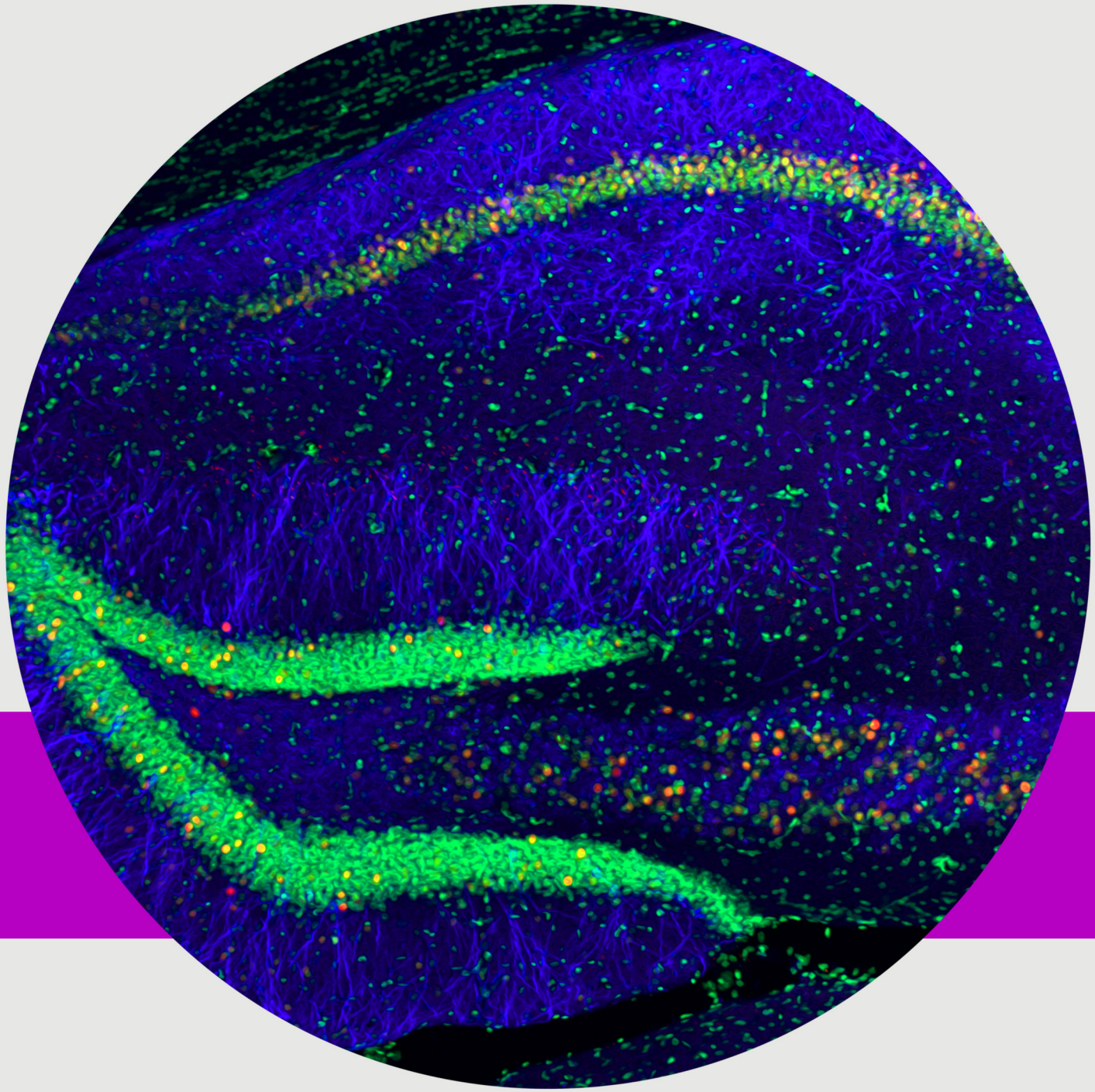

ZMNH

Center for
Molecular
Neurobiology
Hamburg

Research Report
2015 - 6/2017

Universitätsklinikum
Hamburg-Eppendorf

University Medical Center Hamburg-Eppendorf (UKE)
Center for Molecular Neurobiology Hamburg (ZMNH)
Falkenried 94
20251 Hamburg
Germany

Phone: +49 40 7410 56271
Fax: +49 40 7410 56261
Email: info@zmnh.uni-hamburg.de
www.uke.de/zmnh

Cover Image: Labeling neurons in the hippocampus active during memory formation (Thomas Oertner, ZMNH Institute of Synaptic Physiology, Hamburg)

Report Design & Layout: Julia Kuhl

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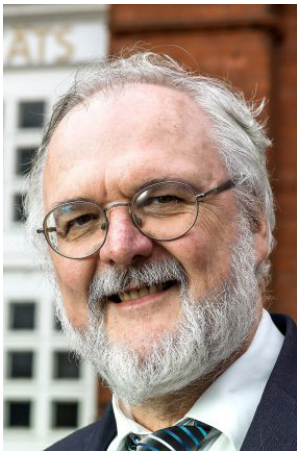
Table of Contents



Welcome Address of the Dean and of the Director of UKE

The ZMNH was established in 1987 as a biomedical research institution focusing on basic molecular neuroscience research. It has rapidly developed into a center of excellence in its field with great national and international visibility. A number of highly regarded world-class scientists have done research at the ZMNH and have investigated the brain at different experimental levels.

Today, the ZMNH continues its success story as a catalyst for various interdisciplinary and translational projects in basic and clinical science. As part of the University Medical Center Hamburg-Eppendorf (UKE) and the Hamburg Center of NeuroScience (HCNS), the ZMNH is embedded into a vital community that ranges from systems to cellular and molecular neuroscience.

The structure of the ZMNH, which comprises departments, junior research groups, and core facilities generates an active research environment that has substantially advanced neuroscience to the highest level. The center justifies its international reputation by an enormous output of highly cited publications in renowned peer reviewed journals, external funding and scientific awards.

Its present generation of principal investigators focuses on fundamental questions in molecular and cellular neuroscience with special emphasis on neuronal transmission and plasticity in health and disease. These scientific problems are investigated using complementary techniques including biochemical, cell biological, physiological, genetic and optogenetic methods.

During the last three years, the ZMNH has been a driving force in the establishment of a research network funded by the Federal State of Hamburg (*Landesforschungsförderung*, Speaker: Matthias Kneussel) and initiated a research group funded by the German Research Foundation (DFG) on the molecular mechanisms underlying synaptic

plasticity and stability (FOR 2419, Speaker: Matthias Kneussel). The ZMNH is also an engine in a national Cluster of Excellence Initiative (Exlni, ADAPT, Speaker: Thomas Oertner).

To further strengthen basic neuroscience research at the ZMNH, four new research group leaders have been appointed since 2015 with Marina Mikhaylova (DFG-Emmy Noether funding), Meliha Karsak (UKE funding), Simon Wiegert (ERC funding) and Michael Kreutz (Leibniz Guest Scientist). Moreover, an Institute of Medical Systems Biology (headed by Stefan Bonn) has been established at the ZMNH in August 2017.

We are proud to foster basic research at the University Medical Center Hamburg-Eppendorf. The ZMNH has become a role model over the years, and its success is also owed to an external scientific advisory board that evaluates the performance of the center on a regular basis. We are aware that success comes at a cost and are fully committed to preserve the ZMNH as research environment deserving protection in financial funding, minimal administrative burden and teaching obligations. We are convinced of the ZMNH concept and wish the center success in investigating brain function and fighting brain disease.

Uwe Koch-Gromus, M.D., Ph.D., Dean of the Medical Faculty

Burkhard Göke, M.D., Director UKE

ZMNH Director's Message

The Center for Molecular Neurobiology Hamburg (ZMNH), established in 1987, is a biomedical research unit of the faculty of Medicine at the University Medical Center Hamburg-Eppendorf (UKE). Scientists at the ZMNH conduct basic research focusing on the mechanisms underlying neuronal transmission and plasticity in health and disease.

In order to understand the brain as a control center for mental and cognitive function, as well as the disorders associated with it, we need a fundamental understanding of basic molecular and cellular mechanisms. The ZMNH has a longstanding expertise in the analysis of cellular communication and connectivity in plastic neuronal networks. Different groups investigate activity-dependent neuronal gene expression, protein targeting and the dynamic turnover of molecules and organelles that regulate the structure and function of synaptic connections underlying learning and memory. In addition, translational projects focus on genetic polymorphisms or protein dysfunction in animal models of neural diseases. We believe that a solid understanding in molecular neuroscience is prerequisite for the development of new therapeutics against neurological and mental illnesses.

Besides its strong commitment to research, the ZMNH is involved in advanced teaching in neuroscience and related disciplines. A two-year graduate training program in molecular biology and a PhD-program are widely appreciated and well accepted across faculties and local research institutions.

Over the last three years, scientists at the ZMNH have initiated new research networks and became leaders in coordinated programs. The funding of a local neuroscience network *Landesforschungsförderung* (LFF) by the Federal State of Hamburg (Speaker: Matthias Kneussel) became a catalyst in the initiation of a new DFG-funded Research Group FOR 2419, focusing on understanding plasticity and stability of neuronal synapses (Speakers: Marcus Altfeld, Petra Arck and Thomas Oertner). Moreover, a current ZMNH initiative to apply for a national neuro-immunology excellence cluster "ADAPT" (Speakers: Marcus Altfeld, Petra Arck and Thomas Oertner) integrates the ZMNH, UKE, University and Leibniz association researchers across Hamburg. Finally, the second funding period for the DFG priority program SPP 1665 (Speaker: Ileana Hanganu-Opatz) complements this success.

Since 2015, many scientists at the ZMNH have become principal investigators in national and international research programs. For example, Simon Wiegert and Peter Šoba participate in the priority program SPP 1926 to develop and apply novel optogenetic tools. Manuel Friese is funded by BMBF, FOR 2289, NEU2 and the clinical research group KFO 296 focusing on multiple sclerosis and antigen-specific immune modulation to establish tolerance in MS. Thomas Oertner investigates synapse physiology with optogenetic approaches in SFB 936 together with Fabio Morellini and is also a prinicipal investigator in SPP 1665. Dietmar Kuhl has been part of SFB 936 and heads a project in the LFF network to study Arc/Arg 3.1 protein function. Michael Frotscher has studied the role of reelin in radial glial cells

in a project funded by the priority program SPP 1775. Matthias Kneussel investigates cytoskeleton-dependent protein trafficking mechanisms in a GRK 1459 project. Froylan Calderon de Anda is supported by the FOR 2419 and LFF funds, while LFF also supports Kent Duncan in investigating neuronal protein translation.

We are proud of a new institute and four new research groups that joined the ZMNH recently. In 2015, Marina Mikhaylova started a DFG-funded Emmy Noether group investigating neuronal cytoskeleton transport. In the same year, Meliha Karsak joined the ZMNH to investigate neuronal signal transduction. These topics are complemented by a new guest group headed by Michael Kreutz, who is concerned with secretory vesicle and organelle trafficking. In 2017, Simon Wiegert received an ERC grant to establish his own lab at the ZMNH, studying Schaffer collateral synapses with optogenetic methods. In August 2017, Stefan Bonn was appointed as director of a newly established ZMNH institute entitled "Medical Systems Biology". Together, these groups fit well into the overall molecular neuroscience concept of the ZMNH and strengthen its translational aspects and its attempts to interact closely with clinical scientists.

Dietmar Richter (founder of the ZMNH) and Melitta Schachner are two emeritus professors who actively participate in ZMNH activities, by either organizing the annual Blankenese Conference or running a productive lab studying neuronal cell adhesion, respectively.

Finally, all ZMNH researchers greatly benefit from close interaction with different core facilities that provide expertise and practical support in transgenic and CRISPR/Cas9 animal techniques, electron microscopy, DNA sequencing and bioanalytics. We are also grateful for the continuous support from administration, IT service, the technical workshop and the ZMNH library.
Having mentioned these positive developments at the ZMNH, it is with great sadness that we mourn the recent loss of our colleague and friend Michael Frotscher, who passed away in May 2017. Michael Frotscher was a senior professor and head of the Institute of Structural Neurobiology funded by the Hertie Foundation. He was elected as head of the ZMNH in 2015 and initiated many positive developments at the center. His pleasant character and his scientific input will be missed greatly. However, it would have been Michael Frotscher's wish to end this message with the statement that the ZMNH is on the right track to address new challenges in future neuroscience research.

Together with our colleagues at the UKE and the many collaborators worldwide, I am optimistic that the ZMNH will significantly contribute to our understanding of brain function and disease in future years. Please find a summary of the current ZMNH research activities in this booklet.

Matthias Kneussel, PhD, Director, Center for Molecular Neurobiology (ZMNH), University Medical Center Hamburg-Eppendorf (UKE)

Scientific Advisory Board of the ZMNH 2014-2017

Prof. Dr. Frank Bradke
German Center for Neurodegenerative Diseases (DZNE)
Bonn, Germany

Prof. Dr. Christine M. Gall
Department of Anatomy and Neurobiology, Gillespie Neuroscience Research Facility, University of California, Irvine, CA, USA

Prof. Dr. Magdalena Götz
Institute of Stem Cell Research at Helmholtz Center Munich; LMU Dept. of Physiological Genomics
Munich, Germany

Prof. Dr. Eckart D. Gundelfinger
Leibniz-Institute of Neurobiology
Magdeburg, Germany

Prof. Dr. Reinhard Hohlfeld
Institute of Clinical Neuroimmunology, Ludwig-Maximilians-University (LMU)
Munich, Germany

Prof. Dr. Jackie Schiller
Department of Physiology and Biophysics, Ruth and Bruce Rappaport Faculty of Medicine
Haifa, Israel

Prof. Dr. Dietmar Schmitz
German Center for Neurodegenerative Diseases (DZNE), CharitéCrossOver
Berlin, Germany

Prof. Dr. Dr. Antoine Triller
Institut de biologie de l'ENS (IBENS)
Paris, France

Structure of the ZMNH

Research Institutes

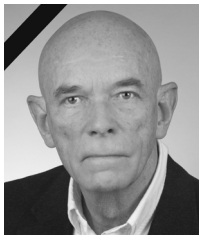
(ordered by date of establishment)

Neuroimmunology and Multiple Sclerosis - INIMS
(established in April 2014)
Director: Prof. Dr. Manuel Friese

Phone: +49 (0) 40 7410 - 56615
Email: manuel.friese@zmnh.uni-hamburg.de

Synaptic Physiology *(established in October 2011)*
Director: Prof. Dr. Thomas Oertner

Phone: +49 (0) 40 7410 - 58228
Email: thomas.oertner@zmnh.uni-hamburg.de



Structural Neurobiology *(established in May 2011)*
Director: Prof. Dr. Dr. h. c. Michael Frotscher

Phone: +49 (0) 40 7410 - 56275
Email: matthias.kneussel@zmnh.uni-hamburg.de

Molecular Neurogenetics *(established in February 2010)*
Director: Prof. Dr. Matthias Kneussel

Phone: +49 (0) 40 7410 - 56275
Email: matthias.kneussel@zmnh.uni-hamburg.de

Molecular and Cellular Cognition *(established in October 2008)*
Director: Prof. Dr. Dietmar Kuhl

Phone: +49 (0) 40 7410 - 56278
Email: dietmar.kuhl@zmnh.uni-hamburg.de

Research Groups

(ordered by date of establishment)

Synaptic Wiring and Information Processing *(established in April 2017)*
Head: Dr. J. Simon Wiegert

Phone: +49 (0) 40 7410 - 55354
Email: simon.wiegert@zmnh.uni-hamburg.de

Emmy Noether Group Neuronal Protein Transport
(established in April 2015)
Head: Dr. Marina Mikhaylova

Phone: +49 (0) 40 7410 - 55815
Email: marina.mikhaylova@zmnh.uni-hamburg.de

Neuronal and Cellular Signal Transduction *(established in January 2015)*
Head: Prof. Dr. Meliha Karsak

Phone: +49 (0) 40 7410 - 54811
Email: meliha.karsak@zmnh.uni-hamburg.de

Behavioral Biology *(established in October 2013)*
Head: Dr. Fabio Morellini

Phone: +49 (0) 40 7410 - 56650
Email: fabio.morellini@zmnh.uni-hamburg.de

Neuronal Development *(established in July 2012)*
Head: Dr. Froylan Calderon de Anda

Phone: +49 (0) 40 7410 - 56817
Email: froylan.calderon@zmnh.uni-hamburg.de

Neuronal Patterning and Connectivity *(established in December 2010)*
Head: Dr. Peter Šoba

Phone: +49 (0) 40 7410 - 58281
Email: peter.soba@zmnh.uni-hamburg.de

Neuronal Translational Control *(established in May 2010)*
Head: Dr. Kent Duncan

Phone: +49 (0) 40 7410 - 56274
Email: kent.duncan@zmnh.uni-hamburg.de

Development and Maintenance of the Nervous System
(2008 – February 2016)
Head: PD Dr. Edgar Kramer

Emeritus Group Biosynthesis of Neural Structures
(since 2011 Emeritus Group)
Head: Prof. Dr. Dr. h.c. Melitta Schachner Camartin

Phone: +49 (0) 40 7410 - 56292
Email: melitta.schachner@zmnh.uni-hamburg.de

Emeritus Group Cell Biochemistry and Clinical Neurobiology
(established in 2005)
Head: Prof. Dr. Dietmar Richter, Founding Director of ZMNH

Phone: +49 (0) 40 7410 - 53344
Email: richter@uke.uni-hamburg.de

Guest Groups

(ordered by date of establishment)

Dendritic Organelles and Synaptic Function *(since 10/2015)*
Head: Dr. Michael R. Kreutz
Leibniz Institute of Neurobiology Magdeburg

Phone: +49 (0) 40 7410 - 55818
Email: michael.kreutz@zmnh.uni-hamburg.de

Experimental Neuropediatrics *(since 01/2014)*
Head: Priv.-Doz. Dr. Axel Neu
UKE Dept. of Pediatrics

Phone: +49 (0) 40 7410 - 56651
Email: axel.neu@zmnh.uni-hamburg.de

Developmental Neurophysiology *(since 10/2013)*
Head: Prof. Dr. Ileana Hanganu-Opatz
UKE Institute of Neuroanatomy

Phone: +49 (0) 40 7410 - 58966
Email: ileana.hanganu-opatz@zmnh.uni-hamburg.de

Fraunhofer IME ScreeningPort *(since 06/2011)*
Head: Dr. Ole Pless

Phone: +49 (0) 40 7410 - 56554
Email: Ole.Pless@ime.fraunhofer.de

ZMNH Core Facilities

Bioanalytics
Head: Priv.-Doz. Dr. Sabine Hoffmeister-Ullerich

Phone: +49 (0) 40 7410 - 56662
Email: hoffmeis@zmnh.uni-hamburg.de

Electron Microscopy and Morphology
Head: Dr. Michaela Schweizer

Phone: +49 (0) 40 7410 - 55084
Email: michaela.schweizer@zmnh.uni-hamburg.de

Transgenic Mouse Facility
Head: Priv.-Doz. Dr. Irm Hermans-Borgmeyer

Phone: +49 (0) 40 7410 - 56663
Email: irm.hermans-borgmeyer@zmnh.uni-hamburg.de

IT Service and Development
Head: Dr. Hans-Martin Ziethen

Phone: +49 (0) 40 7410 - 54985
Email: hans-martin.ziethen@zmnh.uni-hamburg.de

ZMNH Administration and Central Services

Managing Director: Katja Husen

Phone: +49 (0) 40 7410 - 56270
Email: husen@zmnh.uni-hamburg.de

Committees: ZMNH *Kollegium* and WIKO

According to the ZMNH statutes, the ZMNH *Kollegium* is the decision-making committee for all fundamental issues concerning the ZMNH. It consists of the directors of the ZMNH Institutes, one representative elected by the ZMNH Research Groups, one representative elected by the WIKO and the ZMNH managing director. The ZMNH *Kollegium* elects the ZMNH Director for a term of office of three years. Prof. Dr. Dietmar Kuhl, Director of the ZMNH Institute of Molecular and Cellular Cognition, was the ZMNH Director from 2009 to 08/2015 followed by Prof. Dr. Dr. h.c. Michael Frotscher, Director of the ZMNH Institute of Structural Neurobiology, and the deputy ZMNH director Prof. Dr. Matthias Kneussel, Director of the ZMNH Institute of Structural Neurobiology. After the sudden death of Prof. Frotscher, Prof. Kneussel was elected as Director of ZMNH with Prof. Dr. Thomas Oertner, Director of the Institute of Synaptic Physiology, as Deputy Director of ZMNH in June 2017.

