rockefeller University, New York, USA
"Adult experience-dependent plasticity involves axonal pruning via apoptotic pathways"

Keisuke Yonehara, Friedrich Miescher Institute, Basel
"Development and function of motion-sensitive circuits in the retina"

Chair: Dietmar Kuhl

06/09/13 Mini-Symposium *"Synapses and Circuits"* on the occasion of the 25th anniversary of the ZMNH

Rainer Friedrich, Basel
"Reverse engineering of neuronal circuits in the olfactory system"

Dominique Muller, Geneva
"Structural plasticity of hippocampal excitatory and inhibitory networks"

Thomas Oertner, ZMNH
"New optical methods to probe synaptic function and plasticity"

Chair: Dietmar Kuhl

13-15/09/12 ZMNH-Symposium *"From Adhesion to Regeneration and Learning"* in Honor of Melitta Schachner in the Erika-Haus at the UKE

Alexander Dityatev, Genoa
"Cell adhesion and extracellular matrix molecules in synaptic plasticity"

Andreas Faissner, Bochum
"Molecular structure and functions of priviledged neural extracellular matrix micro-environment"

Fritz G. Rathjen, Berlin
"Molecular analysis of neuronal connectivity"

Elisabeth Pollerberg, Heidelberg
"A look on and into the axonal growth cone"

Peter Jonas, Klosterneuburg, Austria
"Nanophysiology"

Helmut Kettenmann, Berlin
"Properties of microglial cells"

Jaqueline Trotter, Mainz
"Wrapping it up: Functions of NG2 glia in myelination and at synapses"

Frank Kirchhoff, Homburg/Saar
"Mechanisms of neuron-glia interactions in vivo"

Rudolf Martini, Würzburg
"Impact of immune cells in genetically caused diseases of the central and peripheral nervous system"

Klaus-Armin Nave, Göttingen
"New views on oligodendrocytes"

Dietmar Kuhl, Hamburg
"Learning about Arc/Arg3.1 and long-term memories"

Matthias Kneussel, Hamburg
"Transport and turnover of synaptic proteins underlying neuronal plasticity, learning and memory"
Dirk Isbrandt, Hamburg
"Treatment in critical period prevents epileptogenesis in Kv7 channelopathy"

Peter Soba, Hamburg
"Exploring the molecular control of sensory circuit development in Drosophila"

Ileana Hanganu-Opatz, Hamburg
"Rhythms of the neonatal brain in health and disease"

Manuel Friese, Hamburg
"Inflammation-induced neuroaxonal channelopathies in multiple sclerosis"

Edgar Kramer, Hamburg
"Development and maintenance functions of GDNF receptors in the nervous system"

Thomas Oertner, Hamburg
"The adaptive value of dendritic spines"

Kent Duncan, Hamburg
"Translational control of cell growth and neuronal development"

Froylan Calderon de Anda, Hamburg
"The role of TAO2 in brain development"

Michael Frotscher, Hamburg
"Structural plasticity of synapses revealed by high-pressure freezing"

Eckart Gundelfinger, Magdeburg
"Regulation of synaptic maturation and plasticity by cell adhesion molecules and the extracellular matrix"

Organizer: Michael Frotscher

28/04/11 – 01/05/11 Symposium *"New Frontiers in Ion Channel Physiology"* on the occasion of the 66th birthday of Olaf Pongs in the Elsa-Brandström-Haus Hamburg-Blankenese

Originally, the symposium was planned for 2010. However, the ash eruptions of the islandic volcano Eyjfjallajökull made air traffic at that time (April 18-21, 2010) impossible, therefore the symposium had to be postponed. Main financial support was provided by the Deutsche Forschungsgemeinschaft (Schw 292/15-1), Hertie-Stiftung, Fonds der Chemischen Industrie and Bayer.

Eduardo Perozo, Chicago
"Structural basis for activation and inactivation gating in KcsA"

Marc Baldus, Utrecht
"Structure-function studies in a potassium channel using solid-state NMR"

Ofer Yifrach, Beer Sheva
"Thermodynamic linkage, potassium channels gating and electrical signaling"

Bernd Fakler, Freiburg
"Nano-environments of ion channels analysed by high resolution proteomics"

John Adelman, Portland
"Physiology of SK channels in CA1 pyramidal neurons"

Hannah Monyer, Heidelberg
"GABAergic interneurons and their role in oscillatory activity, learning and memory"

Michel Lazdunski, Valbonne
"Sensing with ion channels"

Martin Stocker, London
"The odd ones: Modulatory potassium channel α-subunits"

David Brown, London
"M-type potassium channels and their regulation"

Bernardo Rudy, New York
"Potassium channel diversity and signal generation in CNS neurons"

Bernard Attali, Tel Aviv
"Gated motions and assembly modalities of voltage-gated Kv7 potassium channels"

Klaus Benndorf, Jena
"How subunits cooperate in HCN2 pacemaker channels"

Michael Häusser, London
"Dendritic computation"

Jan Storm, Oslo
"Ionic mechanisms of intrinsic theta resonance and filtering in hippocampal neurons: an interplay between K and Na 'threshold' channels"

Peter Jonas, Vienna
"The in and out of GABAergic interneurons"

Joel Nargeot, Montpellier
"NALCN: an atypical four domains ion channel"

Benjamin Kaupp, Bonn
"K+-selective CNG channels – at last"

Frances Ashcroft, Oxford
"ATP-sensitive potassium channels and diabetes: from molecule to malady"

Peter Seeburg, Heidelberg
"Ligand-gated ion channels"

Jochen Röper, Frankfurt/M.
"The role of neuronal K-ATP channels in the intact brain"

Thomas Jentsch, Berlin
"Ion homeostasis in endosomes and lysosomes: role for endocytosis and lysosomal degradation"

Walter Stühmer, Göttingen
"A potassium channel as tumor marker"

Steve Goldstein, Chicago
"Designer peptide neurotoxins: phage display using natural scaffolds"

Gregory Kaczorowski, Rahway
"Targeting ion channels to treat chronic pain"

Martin Biel, Munich
"TPCNs, a novel class of intracellular calcium channels"

Franz Hofmann, Munich
"L-type calcium channel and cardiac function"

Heinz Terlau, Kiel
"The exciting features of potassium channel pharmacology"

Marie F. Martin-Eauclaire, Marseille
"A scorpion toxin´s story"

Oliver Dolly, Dublin
"Positioning of α subunits in Kv1 channels: biophysical and pharmacological implications"

Maria Garcia, Rahway
"Discovery of novel, small molecule, ion channel modulators"

Organizers: Jürgen R. Schwarz (ZMNH) and Jens Rettig (Homburg)

14/04/11 ZMNH-Symposium *"Advances in Neural Plasticity"*

Ewa Bednarek, Friedrich Miescher Institute for Biomedical Research, Basel
"Impact of hippocampal structural rearrangements on learning and memory"

Froylan Calderon de Anda, Picower Institute for Learning and Memory, MIT
"Understanding neuronal differentiation in the neurocortex"

Lorenzo Cingolani, MRC Laboratory for Molecular Cell Biology, London, UK
"Homeostatic control of synaptic strength: a role for cell adhesion"

Christian Wozny, MRC Laboratory of Molecular Biology, Cambridge, UK
"Interneurons in neocortical microcircuits"

Chair: Dietmar Kuhl

15/02/10 ZMNH-Symposium *"Trends in Molecular Neurobiology"*

Kent Duncan, EMBL Heidelberg
"Mechanistic insights into control of mRNA translation by RNA-binding proteins"

Wulf Haubensak, California Institute of Technology Pasadena, CA
"Fear control by inhibitory gating in the amygdala"

Jinhyun Kim, Howard Hughes Medical Institute Ashburn, VA
"Visualization of synaptic molecular dynamics and neuronal circuits"

Martin K. Schwarz, MPI for Medical Research Heidelberg
"Gamma-Protocadherins: modulators of adult neurogenesis"

Peter Šoba, Howard Hughes Medical Institute San Francisco, CA
"Molecular mechanisms of dendrite patterning and circuit formation"

Wolfdieter Springer, Hertie Institute for Clinical Brain Research Tübingen
"Parkinson's disease - Linking ubiquitin to damaged mitochondria for selective autophagy"

Deepak Prakash Srivastava, Northwestern University Chicago
"Control of synaptic structural plasticity in neural circuits by neurosteroids"

Chair: Dietmar Kuhl

2-13/11/10 Symposium of the Institute for Neuroimmunology and Multiple Sclerosis Research *"Mechanisms of autoimmune diseases"*

Federica Sallustro, Bellinzona
"Characterizing the human immune system"

Andreas Radbruch, Berlin
"Autoantibodies and immunotherapy"

Michael Hertl, Marburg
"Autoimmune bullous skin disorders"

Frank Nestle, London
"Psoriasis"
Lucienne Chatenoud, Paris
"Diabetes mellitus type I"

Markus F. Neurath, Erlangen
"Inflammatory bowel diseases"

Ludvig Sollid, Oslo
"Celiac disease"

Roland Martin, Hamburg
"Multiple sclerosis"

Falk Hiepe, Berlin
"Systemic lupus erythematodes"

Organizers: Roland Martin and Manuel Friese

26-27/06/09 Symposium of the Institute for Neuroimmunology and Multiple Sclerosis Research *"Regeneration and Rehabilitation in MS"*

Nicole Schaeren-Wiemers, Basel
"Neuroprotective mechanisms in early demyelinating lesions of MS"

Martin E. Schwab, Zürich
"Overcoming negative signals for CNS regeneration"

Hannelore Ehrenreich, Göttingen
"Studies on neuroprotection – epo as a candidate?"

Raju Kapoor, London
"Neuroprotective approaches in MS – lamotrigine?"

Kirsten Hötting, Hamburg
"Exercise and the brain – human perspective"

Anders Romberg, Masku
"Exercise training in MS – what's the evidence and where to go?"

Stefano Pluchino, Milan
"Stem cells for regeneration"
Matilde Inglese, New York
"Imaging regeneration in vivo"

Maria Pia Amato, Florence
"Cognitive dysfunceion in MS – measurement and treatment"

Allesandra Solari, Milan
"Education as disease modifying intervention"

Thomas Henze, Nittenau
"Rehabilitation in MS – which approach is relevant? which trials are needed? "
(moderated round-table)

Organizers: Roland Martin and Christoph Heesen

ZMNH Seminars

08/12/14 Manuela Simonetti, Dept. of Molecular Pharmacology, University Heidelberg
"Wnt signaling in pain sensing neurons"

05/12/14 Stephan Kröger, Physiological Institute, LMU München
"Synapse formation in developing murine muscle spindle"

06/11/14 Casper Hoogenraad, Dept. of Biology, Utrecht University
"Intracellular protein trafficking underlying neuronal development and function"

30/10/14 Craig C. Garner, Nancy Pritzker Laboratory, Stanford, CA, USA
"Molecular mechanisms regulating presynaptic autophagy"

01/09/14 Fritjof Helmchen, Brain Research Institute, University of Zurich
"In vivo calcium imaging of behavior-related neocortical dynamics"

26/08/14 Sven Loebrich, The Picower Institute for Learning and Memory, MIT, Cambridge, MA USA
"CPG2 physically links glutamate receptor endocytosis to the F-actin cytoskeleton"