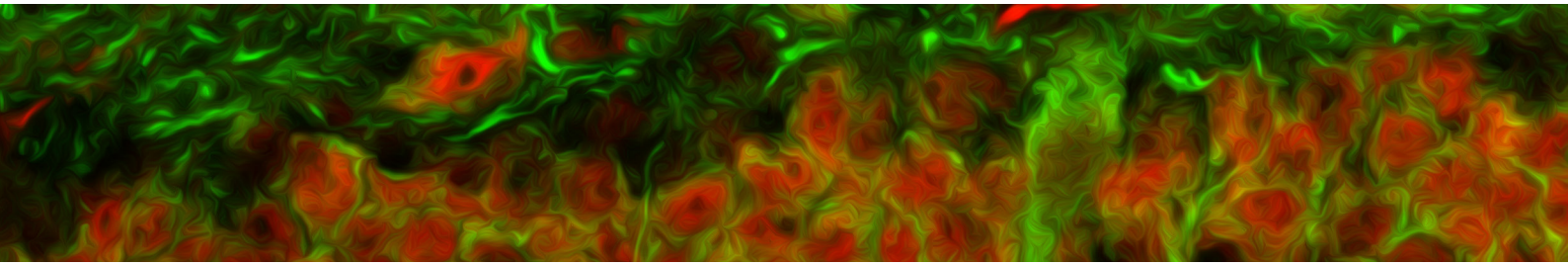
Scientists'Conference(*Wissenschaftlerkonferenz,* WIKO) of the ZMNH is the assembly of the scientific staff including technical assistants, students, post¬doctoral fellows and professors. The aim of the WIKO is to involve the scientific staff in internal decisions regarding ZMNH. Every two years, the WIKO elects one representative for the ZMNH *Kollegium*. In taking his/her decisions, the representative is supported by a standing committee that meets before and after each meeting of the ZMNH *Kollegium*. The standing committee is generally composed by one member from each institute, one member from the research groups, one member from the core facilities and one member of the tech¬nical 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 *Kollegium*. The WIKO representative has a vote and his/her opinions and suggestions count for final decisions taken by the ZMNH *Kollegium*. Also the Ombudspersons for the ZMNH PhD program are elected in plenary WIKO meetings. Finally, in addition to plenary meetings, the WIKO organizes the scientific program of the yearly ZMNH Retreats.

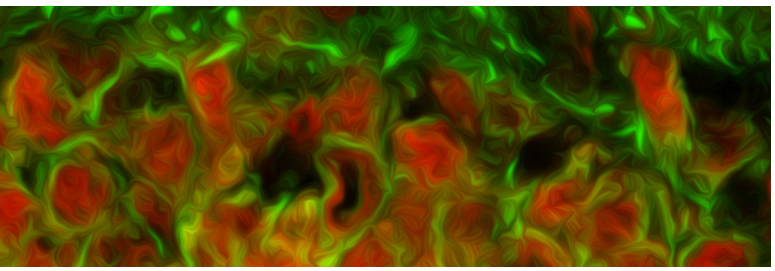
In the reporting period, WIKO meetings were held on 28/02/2017, 01/03/2016 and 19/05/2015.

Representative in ZMNH *Kollegium*:
Dr. Fabio Morellini (since 2014)

Deputy Representative in ZMNH *Kollegium*:
Dr. Alexander Drakew (since 2014)

Standing WIKO committee:
Priv.-Doz. Dr. Uwe Borgmeyer
Achim Dahlmann
Dr. Torben Hausrat
Dr. Nina Hoyer
Priv.-Doz. Dr. Irm Hermans- Borgmeyer
Peggy Putthoff (since 2017)
Dr. Benjamin Schattling
Dr. Simon Wiegert





Research Reports of the ZMNH Institutes

Institute of Neuroimmunology and Multiple Sclerosis (INIMS)

Director: Prof. Dr. Manuel Friese

The ZMNH Institute of Neuroimmunology and Multiple Sclerosis (INIMS) seeks to better understand the development and progression of neuroimmunological and neuroinfectious diseases with particular emphasis on multiple sclerosis, to translate molecular findings into drug treatment and improve clinical care. In order to achieve this goal, we systematically study immunology, neurobiology and patient care using a wide methodological spectrum. Basic research is interlocked with clinical activities ensuring access to patients as well as setting up operative platforms for conducting clinical studies. The INIMS consists of two operational units: It integrates a basic science institute located at the Center for Molecular Neurobiology Hamburg (ZMNH) with a clinical research platform located at the dedicated day hospital for patients with multiple sclerosis and other neuroimmunological diseases (outpatient clinic) affiliated to the Department of Neurology.

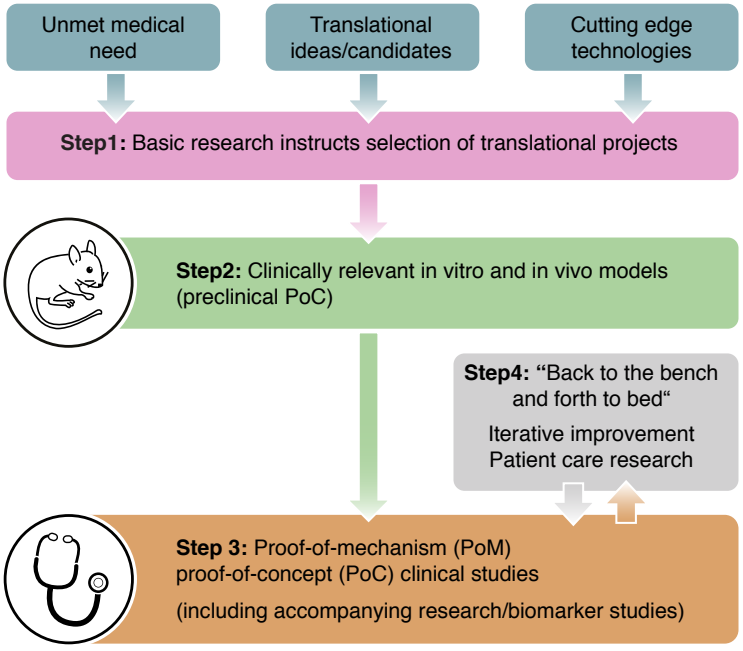
Main scientific goals of the INIMS:

• Translational research – to transform biology into effective therapeutic agents for neuroimmunological diseases:

- to study the aetiology and pathogenesis of multiple sclerosis and other neuroimmunological and neuroinfectious diseases

- to investigate the immune system and the central nervous system and their interactions to understand mechanisms of immune cell dysregulation, neurodegeneration and neuroprotection

- to develop new drugs and behavioural interventions for multiple sclerosis patients and to test them in treatment trials



Representative Projects

IMMUNOLOGY

Our immunological studies focus on what provokes autoimmunity. We want to decipher the deregulated cell types in multiple sclerosis and other neuroimmunological diseases. We want to understand the molecules that serve as regulators and effectors of an autoimmune response. In addition, learning from evolution, e.g. by understanding how pregnancy shapes immune responses, will help the quest for novel immunomodulatory treatments for neuroimmunological diseases. For this purpose we use blood samples from patients, which we store in our 2008 established biobank, as well as the mouse model of multiple sclerosis, experimental autoimmune encephanlomyelitis (EAE) that is induced by immunisation of C57BL/6 mice with a peptide from the myelin-oligodendrocyte glycoprotein.

How are genetic variants predisposing to the risk of multiple sclerosis?

Mechanisms leading to the dysregulation of T cells and CNS infiltration in multiple sclerosis remain to be defined. We aim to define the functional impact of genetic variants that are associated with MS disease risk. While we know that a variant of the CD226 gene predisposes to multiple sclerosis it was unknown how the risk-variant is funcationally involved in the pathogenesis. We discovered that CD226 expression was reduced in regulatory T cells (Treg) of CD226 risk-haplotype carriers and patients with multiple sclerosis, compared to healthy protective-haplotype carriers resulting in reduced Treg suppressive ability. Mimicking the phenotype of human CD226 genetic risk variant carriers, Treg derived from Cd226-deficient mice showed similarly reduced inhibitory activity, eventually resulting in an exacerbated disease course of EAE. Therefore, by combining human and mouse analyses we show that CD226 exhibits an important role in the activation of Treg, with its genetically imposed dysregulation predisposing to multiple sclerosis (Piedavent-Salomon et al., 2015).

How is an autoimmune response generated?

Dendritic cells coordinate innate and adaptive immune responses, including autoimmune responses. However, many fundamental questions are still unanswered and the mechanisms how dendritic cells induce autoimmune responses are ill defined. We study how different molecules regulate the activation and function of dendritic cells. We discovered that the neuronal protein Arc/Arg3.1 is restricted to migratory dendritic

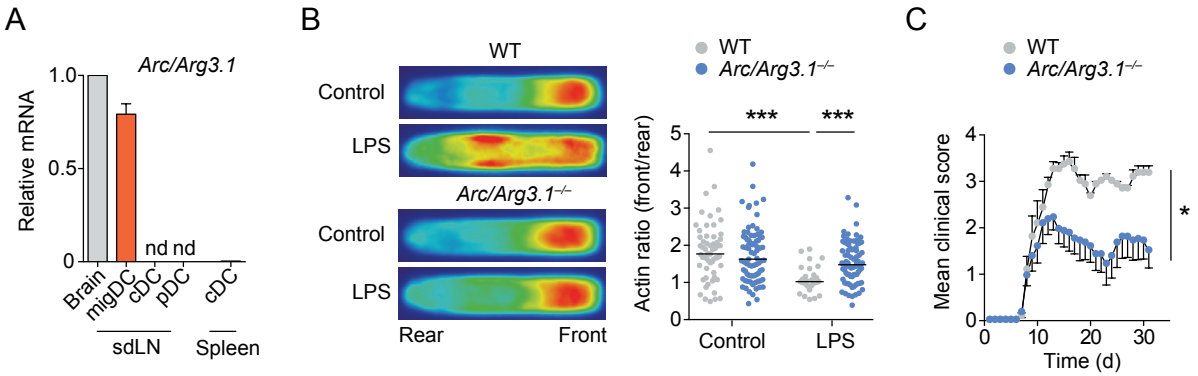


Figure 1. Arc/Arg3.1 is exclusively expressed in migDCs, influences actin dynamics in migration and impacts on T cell stimulation and EAE. (A) Relative Arc/Arg3.1 mRNA of flow cytometry–sorted DC subsets from skin-draining lymph nodes (sdLNs) and spleen. (B) Actin distribution from migrating DCs. Scatter plot shows actin ratio (front to rear) for individual cells. (C) Mean clinical score for EAE groups of different geneotypes. Modified from Ufer et al., Sci Immunol (2016).

cells and drives fast dendritic cell migration by coordinating cytoskeletal changes in response to inflammatory challenges. Accordingly, Arc/Arg3.1-dependent dendritic cell migration was critical for mounting T cell responses in EAE and in allergic contact dermatitis (Ufer et al., 2016). This understanding will help us to devise approaches to treat or prevent autoimmune diseases, such as multiple sclerosis.

How does pregnancy modulate multiple sclerosis disease activity?

Pregnancy in female multiple sclerosis patients is associated with a substantial decrease in relapse rate. However, post-partum the relapse rate increases in a rebounding fashion above the rate seen before pregnancy. Currently the biological mechanisms underlying these pregnancy-related effects in multiple sclerosis are poorly understood. We aim at deciphering these powerful, evolutionary-driven pathways of immunomodulation and at exploiting them to inform novel therapeutic approaches in non-pregnant multiple sclerosis patients. We discovered that T cells are able to directly sense the pregnancy hormone progesterone via their glucocorticoid receptor (GR) resulting in an enrichment of Treg. In EAE, we found that the presence of the GR in T cells confers the protective effect of pregnancy on the disease course, but is not relevant for maintaining pregnancy itself (Engler et al., 2017).

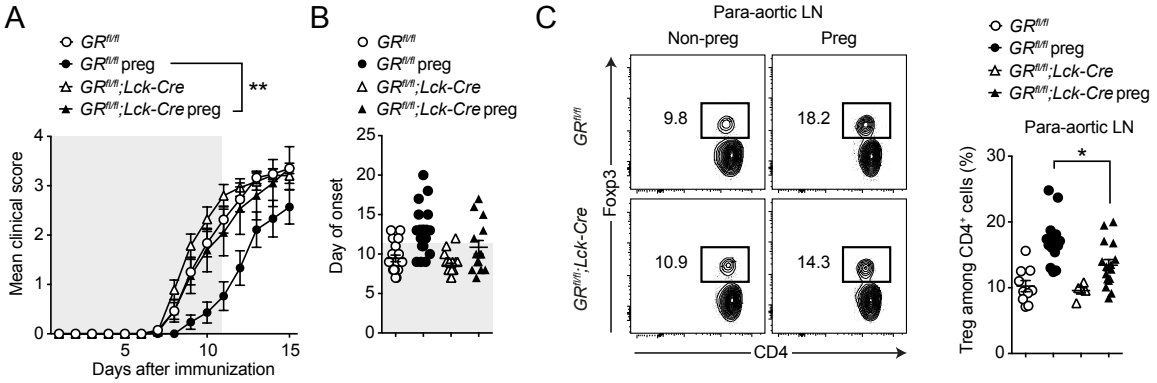


Figure 2. The GR in T cells mediates EAE protection during pregnancy. EAE was induced in nonpregnant and pregnant $GR^{fl/fl}$ and $GR^{fl/fl}$;Lck-Cre mice. (A) Clinical course and (B) day of onset are shown. Gray shaded areas represent pregnancy. (C) Treg frequency in nonpregnant and pregnant $GR^{fl/fl}$ and $GR^{fl/fl}$;Lck-Cre mice treated as in A analyzed by flow cytometry at E18.5. Modified from Engler et al., PNAS (2017).

NEUROBIOLOGY

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 multiple sclerosis. 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. 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 that enhance neuronal resilience to ameliorate neurodegeneration in multiple sclerosis but also other neurodegenerative diseases.

How do neuronal ion channels contribute to inflammation-induced neurodegeneration?

Inflammatory insults in multiple sclerosis determine neurodegeneration by causing mitochondrial dysfunction, energy failure and alterations of ion exchange mechanisms. A long-standing hypothesis holds that the distribution of voltage-gated sodium channels along demyelinated axons contributes to neurodegeneration by increasing neuroaxonal sodium influx and energy demand during central nervous system (CNS) inflammation. We tested this hypothesis *in vivo* by inserting a human gain-of-function mutation in the mouse $Na_V1.2$-encoding gene *Scn2a* that is known to increase $Na_V1.2$-mediated persistent sodium currents. In mutant mice, CNS inflammation in EAE leads to elevated neuroaxonal degeneration, increased disability and lethality compared to wildtype littermate controls. Thus, this study shows that increased neuronal $Na_V1.2$ activity exacerbates inflammation-induced neurodegeneration irrespective of immune cell alterations and identifies $Na_V1.2$ as a promising neuroprotective drug target in multiple sclerosis (Schattling et al., 2016).

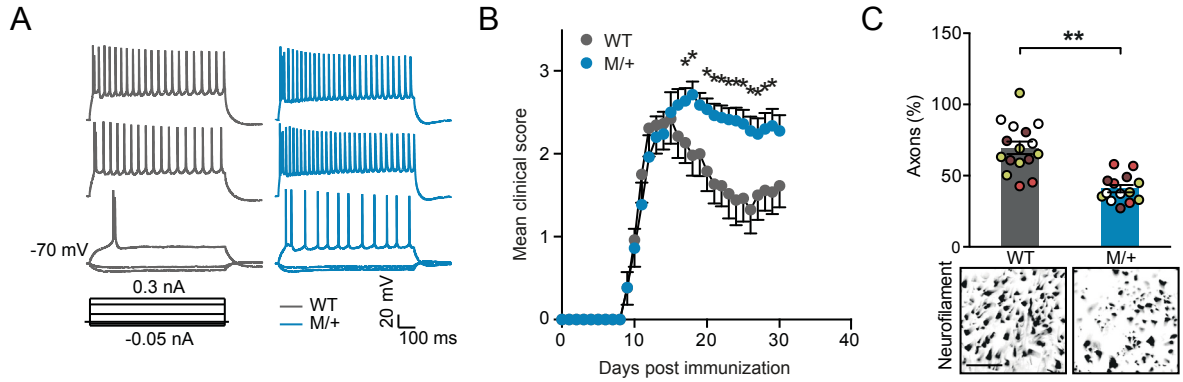


Figure 3. *Scn2a*^{A263V} mutation (M/+) leads to an exacerbated EAE disease course. (A) Representative traces of current-clamp recordings from P10 to P12 hippocampal CA1 pyramidal neurons of wild-type and M/+ mice. (B) Clinical disability scores of female EAE mice. (C) Representative histopathological sections and quantification of neurofilament immunostainings from dorsal columns of cervical spinal cord sections from wild-type EAE and M/+ EAE mice 30 days after immunization. Modified from Schattling et al., JCI Insight (2016).

CLINICAL RESEARCH

Based on the concept of health as an ability to adapt to changing personal and environmental settings, clinical research at the INIMS aims to develop treatments with a comprehensive approach. Therefore, clinical care and research include assessment and consideration of psychological and psychosocial aspects of multiple sclerosis as well as the development and evaluation of educational (i.e. evidence-based patient information) and behavioural (i.e. psychological, exercise) interventions. Moreover, we pursue phase I and phase II treatment trials combined with mechanistic laboratory studies in the area of unmet clinical needs such as safe treatments in early multiple sclerosis (i.e. boswellic acids, immunological tolerance induction), highly immunosuppressive approaches for aggressive disease (i.e. autologous hematopoietic stem cell transplantation) but also neuroprotective concepts (i.e. erythropoietin). Complementing this approach, we conduct research to improve assessment tools, develop outcome parameters with clinical relevance (novel clinical assessments and neuroimaging), and optimise study designs.

How can standardised psychological interventions be effective and made available to manage multiple sclerosis?

Neuropsychiatric symptoms such as depression have a considerable impact on activity and participation. Depression is the most common comorbidity in multiple sclerosis and affects up to 50% of patients. However, few therapeutic options are available to effectively treat them. Thus, there is an urgent but unmet need to develop novel approaches including psychological interventions that can be implemented at large scale in multiple sclerosis. We develop online and group education programmes based on a framework of complex interventions and conduct randomised controlled trials to test their efficacy. In a recent phase II randomised controlled trial, we demonstrated that a fully automated, internet-based intervention significantly reduced depressive symptoms in MS patients. The effects of this 9-week program were sustained at 6 months follow-up (Fischer et al., 2015).

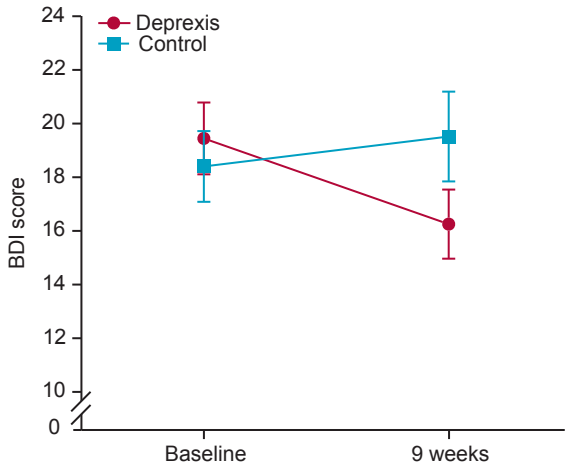


Figure 4. Phase II randomised controlled trial of Deprexis to reduce depressive symptoms in multiple sclerosis. After the 9-week program, depression scores decreased significantly compared to waitlist controls (WLC) (P = 0.015). Modified from Fischer et al., Lancet Psychiatry (2015).

FUTURE PERSPECTIVES

Besides continuing our above outlined research in the three areas (i) immunology, (ii) neurobiology and (iii) clinical research, we will expand our research activites on systems biology to comprehensively describe molecular and cellular components and their interactions in neurons and immune cells. Mechanisms by which neurons alter and maintain their molecular signatures during inflammation are fundamental in their injury process. Similarly, autoimmunity changes gene and protein expression in certain immune cell subtypes. We will explore these neuronal and immune cell alterations in multiple sclerosis and its animal model by use of diverese omic tools. This will enable us to analyse not only the complete molecular signatures of specific cells but also the cascade of events that induce or maintain such signatures. These analyses could yield new targets for future drug development.

Which pathways are deregulated in multiple sclerosis immune cells?

Identification of reliable diagnostic and prognostic biomarkers would enable treatment to be personalised so that patients destined to experience aggressive disease could receive appropriately potent therapies. Using transcriptional and microRNA profiling of circulating pooled and single immune cells and soluble blood components from multiple sclerosis patients with clearly defined disease courses, we aim at identifying distinguishable biomarkers. Furthermore, we expect to identify currently unknown mechanistic pathways contributing to the dysregulation of different immune cell subsets in multiple sclerosis. Certain aspects are jointly analysed with the Fraunhofer IME SP in Hamburg.

Which pathways are activated in neurons exposed to inflammatory stressors?

After neuronal sensing of inflammation, downstream signalling pathways will be activated that drive both neuronal resilience and injury. Thus, accessing the dynamics of gene expression programs during the course of inflammation is a promising approach to identify potentially protective or injurious signalling networks. Here we analyse the neuronal epigenome, translatome, proteome and miRNome to discover novel target structures for neuroprotective treatment strategies in chronic inflammation.

How can new drugs be developed to treat neurodegeneration in multiple sclerosis?

Target identification is a critical step in the drug discovery and development process, however even more critical is the development of lead compounds targeting newly identified neuronal pathways leading to inflammation-induced neurodegeneration. In order to expedite development of new drugs with neuroprotective potentials, we teamed up with pharmaceutical and biotech companies (Evotec AG, Fraunhofer IME SP) to identify compounds, which we can test in pre-clinical models.

Selected Publications

Engler JB, Kursawe N, Solano ME, Patas K, Wehrmann S, Heckmann N, Luhder F, Reichardt HM, Arck PC, Gold SM, Friese MA (2017) Glucocorticoid receptor in T cells mediates protection from autoimmunity in pregnancy. Proc Natl Acad Sci U S A 114:E181-E190.