21/07/14 Alberto Cruz-Martin, University of California, San Diego (USCD) , USA
"From retina to cortex: dissecting visual circuits involved in the detection of directional motion"

02/07/14 Ulrich Dodt, Center for Brain Research, Vienna
"Ultramicroscopy of cleared brains, embryos and tumors"

19/06/14 Christine M. Gall, University of California, Irvine, USA
"Modulators and the spine cytoskeleton: contributions to memory stabilization and a strategy for treating intellectual disability"

12/06/14 Benjamin Cooper and Nils Brose, MPI for Experimental Medicine, Göttingen
"Molecular and morphological correlates of synaptic vesicles priming in neurosecretory cells"

09/05/14 Jay Z. Parrish, University of Washington, Seattle, USA
"Growth control of dendrites"

05/05/14 Steffen B. Wolff, Friedrich Miescher Institute, Basel
"Bidirectional control of fear learning by amygdala interneurons"

31/03/14 Robert Nitsch, Johannes Vogt, Institut für Mikroskopische Anatomie und Neurobiologie, Universität Mainz
"Bioactive lipid signaling at central synapses: a role for cortical information processing"

27/03/14 Iris Salecker, MRC, National Institute for Medical Research, London
"Astrocyte-like glia and Drosophila visual circuit assembly"

20/03/14 Paul Rhodes, Standford University / Evolved Machines Inc., CA, USA
"The synthesis of artificial neural circuitry"

18/03/14 Alexander Gottschalk, Institute of Biochemistry, Goethe University Frankfurt am Main
"Optogenetic analyses of molecules, neurons, networks and behavior in Caenorhabditis elegans"

06/03/14 Bernhard Lüscher, Department of Biology, Pennsylvania State University, USA
"Homeostatic control of depressive and antidepressive brain states"

28/02/14 Mathias Wernet, Department of Neurobiology, Stanford University, CA, USA
"Genetic dissection of visual circuitry in Drosophila"

27/02/14 Robin Wagener, Jochen Staiger, Institute for Neuroanatomy, Göttingen University
"The neocortex of the reeler mouse - Variable cortical phenotypes question the model of a uniform reelin function"

06/02/14 Jan Pielage, Friedrich Miescher Institute for Biomedical Research, Basel
"Molecular mechanisms controlling synapse formation and stability"

27/01/14 Hannelore Ehrenreich, Max-Planck-Institut für Experimentelle Medizin, Göttingen
"Shifting paradigms in neuropsychiatry: The search for biological subgroups of mental diseases"

12/12/13 Benjamin Altenhein, Institut für Genetik, Universität Mainz
"The glial side of life: development and function of glial cells in Drosophila"

03/12/13 Manfred W. Kilimann, Dept. of Otolaryngology, Göttingen University
"BEACH domain proteins as a novel molecular principle in subcellular protein traffic and human diseases"

21/11/13 Andreas Kottmann, The Sophie Davis School of Biomedical Education, City University of New York
"Expanding Spemann's organizer principle to reinforcement learning: The functioins of the morphogen Sonic Hedgehog"

21/11/13 Alexander Schulz, Leibniz Institut für Altersforschung, Jena
"Exploring the pathogenesis of neuropathy in patients with neurofibromatosis type 2 (NF2)"

14/11/13 Oliver Stork, Dept. of Genetics & Molecular Neurobiology, Universität Magdeburg
"Molecular mechanisms of fear memory formation: GABAergic processes and their relavance for posttraumatic stress disorder"

12/11/13 Michael R. Kreutz, Leibniz Institute for Neurobiology Magdeburg
"When synaptic proteins meet the genome - synapse-to-nucleus communication via protein messenger"

31/10/13 Eckard Friauf, Dept. of Biology, Universität Kaiserslautern
"Synaptic inhibition - in the auditory system"

15/10/13 Katrin Willig, Max Planck Institute for Biophysical Chemistry Göttingen
"STED nanoscopy of the living mouse brain"

26/09/13 Cliff Abraham, Brain Health Research Centre, University of Otago, New Zealand
"Metaplasticity: shaping the future of synaptic plasticity"

20/09/13 Marina Mikhaylova, Faculty of Science, Utrecht University
"Extending the molecular toolbox to study polarized protein transport in neurons"

18/07/13 Frank Bradke, DZNE - German Center for Neurodegenerative Diseases
"Cytoskeletal mechanisms of axon growth and regeneration"

15/07/13 Tallie Z. Baram, MD, PhD, Depts. Pediatrics, Neurology & Anatomy/ Neurobiology, University of California/Irvine, USA
"Modern-life stress and your synapses: novel molecules and mechanisms"

13/06/13 Hermann Aberle, Dept. Functional Cell Morphology, University of Düsseldorf
"Motor axon guidance in Drosophila"

06/06/13 Udo Bartsch, University Medical Center Hamburg-Eppendorf
"Photoreceptor replacement and neural stem cell-based neuroprotection in mouse models of degenerative retinal disorders"

14/03/13 Dragos Niculescu, Netherlands Institute for Neuroscience Amsterdam
"BDNF-triggered synaptic activity changes in the developing hippocampus"

08/03/13 Ted Abel, University of Pennsylvania, USA
"Epigenetic Mechanisms of Memory Storage"

22/11/12 Joachim Lübke, Institute for Neuroscience and Medicine, Forschungszentrum Jülich
"Structural determinants of synaptic transmission and plasticity at cortical synapses"

15/11/12 Stephan Sigrist, Institute of Biology, Freie Universität Berlin
"Shedding light on synapse assembly"