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Roche

Sanofi Genzyme

Teva GmbH

Werner-Otto Stiftung

Collaborators

Prof. Dr. Marcus Altfeld
Heinrich-Pette-Institute, Hamburg

Prof. Dr. Petra Arck
University Medical Center Hamburg-Eppendorf

Prof. Dr. Wolfgang Brück
University of Göttingen

Prof. Dr. Ulrik Dalgas
Universiteit Aarhus

Prof. Dr. Veit Flockerzi
University of Homburg

Prof. Dr. Marc Freichel
University of Heidelberg

Prof. Dr. Lars Fugger
University of Oxford

Prof. Dr. Christian Gerloff
University Medical Center Hamburg-Eppendorf

Prof. Dr. Eckart Gundelfinger
Leibniz Institute of Neurobiology, Magdeburg

Prof. Dr. Inge Huitinga
Netherlands Brain Bank, Amsterdam

Prof. Dr. Dirk Isbrandt
University of Cologne and DZNE

Prof. Dr. Jürgen Kasper, University of Tromsö

Prof. Dr. Sascha Köpke
Universitätsklinikum Schleswig-Holstein

Prof. Dr. Tim Magnus
University Medical Center Hamburg-Eppendorf

Prof. Dr. Doron Merkler, University of Geneva

Prof. Dr. Ingrid Mühlhauser
University of Hamburg

Prof. Dr. Friedemann Paul, Charité Berlin

Prof. Dr. Nancy Sicotte
University of California Los Angeles

Dr. Alessandra Solari
Istituto Besta Milano

Dr. Jack van Horssen
VU University Medical Center, Amsterdam

Dr. Pablo Vargas
Institut Curie, Paris

Team

Director: Prof. Dr. Manuel Friese

Principal investigators:
- Prof. Dr. Christoph Heesen
- Prof. Dr. Stefan Gold

Scientific coordinators:
- Dr. Sabine Fleischer
- Dr. Anne Willing

Basic and medical scientists:
- Dr. Lars Binkle
- Dr. Jan-Broder Engler
- Dr. Daniel Mensching
- Dr. Elena Montes-Cobos
- Dr. Konstantinos Patas,
- Dr. Benjamin Schattling
- Dr. Anne Willing

Clinician scientists:
- Dr. Anna Alegiani née Krützelmann
- Dr. Sibylle Hodecker
- Dr. Max Kaufmann
- Dr. Barbara Kaulen
- Dr. Sabine Rösner
- Dr. Sina-Cathérine Rosenkranz
- Dr. Insa Schiffmann
- Dr. Jan-Patrick Stellmann
- Dr. Klarissa Hanja Stürner
- Dr. Friederike Ufer
- Dr. Kim Lea Young

Psychology/Health scientists:
- Stefanie Lau
- Dr. Katrin Liethmann
- Dr. Jana Pöttgen

Research nurses:
- Imke Backhus
- Kristina Grentzenberg
- Andrea Mönch
- Zehra Oguz-Cöloglu
- Stefanie Reinhardt
- Sven Schammler

PhD students:
- Britta Eggert
- Nina Heckmann
- Gesa Pust
- Caren Ramien
- Karin Riemann-Lorenz
- Nicola Rothammer
- Artem Shaposhnykov
- Benthe Untiedt
- Mark Walkenhorst
- Nadine Wanke
- Iris Winkler
- Ingo Winschel

Master students:
- Aparajita Bose
- Lena Feddersen
- Valeria Mussetto
- Vanessa Roth
- Mahmoud Tarayrah

MD students (Supervision Prof. Dr. Manuel Friese):
- Carsten Heidermann
- Aliona Solomonova
- Joseph Tintelnot
- Constantin Volkmann
- Hana Winkler née Smajlovic

MD students (Supersion Prof. Dr. Christoph Heesen):
- Lisa Baquet
- Yasemin Bay
- Lisa Biedermann
- Judith Brandt
- Sven Briken
- Hanife Cetin
- Marlene Eilers
- Katharina Engels
- Eghbal Ghezelbash
- Mina Ghoncheh
- Johanna von Gumberz
- Ayleen Hofmann
- Yannik Hülsmann
- Midia Jlussi
- Barbara Kaulen
- Ina Lorenz
- Mina Mamoudi
- Goncheh Mina
- Navina Nasseri
- Christina Riechel
- Dorit Röhr
- Laura Schäfer
- Gainet Weißflog
- Janina Wendebourg
- Damian Wenzel
- Yuyang Zhai

MRI / Neuroradiology:

Michaela Andritzki (Neurorad.)
Dirk Kilian
Dushyant Kumar, PhD
Daniel Kutzner
Wiebke Schmidt
Dr. Susanne Siemonsen
Ginette Wortmann

Technicians:

Simone Bauer
Nina Kursawe
Michael Moles
Emanuel Pora
Stefanie Reinhardt
Eva-Maria Stübe
Simone Träger
Nina Verse

Media kitchen:

Anke Heins

Administrative assistants:

Ines Busch
Inken Jensen
Bärbel Müller
Sabine Nagel
Anne Weyand

Publications 2015 – 6/2017

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Doctoral/PhD Theses

Britta Eggert (2017) Regulation of autoimmune neuroinflammation by Hv1 proton channels. Dr.rer.nat., MIN Faculty, Universität Hamburg

Dr. med. Jan Broder Engler (2016) Mechanisms of pregnancy-induced tolerance in an animal model of multiple sclerosis. Dr. rer. biol. hum., Faculty of Medicine, Universität Hamburg

Dr. med. Konstantinos Patas (2016) Neuroinflammation in multiple sclerosis associated depression. PhD, Faculty of Medicine, Universität Hamburg

Medical Doctor Theses

Yasemin Bay (2016) Evaluation einer neuen Darstellungsmethode für Wahrscheinlichkeiten von Nutzen und Schaden in der Risikokommunikation mit Patienten im Bereich der multiplen Sklerose. Faculty of Medicine, Universität Hamburg

Judith Brand (2016) Magnetic resonance imaging in MS – patients experiences, information interests and responses to an education programme. Faculty of Medicine, Universität Hamburg

Ina Lorenz (2016) Repetitive, tiefe transkranielle Magnetstimulation bei Patienten mit MS und Depression. Eine kombinierte PhaseI/IIa Studie. Faculty of Medicine, Universität Hamburg

Ghoncheh Mina (2016) Klassische Konditionierung immunologischer Reaktionen bei Patienten mit Multipler Sklerose während Mitoxantrongabe. Faculty of Medicine, Universität Hamburg

Christina Riechel (2016) Subjective and objective knowledge and decisional role preferences in cerebrovascular patients compared to controls. Faculty of Medicine, Universität Hamburg

Janina Wendebourg (2016) Development and pilot study of an evidence-based patient education programme for managing fatigue in MS (FatiMa). Faculty of Medicine, Universität Hamburg

Sven Briken (2015) Effects of exercise on fitness and cognition in progressive MS: a randomized, controlled pilot trial. Faculty of Medicine, Universität Hamburg

Barbara Kaulen (2015) Diagnostische und prognostische Faktoren für die Entwicklung einer multiplen Sklerose bei Patienten mit klinisch isoliertem Syndrom. Faculty of Medicine, Universität Hamburg

Jana Pöttgen (2015) Metakognitives und alltagsrelevantes Training für Patienten mit Multipler Sklerose (MATiMS) – Entwicklung und Pilotierung eines Schulungsprogramms zu neuropsychiatrischen Störungen bei MS. Faculty of Medicine, Universität Hamburg

Dorit Röhr (2015) Okulomotorik- und Aufmerksamkeitsprüfung als objektive Diagnoseverfahren für Fatigue bei multipler Sklerose. Faculty of Medicine, Universität Hamburg

Diploma Theses

Milan Götze (2016) Der Einfluss von Persönlichkeit auf Theory of Mind und Empathie bei Menschen mit Multipler Sklerose. Faculty of Arts and Humanities, Christian-Albrechts-Universität zu Kiel

Swantje Schnell (2015) Theory of Mind und Empathie bei Multipler Sklerose – Auswirkungen auf Lebensqualität und soziales Netzwerk. Faculty of Arts and Humanities, Christian-Albrechts-Universität zu Kiel

Master Theses

Mahmoud Tarayrah (2017) CD8 T cells miRNAs profile in multiple sclerosis pregnant women: 3rd trimester vs. postpartum. PMC Sorbonne Universités, Paris

Valeria Mussetto (2017) Die Rolle von TLE3 bei der entzündlichen autoimmunen Enzephalomyelitis. Università degli Studi di Roma "La Sapienza", Facoltà di Medicina e Odontoiatria, Roma

Bachelor Theses

Luisa Kammler (2016) Validierung der deutschen Version des PDQ (Perceived Deficits Questionnaire) für MS Patienten. MSH Medical School Hamburg

Awards and Distinctions

01/10/2016

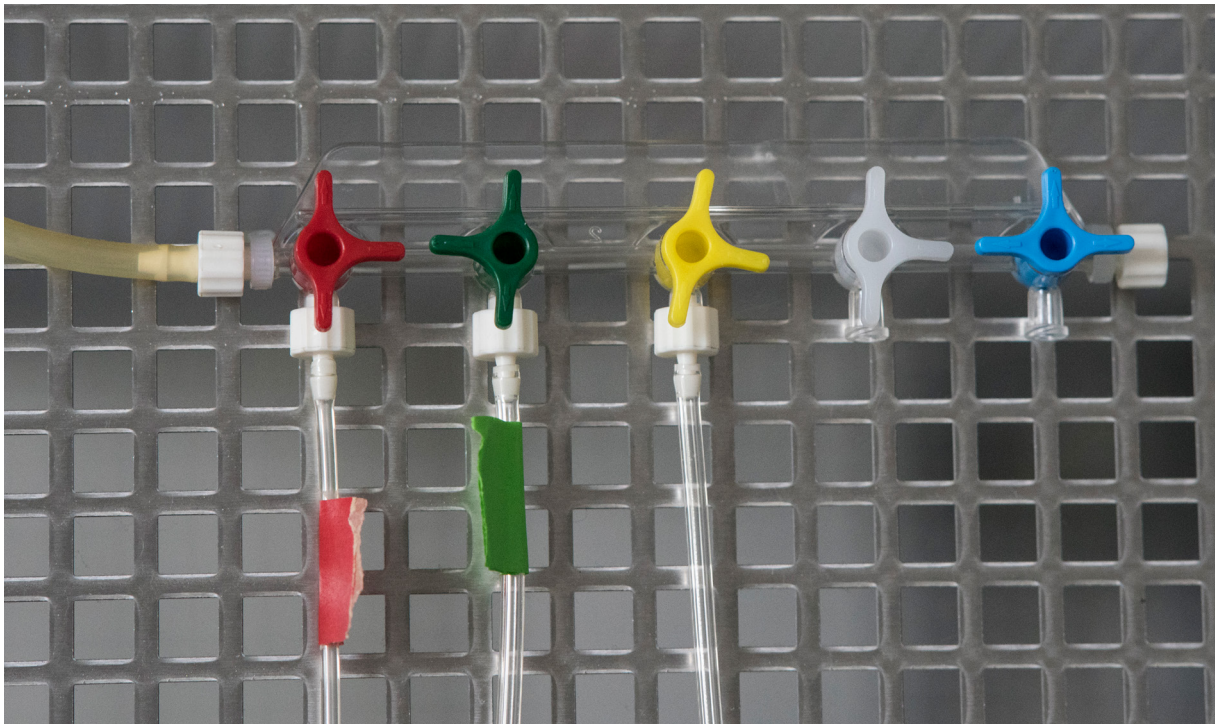
Grant of Hertie Foundation's medical student programme
Marcel Seungso Woo, ZMNH Institute of Neuroimmunology and Multiple Sclerosis

22/09/2016

Oppenheim Prize for Multiple Sclerosis 2016 by Novartis Pharma GmbH
Dr. Benjamin Schattling, ZMNH Institute of Neuroimmunology and Multiple Sclerosis

31/05/2016

Support by the gender equality programme "Research time for female clinicians" of the Medical Faculty, Universität Hamburg
Dr. Friederike C. Ufer, ZMNH Institute of Neuroimmunology and Multiple Sclerosis



Institute of Synaptic Physiology

Director: Prof. Dr. Thomas Oertner

The ZMNH Institute of Synaptic Physiology studies the communication between neurons in the central nervous system. Depending on the activity of pre- and postsynaptic cells, chemical synapses 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 optophysiological experiments in intact brain tissue with high spatial and temporal resolution. Using genetically encoded probes, we monitor the activity of single synapses 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 detail. Microglia, the resident immune cells in the brain, are suspected to actively remove synapses under physiological conditions, a hypothesis we will test experimentally.

The aim of our research is to understand the rules and molecular mechanisms that govern our extraordinary ability to learn and to remember.

Dr. Simon Wiegert was awarded a Starting Grant from the European Research Council. With further support by the DFG and the UKE, he has launched an independent research group on the topic of 'Synaptic wiring and information processing' in April 2017. More information about this new group can be found in the corresponding section of this report.

Optogenetic investigation of spike-timing dependent plasticity

Christine E. Gee, Margarita Anisimova, Bas van Bommel

The discovery of spike-timing-dependent plasticity (STDP) revealed the exquisite sensitivity of synapses to temporal correlations between pre- and postsynaptic spike patterns (Hao and Oertner, 2012). This form of plasticity is usually tested with electrophysiological approaches, eventually killing the recorded neurons. The recent discovery of Channelrhodopsin variants that are sensitive to red light (Klapoetke et al., 2014) enabled 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 inves-

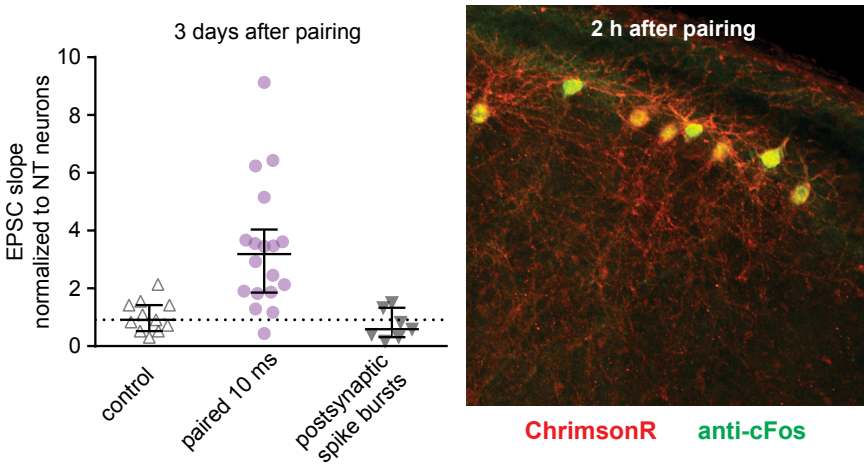


Figure 1. Dramatic potentiation of synaptic connections 3 days after STPD protocol. Left: Selective cFos expression in 'paired' neurons (yellow).

tigating the sensitivity of individual synapses to temporal correlations in pre- and postsynaptic activity patterns. We found very strong potentiation of paired connections 3 days after the induction protocol (Fig. 1). Paired neurons received up to 9 times stronger input than control cells, a degree of potentiation that is never seen in tradtional STDP using patch-clamp electrodes.

Activity-dependent regulation of synaptic lifetime

J. Simon Wiegert, Iris Ohmert

While 'analog' synaptic plasticity seems to be essential for our ability to learn and to remember, formation of novel connections and removal of obsolete synapses might be key for more stable forms of memory. We know this form of 'binary' memory storage from our digital computers. Using optogenetic stimulation and read-out, 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.

Neuronal silencing with light-gated chloride channels

J. Simon Wiegert

The discovery of Channelrhodopsin-2, 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. Light-induced inhibition of neuronal activity is more difficult to achieve (Wiegert and Oertner, 2016). Collaborating with Prof. Peter Hegemann (HU 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., 2015, 2014). We have further improved the ion selectivity of this new tool to enable optical silencing of select neuronal populations in intact animals (Takahashi et al., 2016; Wietek et al., 2015). Variants with altered spectral sensitivity and prolonged open times are currently being characterized.

Manipulating spatial memory traces in mouse hippocampus

Paul Lamothe-Molina, Andreas Franzelin, Fabio Morellini

The hippocampus contains neurons that are highly active when the animal is moving through a certain position in space. These place cells are thought to be part of larger assemblies of neurons that constitute a memory trace (*engram*). We use opto- and chemogenetic methods together with

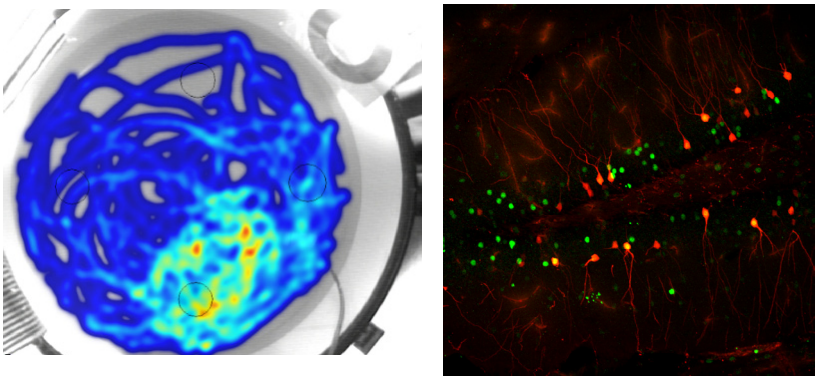


Figure 2. Swim pattern of a trained mouse in search of a platform hidden in the bottom quadrant of the tank (black circle). Right: Neurons in dentate gyrus (DG) that were active during training express an optogenetic inhibitor and a red fluorescent protein. Green cells were active in a different behavioral task.

activity-dependent expression systems (Tet-*off*) to inhibit the reactivation of a specific set of hippocampal neurons, namely the neurons that were highly active when the mouse found a hidden escape platform in a water-filled tank (Fig. 2). The central question is the degree of separation of different spatial memories: Can one memory be transiently suppressed without interfering with the recall of other spatial memories? In different areas of the hippocampus, we expect different degrees of separation between specific memories.

Functional role of *endoplasmic reticulum* and spine neck diffusion

Alberto Perez-Alvarez, 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. 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 using time-lapse two-photon imaging to investigate movements of dynamic ER in hippocampal neurons, using 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. Understanding the physiological role of ER and diffusional isolation by the spine neck is the goal of this project.

Cyclic nucleotide signaling in synaptic plasticity

Oana Constantin, Daniel Udwari, Christine E. 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'. 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. Using cell-type specific expression of bPAC, we will dissect the precise location of cAMP action. Furthermore, we discovered the first natural rhodopsin that contains a light-activated cyclase (Scheib et al., 2015). In collaboration with Prof. Viacheslav Nikolaev (UKE), we will continue to develop new tools to control and measure cAMP and cGMP in subcellular compartments (Fig. 3).

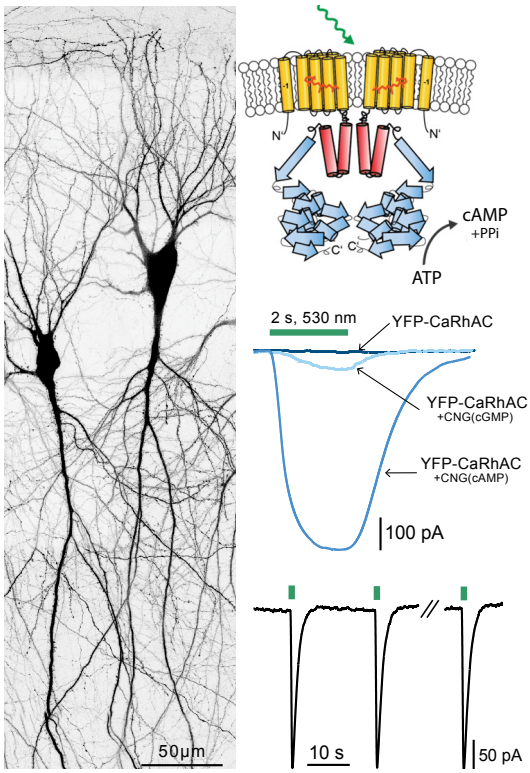


Figure 3. A novel rhodopsin-adenylyl-cyclase produces large cAMP transients in neurons when illuminated with green light.

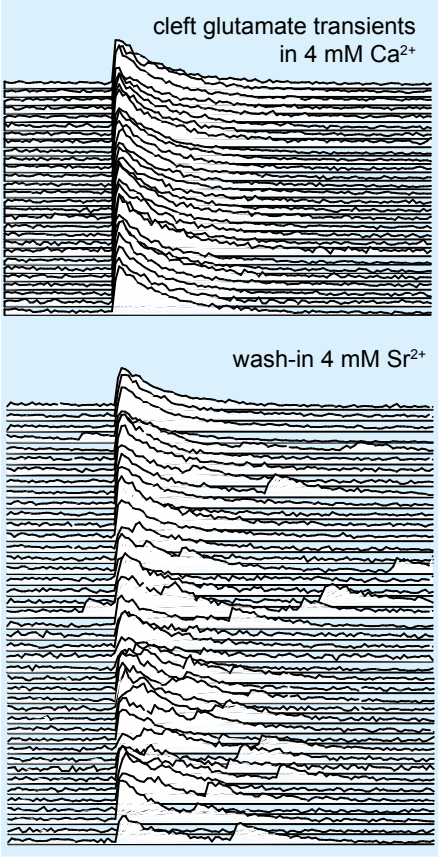


Figure 4. Optical quantal analysis using iGluSnFR. Single-vesicle events can be seen when strontium is applied to desynchronize release.