29/10/12 Ana M. Oliveira, Interdisciplinary Center for Neuroscience Heidelberg
"Rescue of aging-associated decline in Dnmt3a2 expression restores cognitive abilities"

26/10/12 Martin Heine, Leibniz Institute for Neurobiology Magdeburg
"Molecular mobility within the synaptic membrane"

04/10/12 Marc Spehr, Institut für Biologie II, Abt. Chemosensorik, RWTH Aachen
"Of mice and men - on the role of mitochondrial calcium in olfactory signaling"

02/07/12 Kazuo Emoto, Dept. of Cell Biology, Osaka Bioscience Institute, Osaka, Japan
"Signaling mechanisms that coordinate development and remodeling of Drosophila sensory circuits"

12/06/12 Geoffrey Raisman, Centre for Stem Cells and Regenerative Medicine, University College London
"A glio-centric view of CNS repair"

04/06/12 Thimothy E. Kennedy, Ph.D.,Montreal Neurological Institute, McGill University Montreal, Canada
"Novel roles for Netrin-1 regulating cell-cell interactions in the CNS: myelination, synaptogenesis, and synaptic plasticity"

19/04/12 Riccardo Brambilla, Institute San Raffaele Milan
"Mechanisms of mental retardation associated to abnormal Ras-ERK signalling"

29/03/12 David A. Brown, Dept. of Neuroscience, Physiology and Pharmacology, University College London
"M-currents"

15/03/12 Peter Hegemann, Humboldt University Berlin
"Advanced optogenetics with engineered channelrhodopsins"

23/02/12 Olav M. Andersen, Dept. of Medical Biochemistry, Aarhus University
"Identification of amino acids in SorLA that influence APP processing and protect against Alzheimer's disease"

02/02/12 Blanche Schwappach, Dept. of Biochemistry I, Universitätsmedizin Göttingen
"Tuning the electrical properties of cardiac chambers by differential trafficking of KATP channels"

26/01/12 Mart Saarma and Jukka Kallijärvi, Institute of Biotechnology, University of Helsinki
"Novel family of neurotrophic factors: mode of action and therapeutic potential & Studies of the Drosophila GDNF receptor like gene"

15/12/11 Stefan Kins, AG Humanbiologie und Humangenetik, TU Kaiserslautern
"Intraneuronal transport and physiological function of the amyloid precursor protein"

01/12/11 Didier Pinault, Inserm, Université de Strasbourg
"The psychotomimetic drug ketamine disrupts thalamocortical sensory information processing"

07/11/11 Franz E. Leichtfried, Epitomics Inc. and Biovest GmbH
"Monospecific high-affinity antibodies for biomarker research, (bio)pharmaceutical development and diagnostics"

23/09/11 Isabelle Aubert, Sunnybrook Health Sciences Centre Toronto, Canada
"Treatments for Alzheimer's disease: halting toxicity, enhancing neurotransmission and promoting regeneration"

01/09/11 Micheal Denker, Institute of Neuroscience and Medicine, Forschungszentrum Jülich GmbH
"The beat of cortical assemblies"

11/0711 Hiromi Hirata, National Institute of Genetics, Mishima, Japan
"Genetic analysis of glycinergic synapse in zebrafish"

27/06/11 Uwe Heinemann, Charite Universitätsmedizin Berlin
"Switching between different types of network activity in rat hippocampal slices"

27/06/11 Andreas Ludwig, Institut für Experimentelle und Klinische Pharmakologie und Toxikologie, Universität Erlangen-Nürnberg
"Function of cardiac HCN channels"

23/06/11 Christine Klein, Klinik für Neurologie, Universitätsklinikum Lübeck
"Genetic parkinsonism: from bedside to bench and back"

16/06/11 Stefan Remy, Deutsches Zentrum für Neurodegenerative Erkrankungen (DZNE), Bonn
"Dendritic integration of synaptic signals during hippocampal rhythmic activity"

19/05/11 Thomas Misgeld, TU München
"In vivo imaging of axon degeneration"

13/05/11 Catherine Collins, Dept. of Molecular, Cellular, and Developmental Biology, University
of Michigan, USA
"Using Drosophila to study regenerative and degenerative responses to axonal injury"

12/05/11 Gavin Rumbaugh, The Scripps Research Institute Florida, USA
"The contribution of F-actin dynamics to synaptic plasticity and memory: myosin motor control over F-actin dynamics in dendritic spines"

05/05/11 Alexander Flügel, Institute for Multiple Sclerosis Research, University of Göttingen
"Life imaging of autoimmune CNS lesions: how T cells invade and attack the nervous system"

03/05/11 Thomas Korn, Klinikum rechts der Isar, TU München
"Cytokine networks and T cellular players in autoimmune neuroinflammation"

07/04/11 Yukiko Goda, MRC University College London
"Synaptic strength regulation across the cleft by *N-cadherins"*

29/03/11 Ken Harris, Imperial College London
"The neural marketplace"

24/03/11 Martin Kerschensteiner, Klinikum der Universität München
"In vivo pathogenesis of neuroinflammatory axon damage"

10/03/11 Victor Tarabykin, Charite Universitätsmedizin Berlin
"Cell fate and connectivity in the neocortex: extrinsic and intrinsic factors"

16/12/10 Stephan Pless, University of British Columbia Vancouver, Canada
"All organic but not natural: Using unnatural amino acids and fluorescence microscopy to investigate voltage- and ligand-gated ion channels"

30/11/10 Michaël Zugaro, CNRS – Collège de France, Paris
"Theta phase precession and hippocampal ripples in memory processing in rodents"

19/11/10 Klaus Benndorf, Dept. of Physiology, University Hospital Jena
"Interdependence of activation gating and ligand binding in HCN and CNG channels"

18/11/10 Werner Kilb, Institute for Physiology and Pathophysiology, University of Mainz
"Depolarizing GABA responses during early development: excitatory or inhibitory?"

2/10/10 Hugues Nury, Institut Pasteur Paris
"Structure of a bacterial pentameric ligand-gated ion channel"

23/09/10 Andrey Irintchev, Dept. of Otorhinolaryngology, University Hospital Jena
"Central nervous system plasticity after peripheral nerve injury and regeneration"

19/08/10 Hiroshi Kawabe, Max Planck Institute Göttingen
"Regulation of Rap2A by the ubiquitin ligase Nedd4-1 controls neurite development"

08/07/10 Matthew Nolan, Centre for Integrative Physiology Edinburgh, UK
"Configuring neuronal responses to synaptic input: from molecular mechanisms to behavioral roles"

17/06/10 Benjamin K. Yee, Laboratory of Behavioural Neurobiology, ETH Zurich

"Modulation of behaviour and cognition via glycine transporter-1 knockout"

27/05/10 Andreas Androutsellis-Theotokis, Laboratory of Molecular Biology, NCI, NIH Bethesda, USA
"A transplantation-free stem cell therapy strategy"

27/05/10 Alexander Dityatev, Dept. of Neuroscience and Brain Technologies, The Italian Institute of Technology, Genova,
"The role of the extracellular matrix in synaptic plasticity: modulation of perisomatic inhibition and L-type calcium channels"

06/05/10 Gaby Schneider, FB Informatics and Mathematics, University of Frankfurt am Main
"Tracing cellular and coding mechanisms with a simple stochastic oscillator"

29/04/10 Lisa Marshall, Dept. of Neuroendocrinology, University of Lübeck
"Slow wave sleep, slow oscillations and memory formation"

29/04/10 Dirk J. Lefeber, Radboud University Nijmegen Medical Centre
"Disorders of the secretory pathway: lessons from genetic glycosylation defects"

22/04/10 Martin Aepfelbacher, Dept. of Medical Microbiology, Virology and Hygiene, UKE
"Bacterial regulation of Rho GTPases: the Yersinia system"

16/04/10 Gerd Multhaup, FU Berlin
"Toxic and non-toxic forms of Aß: evidence for a novel role of Aß in the nucleus"

10/12/09 Bettina Spitzweck, Barry Dickson's lab, IMP, Vienna
"Functional specialization of Robo receptors in Drosophila axon guidance"

05/10/09 Henri Tiedge, Dept. of Physiology and Pharmacology SUNY Health Science Center, Brooklyn, NY, USA
"RNA control in neurons"

14/07/09 Kamran Diba, Center for Molecular and Behavioral Neuroscience, Rutgers University Newark NJ, USA
"Characterizing interneurons by behaviour during network oscillations"

09/07/09 Geert Ramakers, Rudolf Magnus Institute of Neuroscience, UMC Utrecht
"Synaptic integration in the VTA and striatal dopamine release"

09/07/09 George Dragoi, Picower Institute for Learing & Memory, MIT Boston, MA, USA
"Temporal preplay of novel place sequences by hippocampal cellular assemblies"

30/04/09 Jochen Roeper, Physiologisches Institut II, Universität Frankfurt am Main
"The diversity of the dopamine midbrain system in health and disease"

16/04/09 Josephine Adams, Dept. of Bochemistry, University of Bristol
"Protein complexes in cell adhesion signaling pathways"

29/01/09 Sebastian Kügler, Universitätsklinik für Neurologie Göttingen
"The AAV vector toolkit: gene transfer for *genetic therapy and evaluation of the physiology of the brain"*

ZMNH PhD Seminars

13/02/14 Erwin Neher, Max Planck Institute for Biophysical Chemistry, Göttingen
"What happens before and after exocytosis: some insights from the calyx of Held"
Organizers: PhD Seminar Committee

07/11/13 Sean Munro, MRC Laboratory of Molecular Biology, Cambridge
"Arrivals and departures: how G proteins organise membrane traffic at the Golgi apparatus"
Organizers: PhD Seminar Committee

ZMNH Retreats

(Only the speakers of the oral sessions are listed, but not the workshops and posters.)

The ZMNH Retreats were organized by the ZMNH WIKO Committee, the representatives of the ZMNH scientific staff, in collaboration with the ZMNH scientists.

07-08/04/14 ZMNH Retreat 2014 in the Seminaris Hotel Lüneburg

Fabio Morellini, Behavioral Biology Unit
"Behavioral analyses: it is not just about phenotyping"

Daniel Mensching, Institute for Molecular and Cellular Cognition
"Investigation of activity dependent Arl5b mediated signaling in synaptic plasticity"

Oliver Keminer, Biomarker and Translational Drug Discovery Group, ESP
"High Content Screening in translational Drug Discovery - Principles and Examples"

Melanie Richter, RG Neuronal Development
The role of TaoK2 in Autism Spectrum
"Disorder: Morphological and behavioral analysis of the TaoK2 mutant mouse"

Nina Hoyer, RG Neuronal Patterning and Connectivity
"The receptor tyrosine kinase Ret: Dissecting novel functions in dendrite development and behavior"

Mary Muhia, Institute for Molecular Neurogenetics
"Role of Muskelin in the modulation of behavioral processes"

Simon Wiegert, Institute for Synaptic Physiology
"Conversion of Channelrhodopsin into a light-gated chloride channel"

Friederike Ufer, Institute for Neuroimmunology and Multiple Sclerosis
"Exploring the role of Arc/Arg3.1 in the immune system"

Prakash Nidadavolu, RG Development and Maintenance of the Nervous System
"Cell surface receptor signaling for development and maintenance of the dopaminergic system"