Optical quantal analysis of glutamate release in intact tissue

Celine Dürst, Christian Schulze

Presynaptic boutons release neurotransmitters by calcium-dependent vesicle fusion. This process is the fundamental mechanism of information transmission between neurons. Based on the genetically encoded glutamate sensor iGluSnFR, we developed an optical approach that allows us to investigate vesicular release at individual Schaffer collateral terminals. We find that individual boutons can release several transmitter vesicles in response to a single action potential (Fig. 4). On the other hand, if the calcium concentration in the extracellular space is low (1 mM), multivesicular events are very rare at most Schaffer collateral synapses. In collaboration with Dr. Katalin Török in London, we have developed ultrafast versions of iGluSnFR that resolve individual release events during 100 Hz spike trains. With these tools, we can directly study the function of the release machinery without the added complication of receptor desensitization.

New tools to label active synapses

Alberto Perez-Alvarez, Brenna Fearey, Simon Wiegert, Christine Gee

No microscope is fast enough to perform functional imaging of all hippocampal synapses in real time. The goal of this project is to persistently label all synapses that are active in a brief time window so we can map their position in 3D by two-photon laser scanning microscopy. This must work in living tissue so we can repeat the measurements to study the functional stability of synaptic networks. To do so, we have targeted the calcium-dependent photoswitchable protein CaMPARI (Fosque et al., Science 2015) to dendritic spines (Fig. 5). A pulse of UV light converts synaptically anchored CaMPARI from green to red, but only in those spines that were previously active. We use the red-to-green ratio to detect all active spines independent of their size. Our new tool will help us create three-dimensional maps of synaptic function before and after learning.

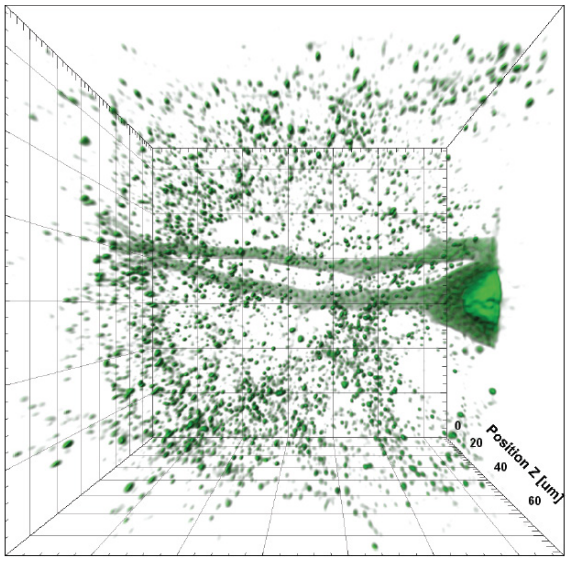


Figure 5. Expression of synaptic tag marking activity (SynTagMA).

The role of microglia in the healthy and the diseased brain

Laura Laprell, Sabine Graf, collaboration with Institute of Neuroimmunology and Multiple Sclerosis

Microglia are the resident immune cells of the brain. In response to pro-inflammatory signals, they dramatically change their morphology, start secreting cytokines and other pro-inflammatory signals. To test various hypotheses about microglia function and their alleged importance for synaptic plasticity, we have developed opto- and chemogenetic tools to switch microglia *on* and *off*. Two-photon imaging allows us to assess microglia changes in response to focal tissue damage or experimentally induced autoimmune encephalitis (Fig. 6). A field recording setup that allows for stable recording of 8 synaptic connections in parallel is used to assess the effects of local microglia activation on synaptic function and long-term plasticity.

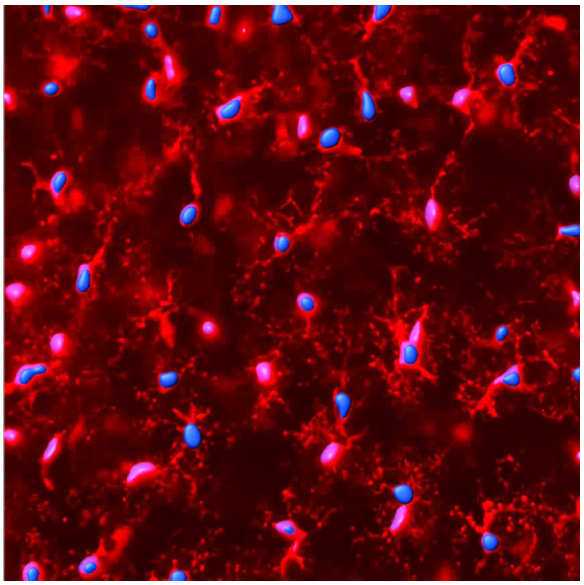


Figure 6. Microglia in organotypic slice culture

Selected Publications

Takahashi N, Oertner TG, Hegemann P, Larkum ME (2016) Active cortical dendrites modulate perception. Science 354:1587-1590.

Blumer C, Vivien C, Genoud C, Perez-Alvarez A, Wiegert JS, Vetter T, Oertner TG (2015) Automated analysis of spine dynamics on live CA1 pyramidal cells. Med Image Anal 19:87-97.

Scheib U, Stehfest K, Gee, C.E, Körschen HG, Fudim R, Oertner TG, Hegemann P (2015) The rhodopsin-guanylyl cyclase of the aquatic fungus Blastocladiella emersonii enables fast optical control of cGMP signaling. Sci Signal 8:rs8.

Wietek J, Beltramo R, Scanziani M, Hegemann P, Oertner TG, Wiegert JS (2015) An improved chloride-conducting channelrhodopsin for light-induced inhibition of neuronal activity *in vivo*. Sci Rep 5:14807.

Wietek J, Wiegert JS, Adeishvili N, Schneider F, Watanabe H, Tsunoda SP, Vogt A, Elstner M, Oertner TG, Hegemann P (2014) Conversion of channelrhodopsin into a light-gated chloride channel. Science 344:409–412.

Support

DFG (FOR 2419 SPP 1665, SFB 936)
CONACYT
DAAD
EMBO
Federal State of Hamburg (Landesforschungsförderung)

Collaborators

Prof. Dr. Manuel Friese
ZMNH/UKE, Germany

Prof. Dr. Ileana Hanganu-Opatz
UKE, Germany

Prof. Dr. Peter Hegemann
Humboldt University,
Berlin, Germany

Prof. Dr. Michael Hoppa
Dartmouth College,
New Hampshire, USA

Prof. Dr. Matthew Larkum
Humboldt University, Berlin, Germany

Prof. Dr. Christian Lohr
Universität Hamburg, Germany

Prof. Dr. Gabriele Rune
UKE, Germany

Prof. Dr. Massimo Scanziani
UCSF, California, USA

Dr. Eric Schreiter
Janelia Farm Research Campus,
Virginia, USA

Dr. Katalin Török
St. George's, London, UK

Team

Director: Prof. Dr. Thomas G. Oertner
Project leaders:
Dr. Christine E. Gee
Dr. J. Simon Wiegert
Postdoctoral fellows:
Dr. Alberto Perez-Alvarez
Dr. Paul Lamothe-Molina
Dr. Laura Laprell
Dr. Christian Schulze
Graduate students:
Céline Dürst
Brenna Fearey
Margarita Anisimova
Oana Constantin
Masters student:
Andreas Franzelin
Technicians:
Iris Ohmert
Sabine Graf
Secretary:
Heike Pehlke

Alumni

Postdoctoral fellow: Dr. Shuting Yin
Master Student: Bas van Bommel

Since 2017, the Institute hosts the Junior Research Group of Dr. J. Simon Wiegert.

Publications 2015 – 6/2017

Bender RA, Zhou L, Vierk R, Brandt N, Keller A, Gee CE, Schafer MK, Rune GM (2017) Sex-dependent regulation of aromatase-mediated synaptic plasticity in the basolateral amygdala. J Neurosci 37:1532-1545.

Bitzenhofer SH, Ahlbeck J, Wolff A, Wiegert JS, Gee CE, Oertner TG, Hanganu-Opatz IL (2017) Layer-specific optogenetic activation of pyramidal neurons causes beta-gamma entrainment of neonatal networks. Nat Commun 8:14563.

Fernandez AM, Hernandez-Garzon E, Perez-Domper P, Perez-Alvarez A, Mederos S, Matsui T, Santi A, Trueba-Saiz A, Garcia-Guerra L, Pose-Utrilla J, Fielitz J, Olson EN, de la Rosa RF, Garcia LG, Pozo MA, Iglesias T, Araque A, Soya H, Perea G, Martin ED, Aleman IT (2017) Insulin regulates astrocytic glucose handling through cooperation with IGF-I. diabetes 66:64-74.

Gee CE, Ohmert I, Wiegert JS, Oertner TG (2017) Preparation of slice cultures from rodent hippocampus. Cold Spring Harb Protoc doi: 10.1101/pdb.prot094888.

Hernandez-Vivanco A, Sanz-Lazaro S, Jimenez-Pompa A, Garcia-Magro N, Carmona-Hidalgo B, Perez-Alvarez A, Caba-Gonzalez JC, Tabernero A, Alonso YGS, Passas J, Blazquez J, Gonzalez-Enguita C, de Castro-Guerin C, Albillos A (2017) Human native Cav1 channels in chromaffin cells: contribution to exocytosis and firing of spontaneous action potentials. Eur J Pharmacol 796:115-121.

Wiegert JS, Gee CE, Oertner TG (2017) Stimulating neurons with heterologously expressed light-gated ion channels. Cold Spring Harb Protoc doi: 10.1101/pdb.top089714.

Wiegert JS, Gee CE, Oertner TG (2017) Viral vector-based transduction of slice cultures. Cold Spring Harb Protoc doi: 10.1101/pdb.prot094896.

Wiegert JS, Gee CE, Oertner TG (2017) Single-cell electroporation of neurons. Cold Spring Harb Protoc doi: 10.1101/pdb.prot094904.

Gee CE, Oertner TG (2016) Neurobiology: Pull out the stops for plasticity. Nature 529:164-165.

Hernandez-Garzon E, Fernandez AM, Perez-Alvarez A, Genis L, Bascunana P, Fernandez de la Rosa R, Delgado M, Angel Pozo M, Moreno E, McCormick PJ, Santi A, Trueba-Saiz A, Garcia-Caceres C, Tschop MH, Araque A, Martin ED, Torres Aleman I (2016) The insulin-like growth factor I receptor regulates glucose transport by astrocytes. Glia 64:1962-1971.

Takahashi N, Oertner TG, Hegemann P, Larkum ME (2016) Active cortical dendrites modulate perception. Science 354:1587-1590.

Wiegert JS, Oertner TG (2016) How (not) to silence long-range projections with light. Nat Neurosci 19:527-528.

Behnke D, Cotesta S, Hintermann S, Fendt M, Gee CE, Jacobson LH, Laue G, Meyer A, Wagner T, Badiger S, Chaudhari V, Chebrolu M, Pandit C, Hoyer D, Betschart C (2015) Discovery of 1H-pyrazolo[3,4-b]pyridines as potent dual orexin receptor antagonists (DORAs). Bioorg Med Chem Lett 25:5555-5560.

Blumer C, Vivien C, Genoud C, Perez-Alvarez A, Wiegert JS, Vetter T, Oertner TG (2015) Automated analysis of spine dynamics on live CA1 pyramidal cells. Med Image Anal 19:87-97.

Kanatsou S, Fearey BC, Kuil LE, Lucassen PJ, Harris AP, Seckl JR, Krugers H, Joels M (2015) Overexpression of mineralocorticoid receptors partially prevents chronic stress-induced reductions in hippocampal memory and structural plasticity. PLoS One 10:e0142012

Scheib U, Stehfest K, Gee, C.E, Körschen HG, Fudim R, Oertner TG, Hegemann P (2015) The rhodopsin-guanylyl cyclase of the aquatic fungus Blastocladiella emersonii enables fast optical control of cGMP signaling. Sci Signal 8:rs8.

Wiegert JS, Oertner TG (2015) Neighborly synapses help each other out. Nat Neurosci 18:326-327.

Wietek J, Beltramo R, Scanziani M, Hegemann P, Oertner TG, Wiegert JS (2015) An improved chloride-conducting channelrhodopsin for light-induced inhibition of neuronal activity *in vivo*. Sci Rep 5:14807.

Master Theses

Oana Constantin (2017) Optogenetic manipulation of cyclic nucleotides in hippocampal slices. Master thesis, Bremen University.

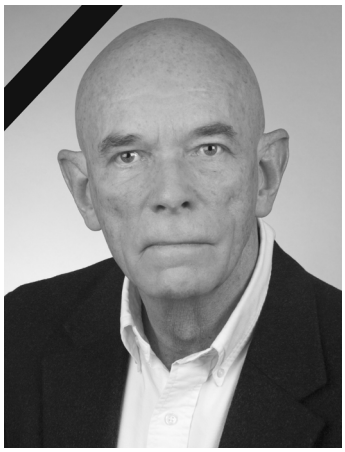
Bas van Bommel (2015) Optic control of spike timing dependent plasticity. Graduate School of Life Sciences, Utrecht University, Holland.

Awards and Distinctions

10/10/2016
ERC Starting Grant
Dr. J. Simon Wiegert, ZMNH Institute of Synaptic Physiology

Institute of Structural Neurobiology

Director: Prof. Dr. Dr. h.c. Michael Frotscher



"But, research requires much time."

- Michael Frotscher

Our colleague and friend Prof. Dr. med. Dr. h.c. Michael Frotscher died after a short serious illness on May 27th, 2017. We will greatly miss his friendly, appreciative manner, his scientific expertise and his tireless efforts to address difficult questions.

With the passing of Prof. Dr. Dr. h.c. Michael Frotscher, we have lost an internationally acclaimed scientist and a wonderful colleague who never lost his curiosity of how the brain works. He was a member of the Faculty of Medicine, Universität Hamburg, a member of the German Research Foundation's Senate Committee on Collaborative Research Centers and Senator of the Section of Neuroscience of the German Academy of Sciences Leopoldina.

In 2011, Michael Frotscher came to Hamburg with a Senior Research Professorship in Neuroscience from the Hertie Foundation and established the Institute of Structural Neurobiology at the Center for Molecular Neurobiology (ZMNH), University Medical Center Hamburg-Eppendorf (UKE). He was elected Director of the ZMNH in 2015.

Michael Frotscher's scientific work on the cyto-architecture and wiring of the brain as well as the structural and functional analysis of synapses is internationally renowned and highly cited. In recognition of his important contributions to the field of neuroanatomy, he received many awards including: the Gottfried Wilhelm Leibniz Prize of the German Research Foundation (DFG) in 1993, the Ernst Jung Prize for Medicine in 2002, an honorary doctorate from Goethe University Frankfurt in 2009 and the Jacob Henle Medal of the Georg-August-Universität Göttingen in 2013. We will treasure our memories of Michael Frotscher, an outstanding scientist and wonderful friend whose heart beat for science.

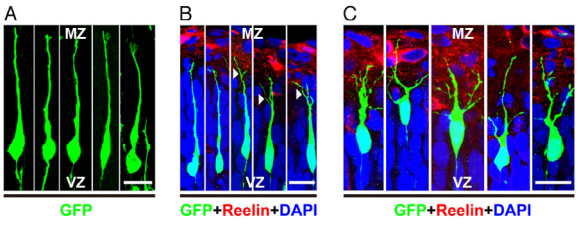
- His colleagues

Reelin signaling stabilize the cytoskeleton of migrating cortical neurons by cooperating with cofilin

Xuejun Chai, Shanting Zhao, Shaobo Wang, Lingzhen Song, Michael Frotscher

The extracellular matrix protein Reelin secreted by Cajal-Retzius cells in the marginal zones of the cerebral cortex and hippocampus plays an important role in controlling neuronal migration. During development cortical neurons that are generated in the ventricular zone have to migrate along the radial glial fibers towards the Reelin-containing marginal zone. Radial glial cells are

Figure 1. Spatial relationship between the Reelin-containing marginal zone (MZ) and the locus of neuronal branching. Brains were transfected with pCAG-GFP at E14.5 and fixed at E17.5. (A) Migrating neurons show bipolar morphology with a long leading process toward the MZ, and a thin trailing process to the ventricular zone (VZ). (B) Neurons with leading processes approaching the MZ develop V-shaped branches (arrowheads). (C) Neurons with their somata contacting the cortical plate and MZ boundary lose their leading processes while forming abundant ramifications. Scale bars: 20 µm (A–C) (modified after Chai et al., 2016).



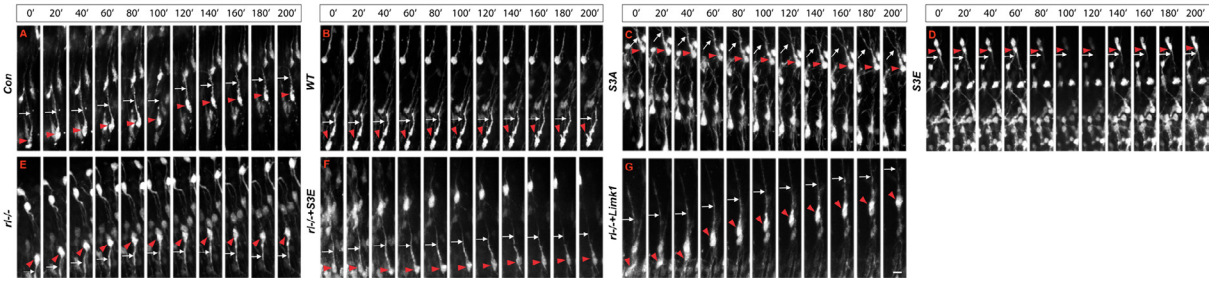


Figure 2. Migratory behavior of neurons transfected with the different constructs 3 days after IUE. (A-G) Individual neurons monitored over a period of 200 min (selected neurons from Movies 1-6). Red arrowheads label cell bodies, white arrows label leading processes. MZ is at the top of the figures, VZ at the bottom. Scale bar: 15 µm (modified after Chai et al., 2016).

bipolar-shaped and span the whole width of the developing cortex. We recently found that branching of migrating neurons and radial glial cells is closely correlated spatio-temporally with the distribution of Reelin. Neurons give rise to more branches from their leading processes as their growth cones contact the Reelin-containing marginal zone, and this is accompanied by translocation of the nucleus and gradual shortening of the leading process (Fig. 1). The branching of the leading processes might be crucial for stabilization of cytoskeleton and termination of nuclear translocation (Chai, et al., 2015).

Our previous study has shown that Reelin signaling induces phosphorylation of cofilin in migrating neurons (Chai et al., 2009). Prof. Witke's lab demonstrated that conditional cofilin knockout mice display migration defects of cortical neurons. Thus, both Reelin and cofilin are indispensable during cortical development. To further study the relation of Reelin with cofilin, we used in utero electroporation and real-time microscopy and found that overexpression of constitutively active form of cofilin (cofilinS3A), and pseudophosphorylated form of cofilin (cofilinS3E) induced migration defects of neurons similar to that in reeler mice, namely, reeler neurons, cofilin S3A- and cofilinS3E-transfected neurons all show aberrant backward migration towards the ventricular zone. Overexpression of cofilinS3E partially rescued the migration defect of reeler neurons (Fig. 2). Therefore, we can conclude that Reelin and cofilin cooperate in controlling cytoskeletal dynamics during neuronal migration.

Reelin from interneurons influences adult neurogenesis in the dentate gyrus

Jasmine Pahle, Janice Graw, Saskia Siegel, Bianka Brunne

Reelin is an extracellular matrix protein which is well known to play a major role in the layering of different brain areas during development while its functions in the adult brain are less well understood. To address this issue we raised a conditional mouse mutant, which lacks Reelin expression exclusively in GABAergic interneurons. Interneurons are the main Reelin source in the adult brain but do not express Reelin during early stages of brain development. In addition, interneurons are the cells that show reduced

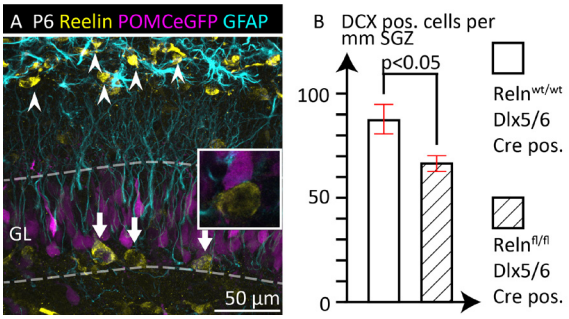


Figure 1. Interogation of single MF synapses. (A) A single MF bouton (open arrow) synapsing on a patched mossy cell was stimulated in cell-attached mode (flash, orange stippled lines). Potential responses varied from trial to trial between subthreshold and suprathreshold EPSPs (black box). Each EPSP is accompanied by a Ca^{2+} transient in a spine head engulfed by the bouton. Gray lines represent single trials, blue and magenta lines indicate median responses. (B) The unlabeled bouton covering the postsynaptic complex spine obtrudes as a dark shadow (open arrow) from the transiently stained extracellular space (XY-two-photon image, scale bar: 5 µm).

Reelin expression in diseases like schizophrenia and epilepsy. In our ongoing project, we focused on several potential functions of Reelin including a stabilization of neuronal structure, the maintenance of adult neurogenesis in the dentate gyrus and a role in synaptic plasticity. We found a significant decrease in the amount of immature neurons in the adult dentate gyrus (Fig. 1). Further studies shall now reveal, which steps of adult neurogenesis are affected and which pathways might be involved.