Bianka Brunne, Institute for Structural Neurobiology
"Reelin function in the developing and adult brain"

Michaela Schweizer, SG Morphology Combining Light- and Electron Microscopy

Irm Hermans-Borgmeyer, SG Transgenic Animals
"News from the < :3)~"

Kent Duncan, RG Neuronal Translational Control
"Translational control of cell growth and neuronal circuit function"

Jelena Katic, Emeritus Group Biosynthesis of Neural Structures
"The role of the cell adhesion molecule CHL1 and its heterophilic interaction partners in cerebellar development"

Chi-un Choe, RG Experimental Neuropediatrics
"Homoarginine in stroke"

Kay Sieben, RG Developmental Neurophysiology
"Theta-gamma oscillatory interplay results from precise timing of synaptic currents from glutamatergic and GABAergic neurons in the neonatal prefrontal cortex in vivo"

Guest speaker: Christian Kubisch, Institute of Human Genetics, Universitätsklinikum Ulm
"Human genetics as a means to identify disease-associated genes and to elucidate gene function"

15-16/04/13 ZMNH Retreat 2013 in the Seehotel Boltenhagen

Manuel Friese, RG Neuroimmunology
"Inflammation-induced neurodegeneration in multiple sclerosis"

Kay Sieben, RG Developmental Neurophysiology
"The development of cross-modal processing in the rat primary somatosensory cortex"

Lars Binkle, Institute for Molecular and Cellular Cognition
"A role for activity-dependent Arc/Arg3.1 in dendritic endosomal sorting"

Kent Duncan, RG Neuronal Translational Control
"Knockout of the translational regulatory protein pum2 in the mouse forebrain reveals a potential role in memory"

Bianka Brunne, Institute for Structural Neurobiology
"Reelin signaling – From brain development to adult stability"

Chun Hu, RG Neuronal Patterning and Connectivity
"Neuron-astrocyte interaction in Drosophila melanogaster"

Jan Broder Engler, RG Neuroimmunology
"Mechanisms of pregnancy-induced tolerance in an animal model of multiple sclerosis"

Jürgen Schwarz, Emeritus Group Schwarz
"Neuronal erg potassium channels mediate subthreshold currents"

Karsten Tillack, RG Development and Maintenance of the Nervous System
"A new genetic approach to visualize and manipulate dopaminergic neurons in mice"

Anna Katharina Schlusche, RG Experimental Neuropediatrics
"Transgenic expression of a dominant negative HCN subunit affects brain development"

Frank Heisler, Institute for Molecular Neurogenetics
"GRIP1 interlinks N-Cadherin and AMPA receptors at vesicles to promote combined cargo transport into dendrites"

Ole Pless, Biomarker and Translational Drug Discovery Group, ESP
"A chemical biology approach to target Alzheimer's disease"

Froylan Calderon de Anda, RG Neuronal Development
"Polarity before polarization: does the centrosome instruct actin polymerization?"

Shu-Ting Yin, Institute for Synaptic Physiology
"Dendritic spines as biochemical and electrical compartments for plasticity"

Guest speaker: Nils Brose, Department of Molecular Neurobiology, Max Planck Institute

of Experimental Medicine, Göttingen
"Dynamic control of presynaptic function - the other type of synaptic plasticity

16-17/04/12 ZMNH Retreat 2012 in the Scandic Hotel Lübeck

Thomas G. Oertner, Institute for Synaptic Physiology
"The dangers of synaptic depression and how to fight it"

Froylan Calderon de Anda, Picower Institute for Learning and Memory, MIT, USA
"Neurons go back"

Ole Pless, Biomarker Plattform ESP
"Translational drug discovery and biomarker research at the ZMNH"

Wolfgang Wagner, Institute for Molecular Neurogenetics
"Myosin-Va transports the endoplasmic reticulum to the dendritic spines of Purkinje neurons"

Devesh Kumar, Institute for Neural Signal Transduction
"Genetic tracing of kisspeptin neural circuitry during embryonic maturation"

Bettina Spitzweck, RG Development and Maintenance of the Nervous System
"Functional Specification of the GDNF Receptors Ret, NCAM and Integrinß1 in the Dopaminergic System"

Gaby Loers, Emeritus Group Biosynthesis of Neural Structures
"Gold nanoparticles functionalized with a fragment of the neural cell adhesion molecule L1 stimulate L1-mediated functions"

Marco Brockmann, RG Developmental Neurophysiology
"Oscillatory coupling of neonatal prefrontal-hippocampal networks is disrupted in a rat model of mild/moderate hypoxic-ischemic injury"

Benjamin Schattling, RG Neuroimmunology
"TRPM cation channels in neurological diseases"

Alexander Drakew, Institute for Structural Neurobiology
"Role of the spine-apparatus in synaptic plasticity: two-photon-microscopy in organotypic hippocampal slice cultures"

Guest speaker: Thomas Jentsch, Dept. Physiology & Pathology of Ion Transport, Leibnitz Institute for Molecular Pharmacology and Max-Delbrück-Centrum for Molecular Medicine Berlin

09-10/05/11 ZMNH Retreat 2011 in the Tagungshotel Jesteburg

Kent Duncan, RG Neuronal Translational Transport
"Translational control of cellular growth and nervous system function"

Peter Soba, RG Neuronal Patterning and Connectivity
"Organization of sensory dendritic fields by cell surface receptors"

Michael Frotscher, Institute for Structural Neurobiology
"Role of Reelin in forming and stabilizing cortical architecture"

Stefan Gold, Department Neuroimmunology and Clinical Multiple Sclerosis Research
"Neuroendocrine-limbic mechanisms of multiple sclerosis associated depression"