Reelin and neuron-glia interactions in the developing dentate gyrus

Shaobo Wang, Jasmine Pahle, Janice Graw, Bianka Brunne

Radial glial cells are known for their function as guiding scaffold for migrating neurons during brain development. In the dentate gyrus two different types of radial glia cells exist. Primary radial glia cells which mainly exist during embryonic stages of development and radial glia-like cells (RGLCs) which assemble in a radial scaffold postnatally. In contrast to radial glial cells the RGLCs in the dentate gyrus are severely affected in reeler mice and their function in neuronal migration has not been investigated yet. Unexpectedly, our life-imaging experiments revealed completely independent migration of neurons and glial cells during postnatal development (Fig. 2A). Immunohistochemical analysis with different markers for RGLCs confirmed the lack of a close alignment and attachment of migrating neurons to these cells in wildtype mice. First preliminary data regarding reeler mice hints to a higher degree of attachment of neurons to RGLCs in the absence of Reelin, which might contribute to the severe defects in granule cells and RGLC morphology in reeler mice (Fig. 2B).

Serine 1283 in Reelin is required for proper mouse brain development

David Lutz, Ahmed Sharaf, Shaobo Wang, Dagmar Drexler, Bianka Brunne

Migrating neurons form laminated brain structures under the control of Reelin, which activates canonical lipoprotein receptor signaling. However, it has remained unclear how Reelin promotes and at the same time arrests neuronal migration. We discovered that Reelin is proteolytically active, which is important for stimulation of non-canonical signaling pathways promoting neuronal migration in the mouse cerebral cortex. Mice carrying a point mutation disrupting the Reelin cleavage site (rlnA/A) revealed a severely abnormal phenotype characterized by impaired neuronal migration, abnormal brain architecture, deficient motor control, tremor, and epileptic seizures. Analysis of the various Reelin fragments showed their functional specification. The Reelin fragment N-R6 promoted migration *in vivo*, whereas the central and C-terminal parts led to migratory arrest. Moreover, in utero electroporation of the N-R6 Reelin fragment rescued the migration defects of rlnA/A mutants. Our study uncovers novel insights into Reelin's dual function as a 'go' and 'stop' signaling molecule.

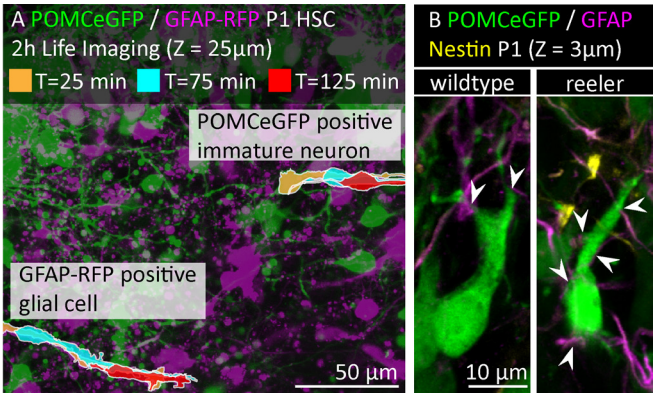


Figure 2. Neuron-glia interactions in the developing dentate gyrus. Life imaging of hippocampal slice cultures from GFAP-RFP / POMCeGFP mice (glial cells – magenta; immature neurons - green) reveals entirely independent migration of neurons and glial cells in the postnatal dentate gyrus (A). Immunohistochemistry confirms that in most cases immature neurons are not clearly aligned or closely connected to RGLCs in wildtype. Interestingly there are much more contacts between those cell types in reeler mice (arrowheads) (B).

Proteolytic cleavage of transmembrane cell adhesion molecule L1 by extracellular matrix molecule Reelin is important for mouse brain development

David Lutz, Ahmed Sharaf, Dagmar Drexler, Bianka Brunne

We found that full-length Reelin and its N-terminal fragments N-R2 and N-R6 bind to the cell adhesion molecule L1 and that full-length Reelin and its N-terminal fragment N-R6 proteolytically cleave L1 to generate an L1 fragment with a molecular mass of 80 kDa (L1-80). Expression of N-R6 and generation of L1-80 coincide in time at early developmental stages of the cerebral cortex. The Reelin-mediated generation of L1-80 promotes neurite outgrowth and stimulates migration of cortical and cerebellar granule neurons. Moreover, morphological abnormalities in layer formation of the cerebral cortex partially overlap with those of Reelin-deficient reeler mice in the cerebral cortices of L1-deficient mice. In utero electroporation of L1-80 into reeler embryos normalized the migration of cortical neurons in reeler embryos. The combined results indicate that the functional interplay between L1 and Reelin and the Reelin-mediated generation of L1-80 contribute to brain development at early developmental stages.

Postnatal Reelin modulates dendritic arborization, synaptic plasticity and electric impedance in Purkinje cells for proper motor learning

David Lutz, Melad Henis, Ahmed Sharaf, Dagmar Drexler, Saskia Siegel

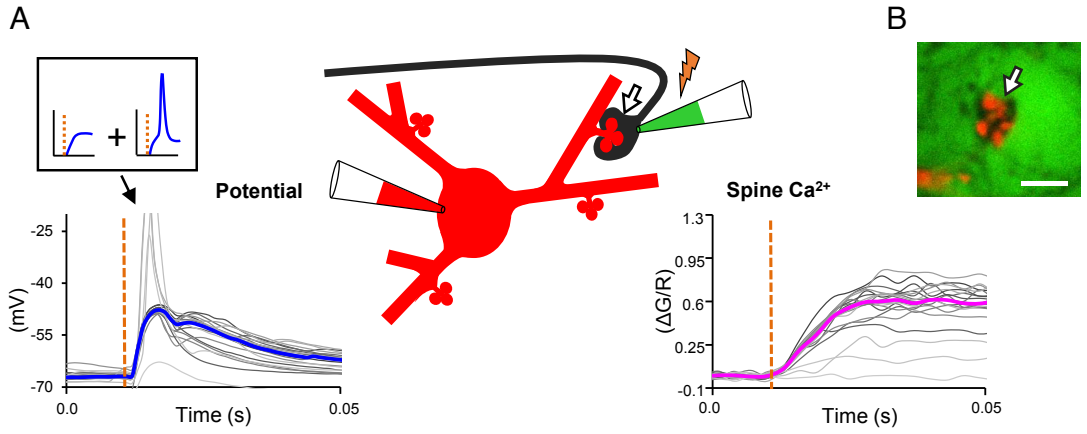
Branching and synaptic connectivity of cerebellar Purkinje cells (PCs) are essential for processing, analysis and retrieval of information concerning body movement control. The glycoprotein Reelin, which is expressed by cerebellar granule neurons (CGNs), is understood to regulate migration and positioning of PCs at early developmental stages, yet its late postnatal functions have remained poorly explored. Here, we studied how conditionally silenced postnatal Reelin expression in CGNs affects dendritic arbor formation, synapse maintenance and electrophysiological response in PCs. We demonstrate that downregulation of postnatal Reelin results in loss of inhibitory Golgi interneurons, altered arbor shape in PCs and impaired synapse formation between PC dendrites and climbing or parallel fibers. The loss of postnatal Reelin expression leads to silencing of spontaneous activity of PCs and a decreased excitability. Additionally, the PCs develop a reduction of a hyperpolarization activated conductance, leading to a reduced hyperpolarization activated sag potential, causing an aberrant electric impedance of the PCs and an altered representation of presynaptic inputs. In transgenic mouse cerebella with ablated postnatal Reelin expression, these structural and physiological deficits manifest into impaired motor learning, highlighting postnatal Reelin as a crucial modulator of autonomous body movement control.

Synaptic transmission and plastisity of individual identified synapses

Alexander Drakew, Urban Maier, Dung Ludwig

Hippocampal mossy fiber (MF) synapses display a heterogeneous morphology of the pre- and postsynaptic component. The large boutons of very variable size and complexity contact simple large spines or multi-headed complex spines. Stimulation of the MF projection results in structural changes of MF synapses. However, little is known about the functional heterogeneity of MF synapses. We focused here on MF synapses on hilar mossy cells, which provide translammilar coupling due to their widespread projection to dentate granule cells and interneurons in the ipsi- and contralateral dentate gyrus. We developed a technique that enabled us to analyze structure to function relationship of individual MF synapses (Fig. 1). Hilar mossy cells were filled with fluorescent dyes via patch pipettes in organotypic entorhino-hippocampal slice cultures. Using two-photon laser scanning microscopy Alexa 594 dextran visualized the morphology of the cells whereas Fluo4-FF reported Ca^{2+} transients in dendritic spines. We adopted “shadow patching” (Kitamura et. al., 2008) to identify and to patch individual MF boutons presynaptic to labelled spines. Boutons were stimulated in loose-seal cell-attached mode to elicit presynaptic APs.

Paired pulse stimulation revealed a remarkable heterogeneity of synaptic strengths and peak Ca^{2+} amplitudes within synapses as well as between synapses, which was in part attributable to a varying release probability of the MF boutons. Most of the synapses displayed subthreshold as well as suprathreshold EPSPs in response to the first stimulus, directly detonating the postsynaptic mossy cells. This is different from MF synapses in CA3 known to require a train of presynaptic APs to detonate the pyramidal cells. When we reevaluated single synapses 30 min. following an associative induction protocol we found potentiated as well as depotentiated responses depending on the initially encountered synaptic state of the synapse. Moreover, we observed in parallel presynaptic and postsynaptic changes in single synapses. The changes in synaptic strengths resulted also in changes of the detonator status. This indicates that synaptic transmission at single MF synapses depends on previous events at these synapses, dynamically adopting synaptic strength and detonation probability to changing input patterns. Thus, single MF synapses on mossy cells modify translaminar coupling in the hippocampus owing to their individual history of synaptic activity.



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Selected Publications

Frotscher M, Zhao S, Wang S, Chai X (2017) Reelin signaling inactivates cofilin to stabilize the cytoskeleton of migrating cortical neurons. Front Cell Neurosci 11:148.

Scharkowski F, Frotscher M, Lutz D, Korte M, Michaelsen-Preusse K (2017) Altered connectivity and synapse maturation of the hippocampal mossy fiber pathway in a mouse model of the fragile X syndrome. Cereb Cortex doi: 10.1093/cercor/bhw408. [Epub ahead of print]

Chai X, Zhao S, Fan L, Zhang W, Lu X, Shao H, Wang S, Song L, Failla AV, Zobiak B, Mannherz HG, Frotscher M (2016) Reelin and cofilin cooperate during the migration of cortical neurons: a quantitative morphological analysis. Development 143:1029-1040.

Guzman SJ, Schlogl A, Frotscher M, Jonas P (2016) Synaptic mechanisms of pattern completion in the hippocampal CA3 network. Science 353:1117-1123.

Dieni S, Nestel S, Sibbe M, Frotscher M, Hellwig S (2015) Distinct synaptic and neurochemical changes to the granule cell-CA3 projection in Bassoon mutant mice. Front Synaptic Neurosci 7:18.

Collaborators

Prof. Dr. Yves-Alain Barde
Cardiff School of Biosciences, Cardiff, UK

Profs. Dr. Petra May and Dr. Hans Bock
University Hospital of Düsseldorf, Düsseldorf, Germany

Prof. Dr. Frank Bradke
DZNE, Bonn, Germany

Prof. Dr. Tom Curran
Children's Research Institute, Kansas City, USA

Prof. Dr. André Goffinet
Psychological Sciences Research Institute, Louvain-la-Neuve, Belgium

Prof. Dr. Florian Grüner
DESY, UHH, Hamburg, Germany

Prof. Dr. Eckart D. Gundelfinger
Leibnitz Institute of Neurobiology, Magdeburg, Germany

Prof. Dr. Carola A. Haas
Department of Neurosurgery, University of Freiburg, Germany

Prof. Dr. Joachim Herz
University of Texas Southwestern Medical Center at Dallas, Dallas TX, USA

Prof. Dr. Peter Jonas
Institute of Science and Technology, Vienna, Austria

Prof. Dr. Frank Kirchhoff
University of Saarland, Homburg, Germany

Profs. Dr. Eva und Dr. Eckhard Mandelkow,
DZNE, Bonn, Germany

Prof. Dr. Patricia Maness
Dept. of Biochemistry and Biophysics, University of Texas, Houston, USA

Prof. Dr. Dr. h. c. Melitta Schachner
ZMNH, Hamburg, Germany

Prof. Dr. Orly Reiner and
Prof. Dr. Menahem Segal
Weizmann Institute, Rehovot, Israel

Dr. Daniel Studer
Institute of Anatomy Bern, Bern, Switzerland

Prof. Dr. Walter Witke
Institute of Genetics, Bonn, Germany

Prof. Dr. Shanting Zhao
North West A&F University, Yang Ling, PR China

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Egyptian Government

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Team

Director/Administration:

Prof. Dr. Dr. h. c. Michael Frotscher
Sibylle Koerner

Postdocs:

Dr. Bianka Brunne
Dr. Xuejun Chai
Dr. Alexander Drakew
Dr. David Lutz
Dr. Ahmed Sharaf

PhD students:

Janine Grawe
Melad Henis
Wenchao Li
Urban Maier
Mevlanu Mamuti
Jasmine Pahle
Lingzhen Song
Kristen Thomsen
Shaobo Wang
Wei Yang

Master students:

Nigar Ahmadova
Sascha Fichter
Frederike Weßel

Technicians:

Dagmar Drexler
Janice Graw
Dung Ludwig
Saskia Siegel

Publications 2015 – 6/2017

Frotscher M, Haas CA (2017) Epilepsy-associated Reelin dysfunction induces granule cell dispersion in the dentate gyrus. In: Reference Module in Neuroscience and Biobehavioral Psychology. Amsterdam: Elsevier Inc. doi:10.1016/B978-0-12-809324-5.00032-8.

Frotscher M, Zhao S, Wang S, Chai X (2017) Reelin signaling inactivates cofilin to stabilize the cytoskeleton of migrating cortical neurons. Front Cell Neurosci 11:148.

Haumann I, Junghans D, Anstötz M, Frotscher M (2017) Presynaptic localization of GluK5 in rod photoreceptors suggests a novel function in the mammalian retina. PloS ONE 12(2):e0172967.

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Ding Y, Huang L, Xian X, Yuhanna IS, Wasser CR, Frotscher M, Mineo C, Shaul PW, Herz J (2016) Loss of Reelin protects against atherosclerosis by reducing leukocyte-endothelial cell adhesion and lesion macrophage accumulation. Sci Signal 9:ra29.

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Lane-Donovan C, Philips GT, Wasser CR, Durakoglugil MS, Masiulis I, Upadhaya A, Pohlkamp T, Coskun C, Kotti T, Steller L, Hammer RE, Frotscher M, Bock HH, Herz J (2015) Reelin protects against amyloid β toxicity *in vivo*. Sci Signal 8:ra67.

Sibbe M, Kuner E, Althof D, Frotscher M (2015) Stem- and progenitor cell proliferation in the dentate gyrus of the reeler mouse. PlosOne 10:e0119643.

Singec I, Knoth R, Vida I, Frotscher M (2015) The rostral migratory stream generates hippocampal CA1 pyramidal-like neurons in a novel organotypic slice co-culture model. Biol Open 4:1222-1228.

Wang JT, Song LZ, Li LL, Zhang W, Chai X.J, An L, Chen SL, Frotscher M, Zhao ST (2015) Src controls neuronal migration by regulating the activity of FAK and cofilin. Neuroscience 292:90-100.

Bachelor Theses

Fichter, Sascha (2015) Zwischen analoger und digitaler Welt – Signalverarbeitung am 2-Photonen-Mikroskop. Department of Biotechnology, Hochschule für Angewandte Wissenschaften Hamburg.

Awards and Distinctions

Dr.-Martini-Preis of Dr.-Martini-Stiftung 2016, Hamburg - Dr. Xuejun Chai

Teacher of the Year 2016 for Neuroanatomy at UKE, Hamburg - Dr. Dipl.-Ing. David Lutz

Institute of Molecular Neurogenetics

Director: Prof. Dr. Matthias Kneussel

The ZMNH Institute of Molecular Neurogenetics studies protein transport and the turnover of synaptic and neuronal disease-related proteins, which depends on a dynamic actin- and microtubule cytoskeleton in axons and dendrites (Fig.1). Under physiological conditions, protein trafficking mechanisms contribute to the regulation of synaptic function and plasticity. In contrast, specific trafficking dysfunctions affect plastic adaptation at synapses, alter learning and memory or participate in mental disease and neurodegeneration.

We study transport mechanisms at three major molecular levels: (1) cytoskeletal actin filaments and microtubules, which represent the tracks for transport, (2) myosin, kinesin and dynein motor proteins, which use ATP as energy source to power the delivery of various molecules across the cell, and (3) cargo adaptors, which mediate specificity of motor-cargo coupling underlying the delivery of specific proteins and organelles.
To investigate subcellular trafficking with respect to neuronal physiology and disease we apply four major technical approaches *in vitro* and *in vivo*. (A) Cell biological methods: we use time-lapse video microscopy and FRAP imaging to measure the direction, velocity and turnover rates of dynamics molecules (Fig. 2A, B). Using TIRF imaging, we detect protein dynamics underneath the plasma membrane. (B) Biochemical methods: using cell surface biotinylation, sucrose gradient centrifugation and co-sedimentation assays, we measure molecular parameters and verify protein-protein interactions in western blot-based experiments. (C) Mouse genetic methods: we deplete protein expression by generating knockout mice or express mutant proteins via mouse knock-in approaches. (D) Mouse behavioral analysis: we assess behavioral parameters in wildtype and mutant mice, studying hyperactivity, anxiety, cognitive performance and social behavior (Fig. 2C and 4). The combination of molecular/cellular transport studies with behavioral analysis of respective mutant mice connects the dynamics of neuronal proteins with cognitive performance and brain disease.

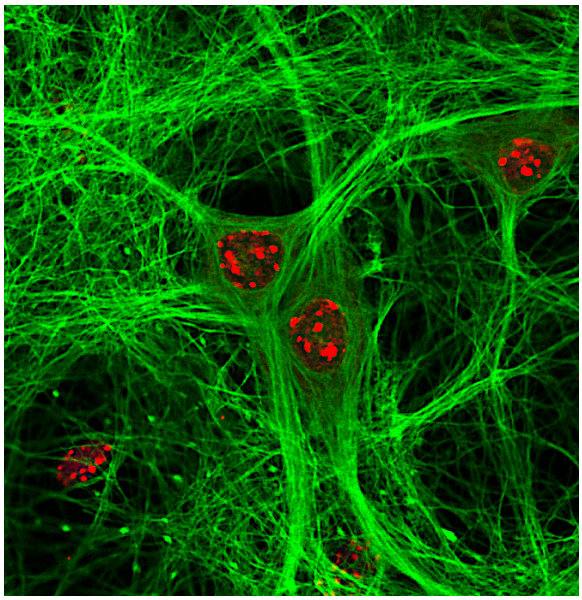

Figure 1. The neuronal microtubule cytoskeleton (green) detected with an antibody specific for beta-3 tubulin. The red marker detects nucleo-somes in the nucleus.

Investigating the dynamic and polyglutamylated microtubule cytoskeleton

Microtubules mediate important functions as tracks for subcellular transport along which motor-cargo complexes move. They are highly dynamic, grow and shrink on a fast time scale and undergo posttranslational modifications that are thought to regulate interaction with microtubule binding proteins. In dendrites, microtubules deliver Golgi-derived membrane proteins and participate in endocytic recycling mechanisms. At synapses, microtubules transiently invade dendritic spines in an NMDA receptor and activity-dependent manner. To access new branches of neurites, microtubules undergo local severing into short pieces, which generates new cones for outgrowth. Finally, kinesin-4 family motors, such as KIF21B, regulate the dynamics of microtubule growth (Muhia…Kneussel et al., (2016) Cell Reports 15, 968-977; Ghiretti…

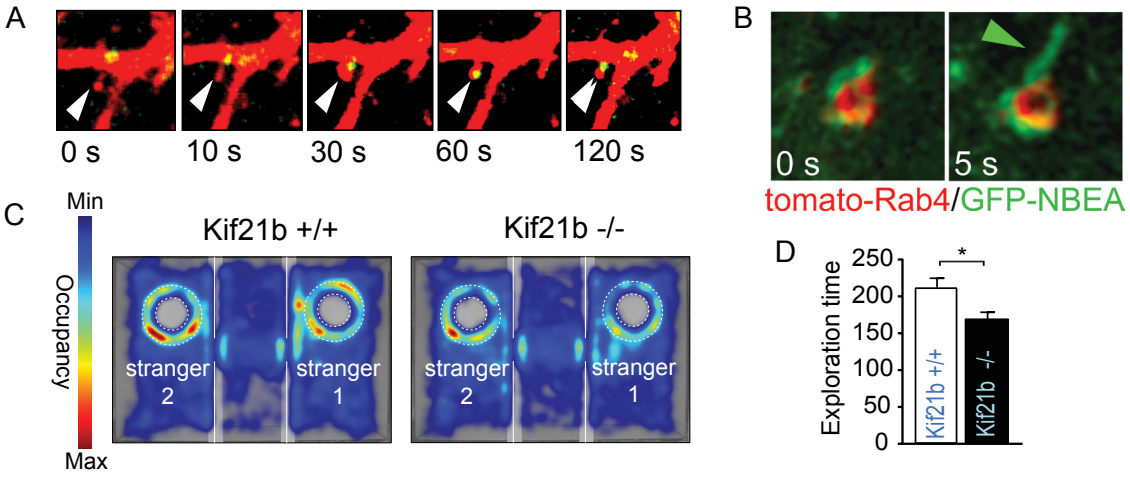

Figure 2. (A) The KIF21B binding protein neurobeachin (NBEA) transiently enters and leaves dendritic spines over a time period of 120 s (A), in an activity-dependent manner (not shown). (B) KIF21B/NBEA interactions regulate the recycling of NMDA receptors (not shown) and GFP-NBEA is a component at Rab4 positive recycling endosomes that form tubular extensions (B). (C, D) Gene knockout of KIF21B in mice causes social preference deficits. Heat plot showing wildtype and KIF21B $^{-/-}$ mice. The exploration time of a familiar versus a stranger mouse is investigated.