Kay Sieben, RG Developmental Neurophysiology
"Multisensory processing within visual-somatosensory cortical networks of the juvenile Brown Norway rat"

David Lutz, Institute for Biosynthesis of Neural Structures
"Generation, nuclear import and possible functional roles of sumoylated transmembrane fragment of the neuronal adhesion molecule L1"

Gregor Sachse, Institute for Neural Signal Transduction
"Causal relationship between smooth muscle BK channel activity and low blood pressure"

Fabio Morellini, RG Experimental Neuropediatrics
"Behavioral and pharmacological modulation of conditioned responses and their extinction"

Tiemo Marquarding, Institute for Molecular and Cellular Cognition
"Activity dependent synaptic strength and structural plasticity mediated by Arc/Arg3.1"

Ulrich Boehm, Institute for Neural Signal Transduction
"Female reproductive maturation in the absence of kisspeptin/GPR54 signaling"

Piedavent Melanie, RG Neuroimmunology
"Analysing the functional phenotypes of the multiple sclerosis-associated gene variants of DNAM1 (CD226)"

Praveen Meka, RG Development and Maintenance of the Nervous System
"Role of parkin in regulating GDNF signal transduction and receptor turnover in neurons"

Dorthe Labonté, Department Molecular Neurogenetics
"Role of the E3-ligase Trim3 in motorprotein-dependent transport"

Guest speaker: Paul Saftig, Biochemical Institute, Christian-Albrechts-University Kiel
"From lysosomes to membrane proteolysis: implications for (neuronal) health and disease"

26-27/04/10 ZMNH Retreat 2010 in the Tagungshotel Jesteburg

Matthias Kneussel, Institute for Molecular Neurogenetics
"Synaptic activity regulates synaptic cytoskeleton transport"

Jürgen Schwarz, Institute for Neural Signal Transduction
"Erg potassium channels and neuronal excitability"

Benjamin Schattling, RG Neuroimmunology
"TRPM cation channels in inflammation-induced neurodegeneration"

Martin Kruse, Institute for Neural Signal Transduction
"Cardiac conduction and I CAN channel trafficking"

Xiasong Mao, Institute for Molecular and Cellular Cognition
"Memory is dynamically encoded by temporal-spatial controlled translation of Arc/Arg3.1"

Melanie Richter, RG Development and Maintenance of the Nervous System
"GDNF/Ret singaling in peroneal nerve guidance decisions"

Lilian Aly, Institute for Neuroimmunology and Multiple Sclerosis Research
"JC virus-specific immune responses and their relation to progressive multifocal leukoencephalopathy"

Torben Hausrat, Institute for Molecular Neurogenetics
"Rho GTPase signaling regulates synaptic GABA-A receptor density"

Ora Ohana, Institute for Molecular and Cellular Cognition
"Fast recruitment of recurrent inhibition in the visual cortex"

Chi-un Choe, RG Experimental Neuropediatrics
"Creatine – an old compound with new functions"

Thomas Tilling, Institute for Biosynthesis of Neural Structures
"Short DNA sequences inserted for gene targeting can interfere with off-target gene expression"

Christian Mayer, Institute for Neural Signal Transduction
"Puberty and Kiss Neurons"

Beatrice Pöschel, RG Neuronal Networks in Developing Brain
"Coordinated interactions within developing prefrontal-hippocampal networks and their cholinergic modulation"

Bibhudatta Mishra, Institute for Biosynthesis of Neural Structures
"Functional role of the interaction between polysialic acid and extracellular histone H1"

Sven Schippling, Institute forNeuroimmunology and Clinical Multiple Sclerosis Research
"Imaging outcomes during early stages of MS"

Guest speaker: Eckart D. Gundelfinger, Leibniz Institute for Neurobiology, Magdeburg
"Converting juvenile into adult plasticity – a role for the brain's extracellular matrix"

27-28/04/09 ZMNH Retreat 2009 in the Tagungshotel Jesteburg

Dietmar Kuhl, Institute for Molecular and Cellular Cognition
"Learning about Arc/Arg3.1 and long-term memories"

Ileana Hanganu-Opatz, RG Neuronal Networks in Developing Brain
"Melody of the neonatal brain: neuronal oscillations in cortico-subcortical networks"

Manuel Friese, RG Neuroimmunology
"CD8+ T cells and neurodegeneration in multiple sclerosis"

Dirk Isbrandt, RG Experimental Neuropediatrics
"A multilevel approach to ion channel function in the mouse: our present strategies and future directions"

Claudia Mahlke, Institute for Molecular and Cellular Cognition
"Auditory discrimination learning in mice"

Karsten Sollich, RG Development and Maintenance of the Nervous System
"A genetic approach to study catecholaminergic neurons in mice"

Pierre Abramowski, Institute for Neuroimmunology and Clinical Multiple Sclerosis Research
"Therapeutic effect of the alkyl-lysopholpholipid edelfosine on immune cells and experimental autoimmune encephalomyelitis"

Han Kyu Lee, RG Protein Trafficking and Synapse Formation
"Synaptic activation modifies microtubules underlying transport of postsynaptic cargo"

Guido Hermey, Institute for Molecular and Cellular Cognition
"Identification and characterization of novel plasticity-related genes"

Martin Kruse, Institute for Neural Signal Transduction
"Impaired endocytosis of TRPM4 channel is associated with progressive familial heart block type I"

Maifang Xiao, Institute for Biosynthesis of Neural Structures
"NCMA modulates dopamine D2 receptor internalization"

Malte Stockebrand, Institute for Neural Signal Transduction
"Analysis of neuronal Calcium sensor-1 interactions in transgenic mice"

Nicole Karl, Institute for Biosynthesis of Neural Structures
"Functional role of CHL1 and its novel interaction partners Sonic hedgehog and vitronectin"

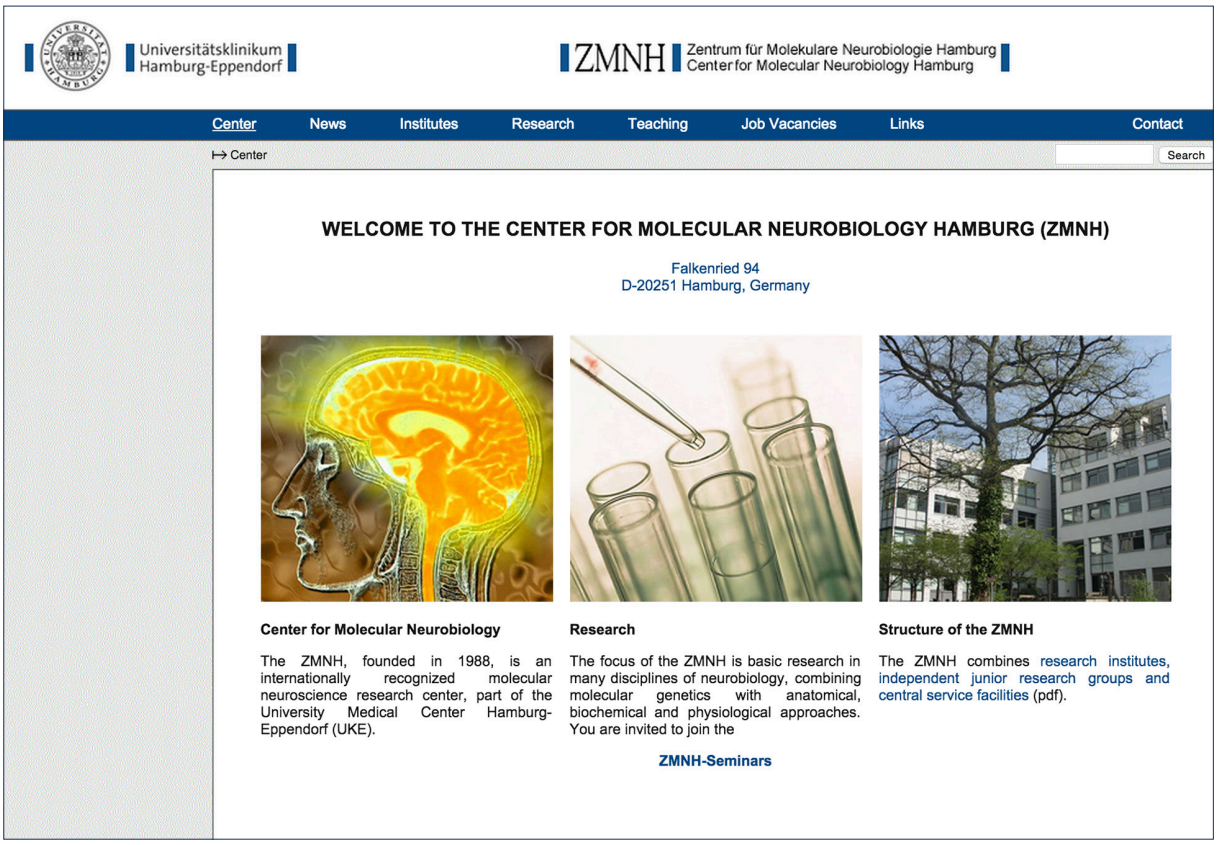
Roland Martin, Institute for Neuroimmunology and Clinical Multiple Sclerosis Research
"The Biopharma project"

Guest speaker: Reinhard Jahn, MPI for Biophysical Chemistry Göttingen

In addition to the above mentioned seminars, symposia and retreats monthly Internal ZMNH-Seminars and Internal Research in Progress-Seminars were held.

Public Relations Activities

In addition to the ZMNH-Seminar series, ZMNH-Symposia and the ZMNH-based Graduate Program in Molecular Biology (ASMB) that address scientists and students, the ZMNH communicates information about its neurobiological research to the public on its own homepage www.zmnh.de and by numerous activities such as press releases, workshops for school classes, the Girls&Boys Day as well as short-term practical training for students and schoolchildren. The ZMNH takes further part in the public understanding of science initiatives of the City of Hamburg and the UKE "Nacht des Wissens" (Night of Knowledge") and "Tag der offenen Tür" (Day of Open Doors).



UKE press releases on ZMNH research projects (in German)

25/08/14 BMBF fördert MS-Forschungsprojekt des UKE mit 1,6 Millionen Euro

15/08/14 Nature Publikation von Wissenschaftlern des UKE und DKFZ: Neues Kontrollsystem bei Gewebewachstum identifiziert

24/07/14 Förderung für UKE – Forscher: UKE erhält mehr als zwei Millionen Euro aus Landesforschungsförderung Hamburg

27/03/14 Ein Lichtsensor im Kopf: UKE-Grundlagenforscher entwickeln neuartigen Schalter fürs Gehirn - Veröffentlichung im renommierten Wissenschaftsmagazin Science

18/03/14 UKE-Forscher identifizieren neuen neurobiologischen Mechanismus

04/11/13 UKE-Forscher gewinnen neue Einblicke ins Gehirn

05/06/13 Neues Verfahren zur Behandlung von Multipler Sklerose entwickelt

20/03/13 Nervenzellen bei der Arbeit zusehen

18/11/12 UKE-Forscher entdeckt wichtigen Mechanismus der Neurodegeneration bei der Multiplen Sklerose

15/04/11 UKE-Forscher: Ein Gen steuert Haarfarbe und Gedächtnis