Kneussel, Holzbaur et al., Neuron (2016) 92, 857-872), by acting as a pausing factor at growing microtubule plus ends.

To investigate the role of microtubule severing, we generated knockout mice of two major severing enzymes katanin and spastin (Brill … Kneussel, Misgeld et al., (2016) Neuron 92, 845-856). Consistent with their role in microtubule severing, neurons deficient for either spastin or katanin exhibit longer microtubules with a higher density in neurite extensions. Both enzymes are found in close proximity to synapses and depletion of either of them decreases glutamate receptor levels at synaptic sites. Spastin KO mice exhibit deficits in motor performance, a finding consistent with spastic paraplegia phenotypes of patients carrying mutations in the spastin gene. Interestingly, we further identified memory deficits in spastin KO animals, suggesting that microtubule severing regulates cognitive performance (manuscript in preparation). Microtubule severing through katanin is protected by the decoration of microtubules through tau, a microtubule-associated protein involved in different tauopathies including Alzheimer´s disease. With respect to katanin knockout mice, we currently investigate the functional relation of katanin, tau and neuronal transport. Recent data suggest that microtubule severing is promoted by polyglutamylation, a posttranslational modification of tubulin that adds negatively charged amino acid residues to the microtubule surface. We therefore generated a tubulin knock-in mouse mutant, in which microtubule polyglutamylation is hindered. Although these animals display normal long-term potentiation (LTP), microtubule growth is reduced and specific transport parameters are affected (unpublished). Together our microtubule mouse models display opposite phenotypes (longer versus shorter microtubules), which allow us to address contrary questions in the analysis of neuronal transport.

With respect to microtubule-regulatory kinesins (kinesin-4 family members), we study the KIF21B motor that mediates a dual function in regulating microtubule growth and cargo transport. Interestingly, in Alzheimer´s disease patients, KIF21B gene expression was found to be upregulated by 500%. We found that KIF21B associates with neurobeachin (NBEA) at endocytic recycling tubular vesicles (Fig. 2B and data not shown). Both factors functionally cooperate in regulating NMDA receptor turnover. Depletion of either of them in mice causes autism-like social deficits, indicating a critical role of microtubule dynamics in social behavior (Gromova et al., under review).

Investigating neuronal motor protein function in synaptic transport and plasticity

Excitatory synapses are frequently located on dendritic spines, small postsynaptic compartments markedly enriched for actin filaments. How postsynaptic actin affects the development, function and plasticity of synapses is still incompletely understood. We aim to shed light on this by investigating the roles of neuronally expressed myosin motor proteins. Myosins represent a large family of functionally diverse cytoskeletal motors that bind to actin filaments (Kneussel and Wagner, (2013), Nat Rev Neurosci 14:233-247). In terms of synapse function, myosin VI is of particular interest because it is present in a complex with AMPA receptors and affects their intracellular trafficking (Fig. 3A). Strikingly, our studies reveal that myosin VI regulates synaptic plasticity at parallel fiber (PF) to Purkinje cell (PC) synapses (manuscript in preparation). Since PCs are central signal integrators of the cerebellar circuitry we generated mice that carry a conditional allele of Myo6 (encodes the myosin VI heavy chain) and investigated whether myosin VI is required in PCs for motor learning and coordination (Fig. 3B). Furthermore, we characterized the *in situ* localization of myosin VI via confocal and immuno-electron microscopy (Fig. 3C) and used live cell imaging to obtain insight into how the myosin regulates AMPA receptors in PCs (Fig. 3D). Among the myosins expressed in PCs are also myosin Id and myosin XVI. Published protein-protein interactions suggest that also these myosins (that are functionally unrelated to myosin VI) might be important for postsynaptic function and plasticity. To elucidate their roles in PCs is currently another research focus in the lab.

In addition to myosin motors, we focus on transport studies of kinesin family proteins (KIFs) and dynein, which travel along microtubules in plus end or minus end directions, respectively. KIF 5 transports AMPA-, $GABA_A$- and glycine receptors (Kneussel, Triller, Choquet (2014) Cell 157, 1738-1783e1) and is a classical marker to image synaptic receptor delivery.

Investigating cargo adapter function in health and neuronal disease

Some years ago, we identified muskelin to mediate critical regulatory and cargo adapter functions in the endocytosis of $GABA_A$ receptors in neurons (Heisler et al., (2011) Neuron 70, 66-81). Through the association with myosin VI motors and a subsequent direct binding to the dynein motor complex, muskelin was suggested to promote switching between actin- and micro-

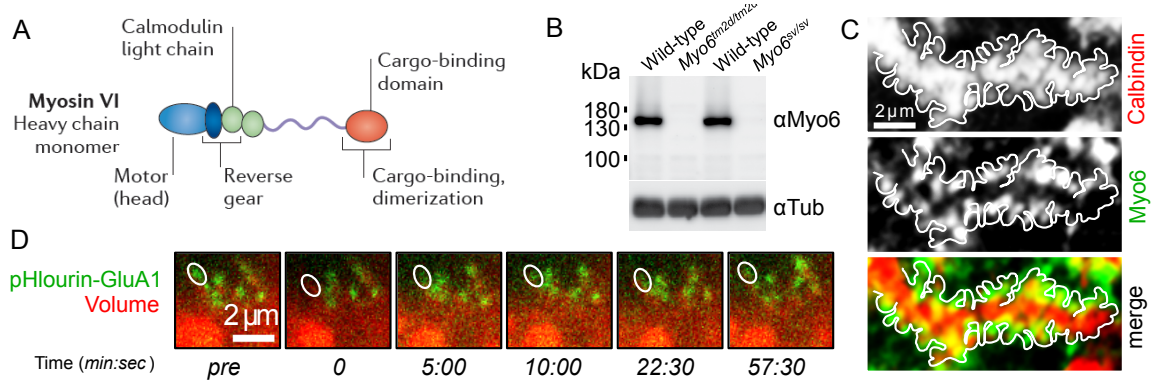

Figure 3. (A) Structural features of myosin VI (modified from Kneussel and Wagner, 2013, Nat Rev Neurosci 14:233-247). (B) Western blot demonstrating that cre-mediated recombination of the conditional Myo6 allele ($Myo6^{tm2d/tm2d}$) disrupts myosin VI expression, as does the *Snell's* waltzer allele ($Myo6^{sv/sv}$). (C) Confocal microscopy of cerebellar sections shows that myosin VI localizes at Purkinje cell spines. (D) Fluorescence recovery after photobleaching (FRAP) approach to study the turnover of surface-exposed AMPA receptor subunit GluA1 at Purkinje cell spines.

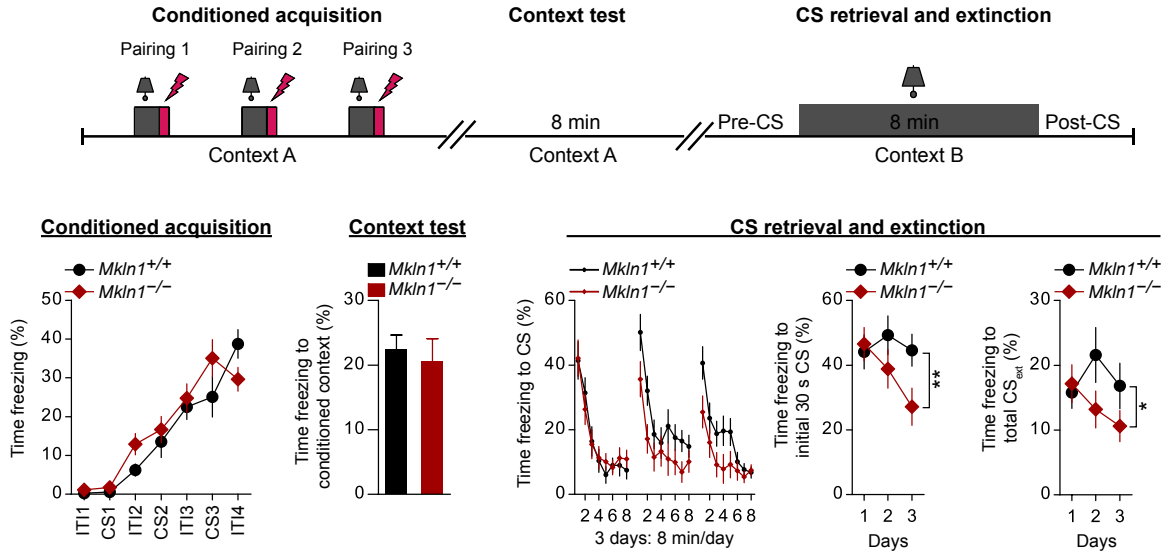

Figure 4. Cued fear¬ conditioning paradigm used to assess associative fear learning and extinction of fear memory. Muskelin depletion does not alter conditioned acquisition, but accelerates fear extinction.

tubule-based vesicle transport. With respect to GABAergic synaptic transmission, we found muskelin to critically balance hippocampal network oscillations, while another lab recently identified muskelin as a potential risk factor for early onset bipolar disorders. At the molecular level, we revealed distinct oligomerization patterns that regulate muskelins differential localization to the cytosol and/or the neuronal nucleus (Delto et al., Structure (2015) 23, 364-373).

Currently, we investigate behavioral phenotypes in muskelin KO mice that demonstrate a critical role for muskelin in mediating *in vivo* function. With respect to cognition, loss of muskelin spares spatial reference memory but facilitates reversal learning, with KO mice demonstrating a stronger preference for the spatial training quadrant. We have also examined the contribution of muskelin to the acquisition, expression and extinction of fear memory. Muskelin KO mice show normal fear acquisition and intact memory for background contextual stimuli. Although loss of muskelin has minimal impact on initial recall of the discrete phasic CS, it promotes fear extinction upon continuous presentation of non-reinforced CS (Fig. 4). Therefore, muskelin depletion enhances adaptive forms of learning that require some degree of behavioral/cognitive flexibility.
Furthermore, we are investigating a neuroprotective role for muskelin in regulating cellular prion protein (PrP^C) vesicle turnover (Heisler et al., in revision). Muskelin and dynein robustly associate with PrP^C transport vesicles, where muskelin coordinates bidirectional PrP^C trafficking and facilitates PrP^C lysosomal degradation versus its release on secreted exosomes (Fig. 5). The conversion of PrP^C to its infectious isoform causes neurodegeneration including Creutzfeldt-Jakob disease. Exosomes participate in the spread of pathogenic prions throughout the nervous system. In this respect, we find that prion disease is accelerated following infection of muskelin KO mice with pathogenic prions (Fig. 5). Our data suggest that muskelin displays a key checkpoint in PrP^C vesicle turnover, by providing a novel connection between intracellular lysosome targeting and extracellular exosome trafficking, which is relevant to the pathogenesis of neurodegenerative conditions.

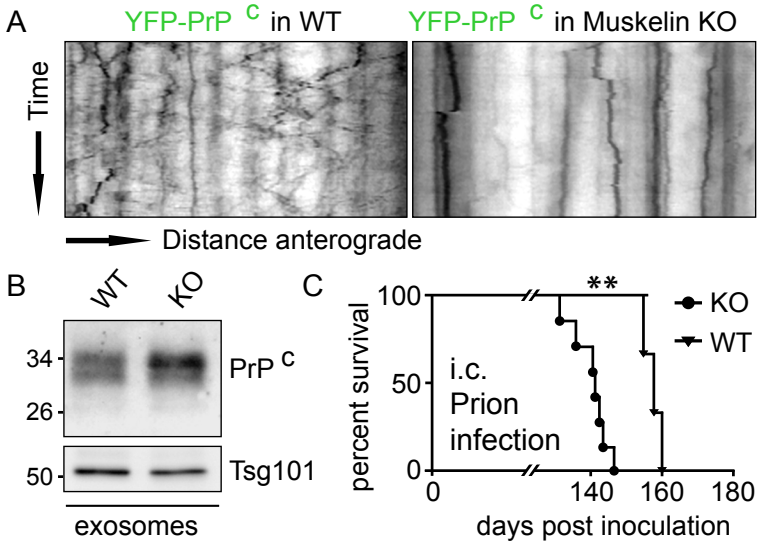

Figure 5. Muskelin regulates PrP^C trafficking and prion disease progression. (A) Reduced mobility of PrP^C vesicles in muskelin KO neurons. (B) Increased PrP^C content on exosomes secreted from muskelin KO neurons. (C) Accelerated prion disease progression in muskelin KO mice.

Selected Publications

Maric HM, Hausrat TJ, Neubert F, Dalby NO, Doose S, Sauer M, Kneussel M, Stromgaard K (2017) Gephyrin-binding peptides visualize postsynaptic sites and modulate neurotransmission. Nat Chem Biol 13:153-160.

Brill MS, Kleele T, Ruschkies L, Wang M, Marahori NA, Reuter MS, Hausrat TJ, Weigand E, Fisher M, Ahles A, Engelhardt S, Bishop DL, Kneussel M, Misgeld T (2016) Branch-specific microtubule destabilization mediates axon branch loss during neuromuscular synapse elimination. Neuron 92:845-856.

Ghiretti AE, Thies E, Tokito MK, Lin T, Ostap EM, Kneussel M, Holzbaur EL (2016) Activity-dependent regulation of distinct transport and cytoskeletal remodeling functions of the dendritic kinesin KIF21B. Neuron 92:857-872.

Muhia M, Thies E, Labonte D, Ghiretti AE, Gromova KV, Xompero F, Lappe-Siefke C, Hermans-Borgmeyer I, Kuhl D, Schweizer M, Ohana O, Schwarz JR, Holzbaur EL, Kneussel M (2016) The kinesin KIF21B regulates microtubule dynamics and is essential for neuronal morphology, synapse function, and learning and memory. Cell Rep 15:968-977.

Hausrat TJ, Muhia M, Gerrow K, Thomas P, Hirdes W, Tsukita S, Heisler FF, Herich L, Dubroqua S, Breiden P, Feldon J, Schwarz JR, Yee BK, Smart TG, Triller A, Kneussel M (2015) Radixin regulates synaptic $GABA_A$ receptor density and is essential for reversal learning and short-term memory. Nat Commun 6:872.

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Collaborators

Prof. Dr. Chris de Zeeuw, Rotterdam, Netherlands
Prof. Dr. Jens Eilers, Leipzig Germany
Prof. Dr. Markus Glatzel, Hamburg, Germany
Prof. Dr. Erika Holzbaur, Philadelphia, USA
Prof. Dr. Manfred Kilimann, Göttingen, Germany
Pro.f Dr. Christine Klein, Lübeck, Germany
Prof. Dr. Christian Lohr, Hamburg, Germany
Prof. Dr. Thomas Misgeld, Munich, Germany
Prof. Dr. Tobias Moser, Göttingen, Germany
Prof. Dr. Dr. Robert Nitsch, Münster, Germany
Prof. Dr. Thomas Oertner, Hamburg, Germany
Prof. Dr. Gabriele Rune, Hamburg, Germany
Prof. Dr. Hermann Schindelin, Würzburg, Germany
Prof. Dr. Trevor Smart, London, UK
Prof. Dr. August Smit, Amsterdam, Netherlands
Prof. Dr. Christian Stromgaard, Kopenhagen, Denmark
Prof. Dr. Dr. Antoine Triller, Paris, France
Prof. Dr. Sachiko Tsukita, Osaka, Japan
Prof. Dr. Dr. Hisashi Umemori, Boston, USA
Dr. Johannes Vogt, Mainz, Germany

Team

Director/Administration:
Prof. Dr. Matthias Kneussel
Angelika Kneussel
Postdocs:
Dr. Kira Brune, nèe Gromova
Dr. Sandra Freitag
Dr. Torben Hausrat
Dr. Frank F. Heisler
Dr. Mary Muhia
Dr. Wolfgang Wagner
Guest scientist:
Prof. Dr. Jürgen Schwarz
PhD students:
Franco Lombino
Andre T. Lopes
Jennifer Radwitz
Mona Roesler
(to Wolfgang Wagner)
MD student:
Lea Cochius
Master student:
Nicola Rothammer
Technicians:
Petra Breiden
Yvonne Pechmann
Edda Thies

Publications 2015 – 6/2017

Maric HM, Hausrat TJ, Neubert F, Dalby NO, Doose S, Sauer M, Kneussel M, Stromgaard K (2017) Gephyrin-binding peptides visualize postsynaptic sites and modulate neurotransmission. Nat Chem Biol 13:153-160.

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Cheng J, Sahani S, Hausrat TJ, Yang JW, Ji H, Schmarowski N, Endle H, Liu X, Li Y, Bottche R, Radyushkin K, Maric HM, Hoerder-Suabedissen A, Molnar Z, Prouvot PH, Trimbuch T, Ninnemann O, Huai J, Fan W, Visentin B, Sabbadini R, Stromgaard K, Stroh A, Luhmann HJ, Kneussel M, Nitsch R, Vogt J (2016) Precise somatotopic thalamocortical axon guidance depends on LPA-mediated PRG-2/Radixin signaling. Neuron 92:126-142.

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Rosso JP, Schwarz JR, Diaz-Bustamante M, Ceard B, Gutierrez JM, Kneussel M, Pongs O, Bosmans F, Bougis PE (2015) MmTX1 and MmTX2 from coral snake venom potently modulate $GABA_A$ receptor activity. Proc Natl Acad Sci U S A 112:E891-900.

Schreiber J, Vegh MJ, Dawitz J, Kroon T, Loos M, Labonte D, Li KW, Van Nierop P, Van Diepen MT, De Zeeuw CI, Kneussel M, Meredith RM, Smit AB, Van Kesteren RE (2015) Ubiquitin ligase TRIM3 controls hippocampal plasticity and learning by regulating synaptic gamma-actin levels. J Cell Biol 211:569-586.

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Vierk R, Bayer J, Freitag S, Muhia M, Kutsche K, Wolbers T, Kneussel M, Sommer T, Rune GM (2015) Structure-function-behavior relationship in estrogen-induced synaptic plasticity. Horm Behav 74:139-148.

Master Thesis

Nicola Rothammer (2016) Neurobeachin, a candidate gene for autism spectrum disorder, regulates endocytic recycling of N-methyl-D-aspartate receptors in hippocampal neurons from Mus musculus. Department of Biology, Universität Hamburg.

Guest scientist

Prof. Dr. Jürgen R. Schwarz

Introduction

Since my retirement in 2006 from the position as head of the *Institut für Angewandte Physiologie* (UKE) I have been a guest scientist in the ZMNH, 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).

My research covers two topics:

1. Functional analysis of neuronal K channels
2. Function of proteins involved in synaptic transport processes.

Neuronal K channels

Function of erg K channels in Purkinje cells

I am interested in the physiology of voltage-dependent ion channels to understand the mechanisms underlying neuronal excitability. Within this general goal I study the function of erg (ether-à-go-go-related gene) K channels in the brain. In our present project we are analysing the function of erg channels in Purkinje cells of the cerebellum and their importance for motor control and coordination. All members of the erg channel family (erg1-3) are expressed in the brain. In contrast to cardiac erg channels neuronal erg K channels are subthreshold channels. Erg channel blockage lowers the threshold potential and increases the frequency of action potentials (Fig.1). The biophysical properties of the native erg current together with results from quantitative PCR and experiments with toxins selective for different erg channel subunits indicated that native erg channels are presumably heteromeric channels, constructed from erg1 and erg3 channel subunits. These data were recently published (Niculescu et al., 2013).

To analyse erg channel function for motor behaviour, we study on the cellular level the effect of erg channel blockage on spontaneous activity of Purkinje cells at body temperature. These data will soon be published. In addition, we tried 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.

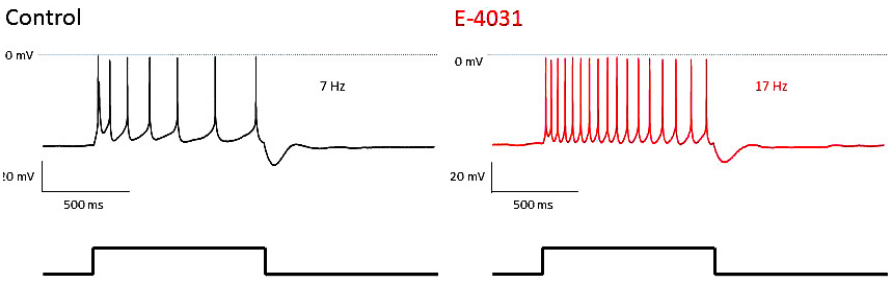

Figure 1. Repetitive activity, mouse Purkinje cell, p8, 22°C, acute slice.

We have injected the viral solution into the lateral ventricle of P1 mice. After 14 days Purkinje cells were selectively stained. Unfortunately, we were not able to reduce the erg current amplitude significantly. Presently we are considering to perform a knock-out of erg channels in Purkinje cells with the CRISPR/Cas method.

Publication:

Niculescu D, Hirdes W, Hornig S, Pongs O, Schwarz JR (2013) Erg potassium currents of neonatal mouse Purkinje cells exhibit fast gating kinetics and are inhibited by mGluR1 activation. J Neurosci 33: 16729–16740.

Function of TRAAK current in the rat node of Ranvier

Recently, Roderick MacKinnon and colleagues (Rockefeller University, New York) crystallized the TRAAK channel (Brohawn et al., Science 335, 436, 2012). TRAAK is a mechano-sensitive voltage-independent K channel (TRAAK:TWICK-related-arachidonic-acid-activated K channel). Unexpectedly, TRAAK channels are localized exclusively to the nodes of Ranvier of peripheral and central nerve fibers (unpublished results). Analysis of these channels in CHO cells after heterologous expression of TRAAK channels in CHO cells showed that they are voltage- and time-independent K-selective leakage channels and are activated by high temperature, arachidonic acid and alkaline solutions (Brohawn et al., 2012). However, the main characteristic of TRAAK channels is their high sensitivity to mechanical stretch. We want to answer the question, why the node of Ranvier contains a stretch-activated K channel. Since I am experienced in doing experiments on single nodes of Ranvier Rod MacKinnon asked me to collaborate and to analyze the function of TRAAK channels in the rat node of Ranvier. Rod MacKinnon visited our lab in Hamburg in January 2017 for two weeks. In March and August 2017 I visited the MacKinnon lab and did experiments in New York. Our initial experiments show that TRAAK channels are functionally present in the rat node of Ranvier, but, as yet, we can not explain why the node is equipped with mechanically activated ion channels.

Modulation of KCNQ1 by intracellular calcium

This project is a collaboration of the Institute of Molecular Neurogenetics with Dr. V. Vardanyan, Yerevan. With support by the VW foundation Dr. Vardanyan has equipped a laboratory in the Institute of Molecular Biology of the National Academy of Sciences in Yerevan. So far, successful experiments on mutated KCNQ1 channels have been performed. The point mutations of the KCNQ1 channels have been done at the Institute of Molecular Neurogenetics, ZMNH. In this project the modulation of KCNQ1 channel function by intracellular calcium is studied. In December 2016 the VW foundation decided to prolong the financial support until 2019.

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

Two micrurotoxins, MmTX1 and MmTX2, were isolated from the venom of a Costa Rican coral snake by Prof. Pierre Bougis, Aix Marseille university. Both toxins bind to GABA(A) receptors at nanomolar concentrations. We have shown that the toxins potentiate the GABA current at low GABA concentrations, whereas at higher concentrations no effect was visible. This work was recently published (Rosso et al., 2015).

Motor proteins and synaptic neurotransmission

The Institute of Molecular Neurogenetics investigates the function of several proteins that are involved in transport processes underlying the regulation of neurotransmission. I am involved in several projects with patch clamp recordings in hippocampal cultures and acute slices. The investigations about $GABA_A$-α5 receptors and Kif21b have already been published (Hausrat et al., 2015; Muhia et al., 2016). Present projects investigate the function of myosin VI, muskelin and spastin.

Selected Publications

Muhia M, Thies E, Labonte D, Ghiretti AE, Gromova KV, Xompero F, Lappe-Siefke C, Hermans-Borgmeyer I, Kuhl D, Schweizer M, Ohana O, Schwarz JR, Holzbaur EL, Kneussel M (2016) The Kinesin KIF21B regulates microtubule dynamics and is essential for neuronal morphology, synapse function, and learning and memory. Cell Rep 15:968-977.

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*equal contribution

Team

Head: Prof. Dr. Jürgen R. Schwarz
Postdoctoral fellow: Dr. Sönke Hornig
(until 2016)

Support

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(Az: DFG Schw292/16-2 until 2016)
and Volkswagen Foundation
(Az: 92111, from 2017 until 2019).
Internal: Prof. Kneussel
(Institute of Molecular Neurogenetics)
and ZMNH administration.

Collaborators

Prof. Dr. Christiane K. Bauer
Institut für Physiologie, UKE, University of Hamburg

Prof. Dr. Roderick MacKinnon
Rockefeller University, New York

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

Dr. Vitya Vardanyan
Institute of Molecular Biology, National Academy of Sciences, Yerevan, Armenia

Institute of Molecular and Cellular Cognition

Director: Prof. Dr. Dietmar Kuhl

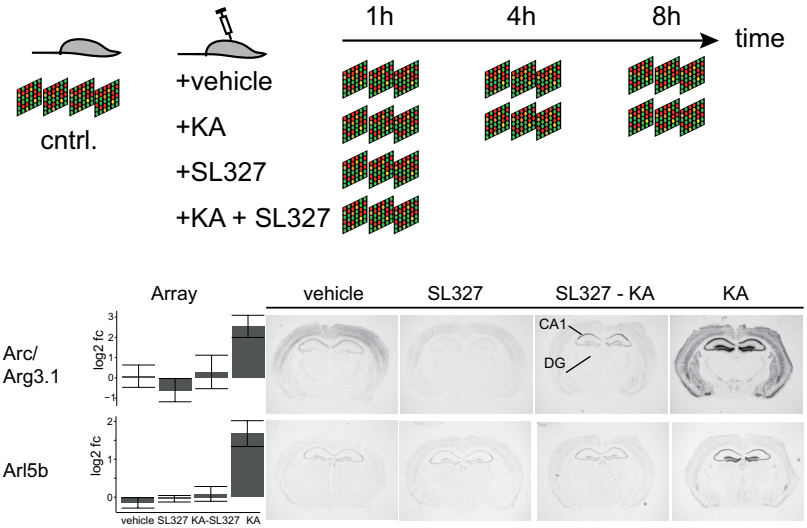
LEARNING ABOUT ACTIVITY-DEPENDENT GENES, SYNAPTIC PLASTICITY AND THE PERSISTENCE OF MEMORIES

Scientists of the IMCC are taking an integrative, multidisciplinary approach to the studies of learning and memory 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. Several of the activity-regulated genes first identified in our laboratory code for proteins that can directly modify the physiology of neurons. 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.

Profiling of the activity regulated transcriptome

Barbara Merz, Andrea Zaisser, Guido Hermey

Enduring forms of synaptic plasticity like long-term memory require activity-dependent gene induction that is important in defining neuronal connectivity in the brain. Many forms of mental disabilities, including neurodegenerative processes and cognitive disturbances, can 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



Transcriptome wide analysis of activity dependent changes Experimental design (upper panel). Expression of activity-regulated MAP-Kinase-dependent genes (lower panel). Bar diagrams (left) and autoradiograms (right) illustrate changes in gene expression (adapted from Sci Rep (2017).

neuronal stimulation (Nature (2010) 465:182-187; PLoS One (2013) 8:e76903; Sci Rep (2017) 7:14). 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 (Int J of Biochem & Cell Biol (2017) in press).

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

SorCS1: *Abuzar Kaleem, Barbara Merz, Andrea Zaisser, Sandra Oetjen, Guido Hermey*

SorCS1 belongs to the Vps10p-Domain receptor family, which defines a group of receptors binding neurotrophic factors (Cell Mol Life Sci (2009) 66, 2677-2689). 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 studies demonstrate that alternative processing can adjust receptor activity (Biochem J (2014) 457, 277-288; Neuron (2014) 82, 1074-87). SorCS1 is genetically linked to Alzheimer's disease (Ann Neurol (2011) 69, 8-10; Neural Regen Res (2015) 10, 1727-1728). We corroborated the interaction of SorCS1 and the amyloid precursor protein (APP), demonstrated their shared intracellular itinerary and that the splice variant SorCS1c modulates anterograde transport of APP (J. Neurochem. (2015) 135, 60-75). We extended our studies by identifying SorCS1 interaction partners. One candidate was CLN3, a protein mutated in the child onset neurodegenerative disease JNCL. We contributed to the basic cellular characterization of CLN3, however, validation of the interaction was unsuccessful (J. Neurochem. (2016) 139, 456-470).

Sgk1: *Ralf Scholz*

Based on a constitutive knockout mouse model generated in our laboratory (J Clin Invest (2002) 110, 1263-1268), we found that the serum and glucocorticoid-inducible kinase SGK1 is physiologically important in a variety of non-neuronal tissues. In a collaboration with Florian Lang's group (University of Tübingen) we identified and explore defects in renal function (e. g. Am J Physiol Renal Physiol (2017) 312, 65-76), muscle homeostasis (EMBO Mol Med (2013) and changed immune responses (Cell Physiol Biochem (2014) 3, 943-54; Arterioscler Thromb Vasc Biol (2015) 35, 547-57) in Sgk1 null mice. In the brain of wild type animals, we observed an activity-dependent and cell-type specific induction of Sgk1 in oligodendrocytes which 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 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. In a complementary approach, we identified novel interaction partners of SGK1. Our data strongly suggests direct involvement of Sgk1 in NMDA receptor signaling pathways leading to MAPK activation, a mechanism well-known to regulate synaptic plasticity.

Arc/Arg3.1: *Xiaoyan Gao, Ute Süsens, Lars Binkle, Joachim Nowock, Guido Hermey, Uwe Borgmeyer, Sergio Castro Gomez, Jasper Grendel, Francesca Xompero, Ora Ohana*

Arc/Arg3.1 is now widely recognized as master regulator of synaptic plasticity and 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 been borne out in studies establishing a function for the protein in multiple forms of protein synthesis-dependent synaptic plasticity, regard-

less 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, we demonstrate 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), for a pro-neurogenic effect following BDNF-induced LTP (Sci Rep (2016) 6:21222), and rhythmic synchronization of hippocampal CA1 neurons during locomotor activity and sleep (Neurobiol Learn Mem (2016) 131:155-165). Conversely, aberrant Arc/Arg3.1 expression has been implicated in psychiatric and neurodegenerative diseases, including Alzheimer's disease (Cell (2011) 147:615-628).

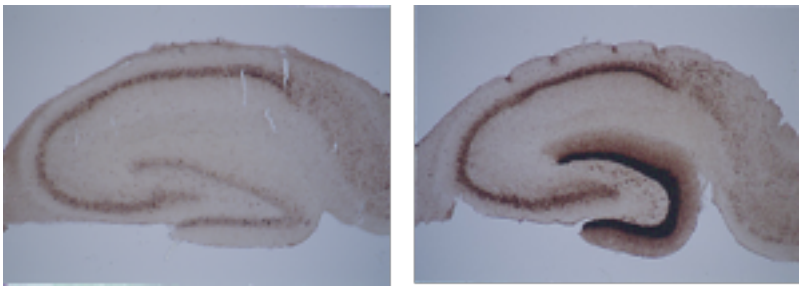
Functional consequences of the subcellular localization of Arc/Arg3.1

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. Our 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. (Proc Natl Acad Sci USA (1995) 92, 5734-5738).

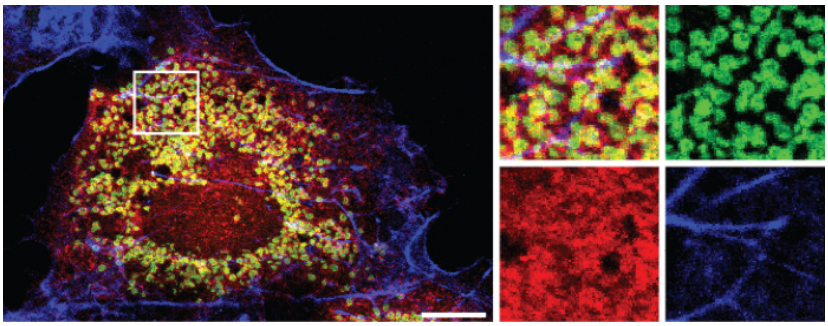
Consequently, Arc/Arg3.1 mRNA may be locally translated at activated synapses and may have a key role in synapse specific modifications during plastic events in the brain. To test this hypothesis we have generated a phage artificial chromosome harboring mutations that completely abolish the targeting 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. To complete these studies we currently examine hippocampal microarchitecture and oscillatory network activity in these 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.

Arc/Arg3.1 function

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 conducted conventional as well as split ubiquitin Y2H screens. These screens yielded several proteins that are resident in the endosomal system, including a so far uncharacterized sorting nexin. This is in agreement with the proposed function of Arc/Arg3.1 in endosomal sorting and might help to explain the versatile role of Arc/Arg3.1 in synaptic plasticity. In the course of these studies, we developed a new microscopy-based method for the analysis of protein-protein interactions (PPIs). The method takes advantage of ectopic localization of one of the proteins of interest, the recruiter, to a subcellular compartment by fusion



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).



Arg3.1 binds to the WAVE regulatory complex Cells expressing a member of the Wave complex (red) and Arg3.1 (green). Arg3.1 is ectopically localized to mitochondria and recruits the WAVE complex member leading to fragmentation of the mitochondria. F-actin is stained with phalloidin (blue).

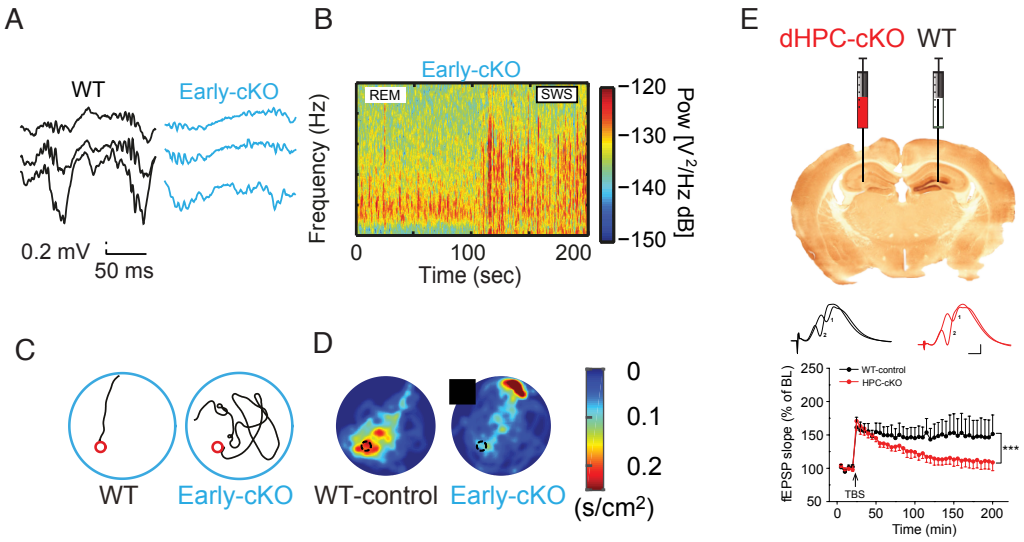
to a localization signal. Our method is fundamentally different to and complements traditional biochemical methods by directly visualizing PPIs within fixed cells thereby preserving the physiological environment of the protein interaction. This study has been submitted for publication.

Conditional Arc/Arg3.1 KO mice

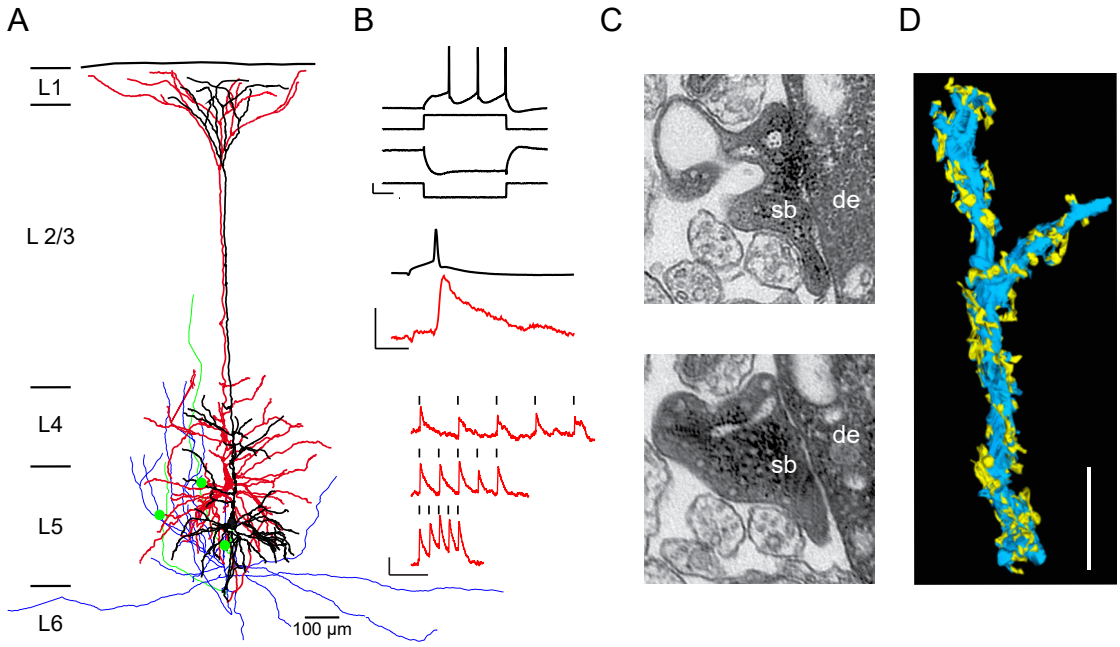
Following memory encoding and retrieval, Arc/Arg3.1 expression increases in various areas of the hippocampus and cortex, suggesting their mutual contribution to memory formation. In addition, we have recently found that Arc/Arg3.1 is expressed in the brain during the first 4 weeks of the critical period 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 removed Arc/Arg3.1 in specific brain regions or time points by injecting rAAV-Cre viruses or by breeding with respective 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.

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 have



Conditional Arc/Arg3.1 KO mice Loss of Arc/Arg3.1 during early postnatal development results in impaired hippocampal oscillatory activity (A-B) and spatial learning (C) and memory (D) in adulthood. Local loss of Arc/Arg3.1 following stereotactic injection of rAAV-Cre (red syringe, left hemisphere) results in loss of Arc/Arg3.1 and of synaptic plasticity, compared to intact expression of Arc/Arg3.1 and LTP in the contralateral control hippocampus (black syringe, right hemisphere).



Functional and structural investigation of adult L5 synapses A) Patch clamp recordings and biocytin/HRP filling of synaptically connected pairs of L5 pyramidal neurons in rat somatosensory cortex. B) Regular spiking and sustained synaptic transmission are characteristic of these neurons. C) EM images of 2 synaptic contacts. D) 3D reconstruction of a HRP-filled L5 dendrite (blue) studded with numerous synapses (yellow).

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. In 2017 we have completed an exceptionally large study of the function and structure of adult L5 synapses. Together with Prof. Joe Lübke (Jülich) and Prof. Claus Hilgetag (UKE, Hamburg), we investigated the nanostructure of L5 synapses at the EM level and correlated it with detailed analysis of synaptic properties. This study has now been submitted for publication.

Future perspectives

The several findings described above open up new avenues and pave the way to investigate mechanisms of plasticity. When disturbed, these mechanisms are the cause of mental diseases, psychiatric disorders or play roles e.g. in addiction, epileptogenesis, ischemia, schizophrenia, 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. A long-term goal of our research is to integrate these findings and translate the specific knowledge at each level into an understanding of information processing and storage and elucidate how mental functions emerge from specific changes at molecular levels.

Selected Publications

Hermey G, Bluthgen N, Kuhl D (2017) Neuronal activity-regulated alternative mRNA splicing. Int J Biochem & Cell Biol in press.

Bluthgen N, van Bentum M, Merz B, Kuhl D, Hermey G (2017) Profiling the MAPK/ERK dependent and independent activity regulated transcriptional programs in the murine hippocampus *in vivo*. Sci Rep 7:14.

Oetjen S, Kuhl D, Hermey G (2016) Revisiting the neuronal localization and trafficking of CLN3 in juvenile neuronal ceroid lipofuscinosis. J Neurochem 139:456-470.

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Kuipers SD, Trentani A, Tiron A, Mao X, Kuhl D, Bramham CR (2016) BDNF-induced LTP is associated with rapid Arc/Arg3.1-dependent enhancement in adult hippocampal neurogenesis. Sci Rep 6:21222.

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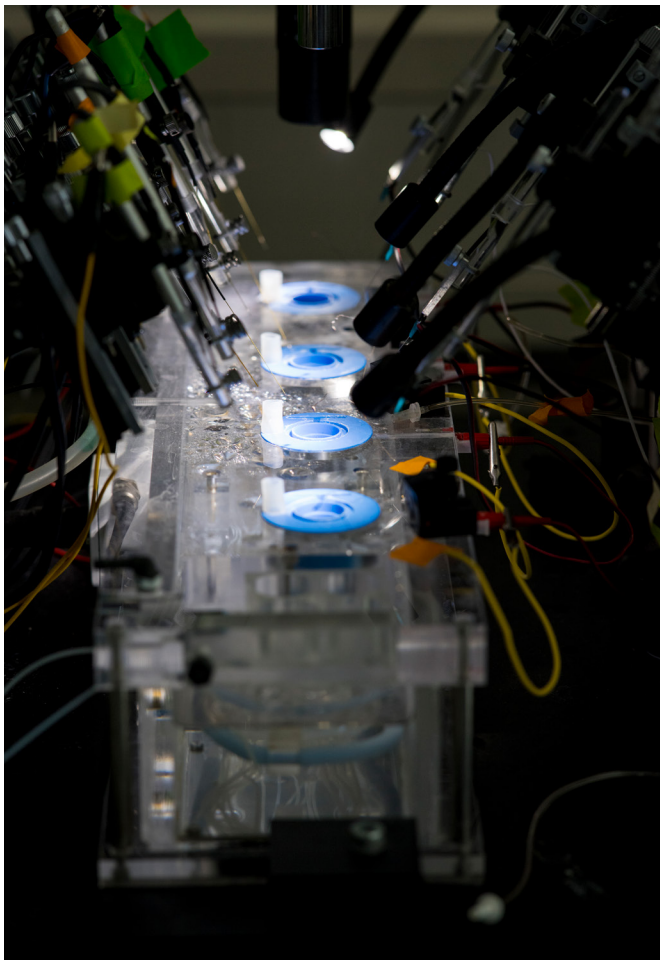

Collaborators

Prof. Dr. Nils Blüthgen
Charité, Berlin, Germany

Prof. Dr. Clive Bramham
University of Bergen, Bergen, Norway

Prof. Dr. Christian Büchel
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Jens Fiehler
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Manuel Friese
ZMNH, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Christian Gerloff
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Michael Greenberg
Harvard University, Boston, MA, USA

Prof. Dr. Claus Hilgetag
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Jan Holstege
Erasmus University Medical Center Rotterdam, Rotterdam, Netherlands

Prof. Dr. Dirk Isbrandt
DZNE Bonn and University Hospital of Cologne, Cologne, Germany

Prof. Dr. Stefan Kindler
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Stefan Kins
Technische Universität Kaiserslautern, Kaiserslautern, Germany

Prof. Dr- Matthias Kneussel
ZMNH, University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Florian Lang
University of Tübingen, Tübingen, Germany

Prof. Dr. David Linden, Johns Hopkins University, Baltimore, MD, USA

Prof. Dr. Joachim Lübke
Forschungszentrum Jülich, Jülich, Germany

Prof. Dr. Kevan Martin, University of Zurich, Zurich, Switzerland

Prof. Dr. Anders Nykjaer
Aarhus University, Danmark and Mayo Medical School, Jacksonville, FL, USA

Prof. Dr. Pavel Osten
CSHL, Cold Spring Harbor, NY, USA

Prof. Dr. Cyriel Pennartz
University of Amsterdam, Amsterdam, Netherlands

Prof. Dr. Claus Munk Petersen
Aarhus University, Aarhus, Danmark

Dr. Kurt Sätzler
University of Ulster, Coleraine, Northern Ireland

Dr. Jan Sedlacik
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Priv.-Doz. Dr. Stephan Storch
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Volker Valon
University of California, San Diego, CA, USA

Prof. Dr. Manfred Westphal
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Prof. Dr. Paul Worley
Johns Hopkins University, Baltimore, MD, USA

Team

Director: Prof. Dr. Dietmar Kuhl
Senior scientists:
Priv.-Doz- Dr. Guido Hermey
Dr. Ora Ohana
Dr. Ralf Scholz
Guest scientist:
Dr. Joachim Nowock
Graduate students:
Xiaoyan Gao
Jasper Grendel
Francesca Xompero
Abuzar Kaleem
Undergraduate student:
Dominika Wawrzyniak
Technicians:
Barbara Merz
Ute Süsens
Andrea Zaisser
Secretary:
Dagmar Boshold

Alumni

Senior scientists:
Dr. Lars Binkle
Priv.-Doz. Dr. Uwe Borgmeyer
Graduate students:
Dr. Sergio Castro Gomez
Hanne Kläschen
Sandra Oetjen
Undergraduate students:
Christian Grüttner
Christina Kroos
Helia Saber
Technician:
Sabine Graf

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Hermey G, Bluthgen N, Kuhl D (2017) Neuronal activity-regulated alternative mRNA splicing. Int J Biochem & Cell Biol in press.

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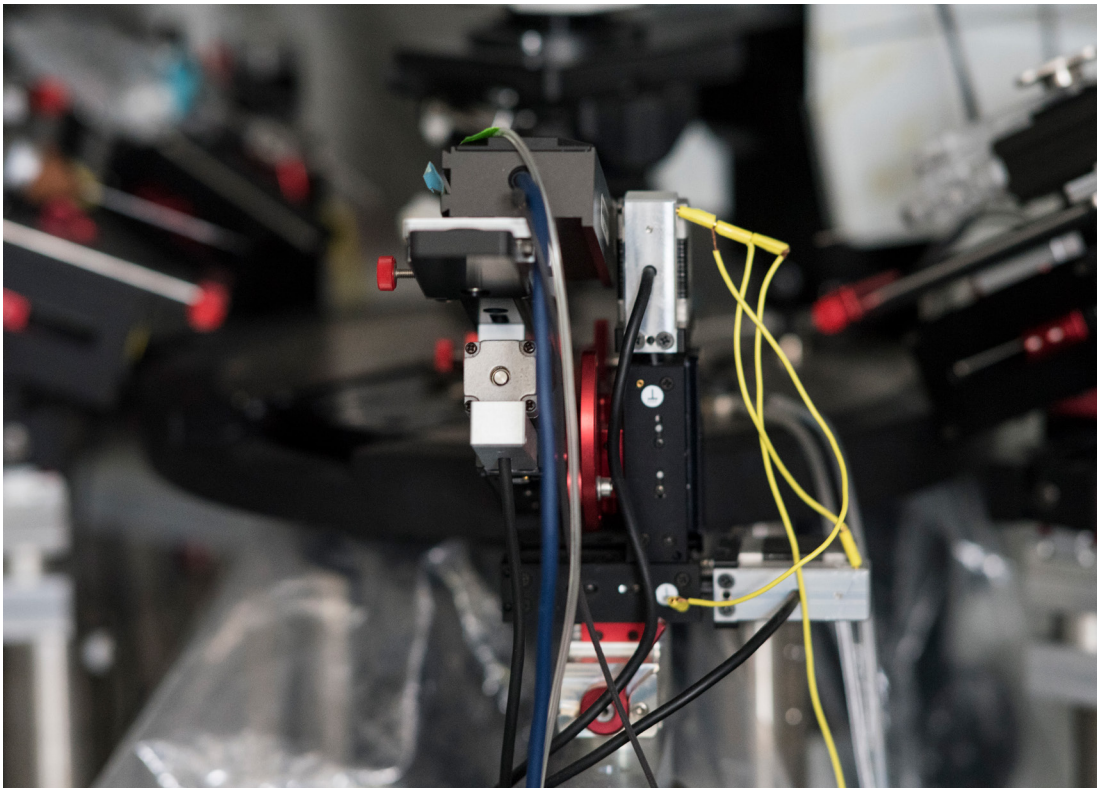
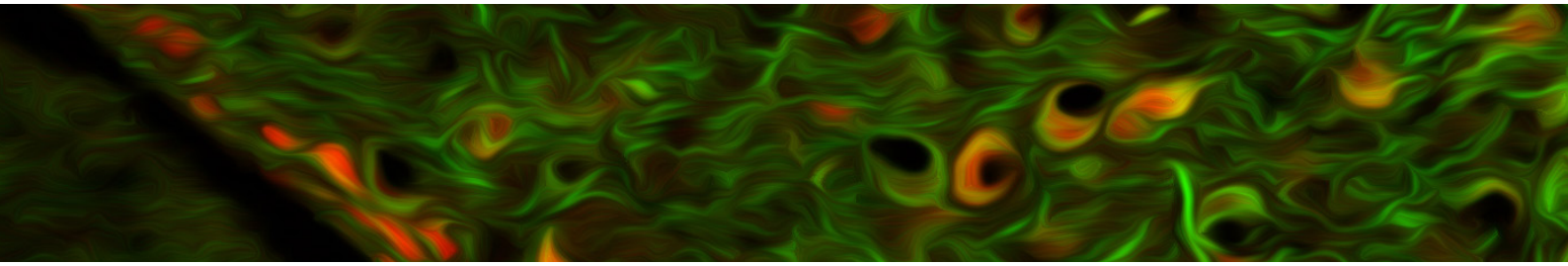
Doctoral/PhD Theses

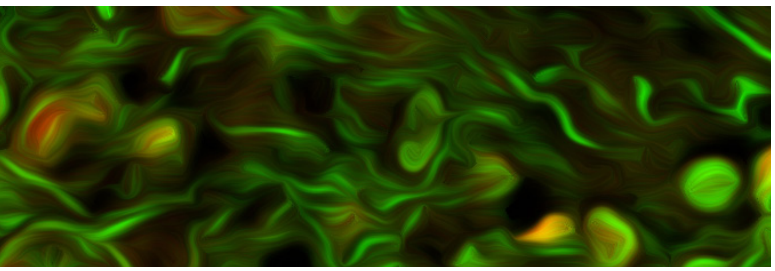
Jasper Grendel (2017) Hippocampal network patterns in Kv7/M-current deficient mice. Department Biology, Universität Hamburg.

Dr. med. Sergio Castro-Gomez (2016) Developmental and adult expression of Arc/Arg3.1 in corticolimbic structures determines memory and emotional control. Department Biology, Universität Hamburg.

Xiaoyan Gao (2016) Dependence of learning and memory consolidation on spatiotemporal expression of Arc/Arg3.1 in hippocampalcortical networks. Department Biology, Universität Hamburg.







Research Reports of the ZMNH Research Groups

Synaptic Wiring and Information Processing

Head: Dr. J. Simon Wiegert

The ZMNH Research Group Synaptic Wiring and Information Processing was founded in April 2017 and is interested in questions concerning the long-term function of synapses in neuronal circuits. Despite decades of research and a plethora of studies investigating synaptic plasticity and information processing, surprisingly little is known about the long-term function of individual central synapses. Our focus lies on the identification of functional synapses in their native environment, manipulation of their activity and investigation of functional and structural parameters. To this end we develop optogenetic tools and methods to gain better control of synaptic function and to selectively label synapses involved in memory processes.

Synaptic wiring of hippocampal circuits

Mauro Pulin, Giovanni Usseglio

Long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission change synaptic pathways in an activity-dependent manner. However, although such changes seem to be stable over days, it is less clear how plasticity affects individual synapses over time. We showed previously that LTD preferably leads to elimination of low release probability synapses (Wiegert and Oertner, 2013), suggesting that weight adjustments affect synaptic lifetime. Together with our unpublished work this suggests that reversible changes in the connectivity of neuronal networks induced by LTD or LTP could be made permanent through synapse elimination and stabilization. Currently we are investigating how multiple plasticity-inducing events and ongoing activity are integrated over time at individual synapses to regulate their persistence. We combine optogenetic and chemogenetic tools to tightly control activity at identified Schaffer collateral synapses in organotypic hippocampal slice cultures. All-optical induction of LTD and LTP in combination with 2-photon calcium imaging allows us to measure the strength of individual synapses and to follow their fate after depression or potentiation over 7 days. In addition, we use DREADD-mediated chemogenetic silencing to test whether chronically changing activity at identified synapses has an impact on their lifetime.

Information processing at Schaffer collateral synapses *in vivo*

Wei Yang, Joaquín Hurtado Zavala

The new possibilities of (opto)genetic activation and silencing of specific cells have spurred a renaissance of the search for the physical underpinnings of learning and memory, which are commonly referred to as ‘engram’ (Josselyn et al., 2015; Semon, 1904; Tonegawa et al., 2015). One popular concept proposes that memory traces are stored in ‘engram cells’, which are distributed over multiple sites within the brain and are

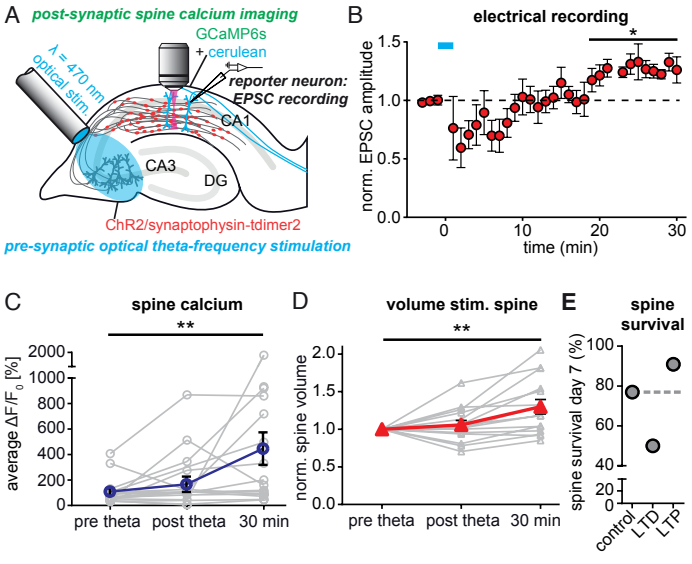


Figure 1. All-optical plasticity experiments at single synapses

"activated by learning, have enduring cellular changes as a consequence of learning, and whose reactivation […] results in memory recall" (Tonegawa et al., 2015). But where is the engram when the neurons are not active? One possibility is that, the 'enduring cellular changes' during memory formation occurred at the synaptic connections, forming a specific circuit that is able to trigger memory recall when active (Hayashi-Takagi et al., 2015). Thus, the engram may be considered a pattern of altered synapses, not a pattern of cell bodies. Our goal is to study the function of individual synapses in neuronal circuits during long-lasting adaptations such as learning and memory formation *in vivo*. We use chronic 2-photon imaging through hippocampal windows in mice and develop methods to identify synapses that had been active during memory formation. In this way we aim to obtain specific information about how their morphological stability and pre- and postsynaptic functional properties are related to lerning and memory formation.

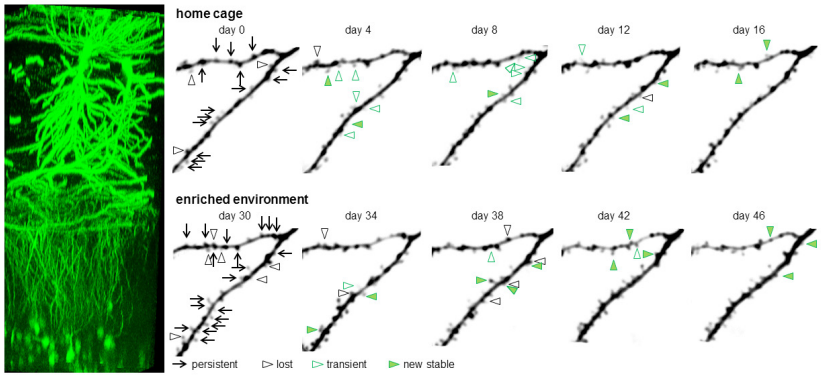


Figure 2. Long-term imaging of spines on CA1 pyramidal cells *in vivo*

Development of optogenetic silencing tools to manipulate neuronal circuits

Silvia Rodriguez-Rozada

Acute and reversible intervention with neural activity by optogenetic means is a powerful approach that has been increasingly used in the neurosciences. Light-gated anion-conducting channel-rhodopsins (ACRs) emerged as promising silencing tools in recent years. After development of the first light-gated anion channel in 2014 (Wietek et al., 2014), we continued our engineering efforts to improve ion selectivity and obtain ACRs with novel biophysical properties. We recently performed an exhaustive and systematic conversion of a wide variety of channelrhodopsins and obtained spectrally tuned ACRs, which can be activated by blue- or red-shifted light, efficiently and faithfully silence hippocampal CA1 neurons and reversibly inhibit behavior in *Drosophila in vivo*. In addition, the novel step-function aACRs allow binary control of circuit function with brief light pulses. This is a major advantage, as extended bright light pulses can be cytotoxic or cause aversive behaviors in small animal models.

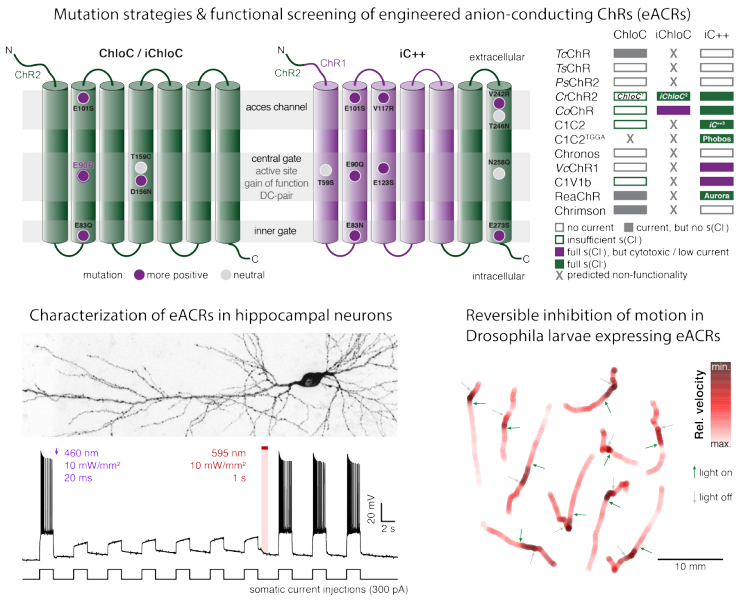


Figure 3. Development of anion channelrhodopsins and their application *in vivo*

Selected Publications

Wiegert JS, Mahn M, Prigge M, Printz Y, Yizhar O (2017) Silencing neurons: tools, applications and experimental constraints. Neuron 95(3):504-529

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China Scholarship Council (to Wei Yang)

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Collaborators

Dr. Peter Šoba
ZMNH, Hamburg, Germany

Prof. Dr. Thomas Oertner
ZMNH, Hamburg, Germany,

Prof. Dr. Peter Hegemann
Humnboldt-University, Berlin, Germany

Dr. Ofer Yizhar
Weizmann Institute of Science, Rehovot, Israel

Dr. Martin Heine
Leibnitz-Institute of Neurobiology, Magdeburg, Germany

Dr. Karel Svoboda, Howard Hughes Medical Institute, Janelia Farm, Ashburn, USA

Team

Head: Dr. J. Simon Wiegert

Postdoc:

Joaquín Hurtado Zavala
(from October 2017)

PhD students:

Mauro Pulin
Silvia Rodriguez-Rozada
Giovanni Usseglio
Wei Yang

Technicians:

Stefan Schillemeit
Kathrin Sauter
(shared with Peter Šoba)

Neuronal Protein Transport

Head: Dr. Marina Mikhaylova

Neuronal synapses form the basis for neuronal communication and the storage of information in brain. The strength and persistence of chemical synapses are tightly regulated and the plastic properties of neighbored dendritic synapses are also determined by molecular and electrical signaling in dendritic segments: potentiation of a dendritic spine favors the potentiation of its neighbor. In this regard, the dendritic branch forms a perfect compartment for confined signaling. The overall aim of our lab is to understand what defines a dendritic segment as a 'plasticity unit' and what are the underlying molecular mechanisms of heterosynaptic plasticity (Fig. 1). We take a multidisciplinary approach by combining electrophysiology with advanced imaging techniques (live imaging, TIRFM, dSTORM, STED, EM) and biochemical/molecular biological methods (*in vitro* reconstitution assays, interaction studies) to tackle two main questions:

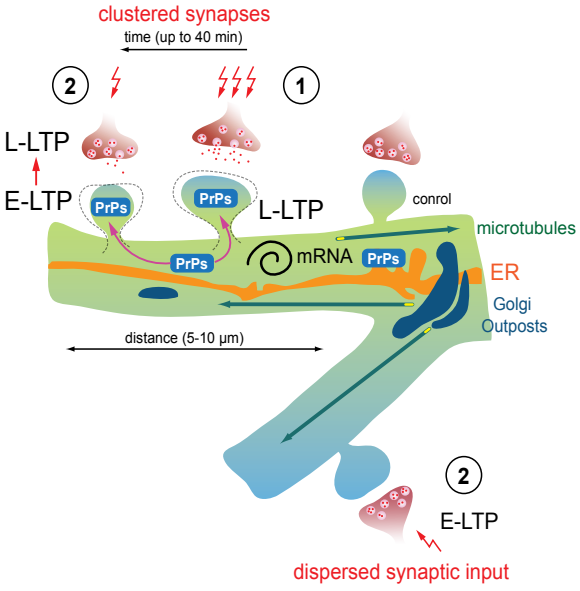

Figure 1. Possible factors contributing to dendritic compartmentalization: local organization of dendritic cytoskeleton and motor-driven active transport; sharing of synaptic proteins; Golgi-related secretory organelles and the recycling of dendritic and synaptic proteins.

1. How are synaptic proteins involved in interactions between nearby synapses and how do they contribute to the establishment of clustered synaptic plasticity within a dendritic branch?

2. What is the role of dendritic secretory trafficking organelles like ER-Golgi intermediate compartment (ERGIC), the dendritic Golgi satellite system, retromer and endosomal systems in establishment and maintenance of dendritic compartments?

Our studies are currently focused on the projects described below.

Activity-dependent reorganisation of actin cytoskeleton in dendritic spines
Julia Bär, Bas van Bommel, Anja Konietzny; collaboration project with Kreutz lab at LIN, Magdeburg

Compartmentalization of Ca^{2+}-dependent plasticity allows for rapid actin remodeling in dendritic spines. However, molecular mechanisms for the spatio-temporal regulation of filamentous actin (F-actin) dynamics by spinous Ca^{2+}-transients are still poorly defined. Here we are investigating a role of the postsynaptic Ca^{2+}-sensor caldendrin in orchestration of nano-domain actin dynamics that are essential for actin remodeling in the early phase of long-term potentiation (LTP). We show that steep elevation in spinous $[Ca^{2+}]_i$ disrupts an intramolecular interaction of caldendrin and allows cortactin binding.

The fast on and slow off rate of this interaction keeps cortactin in an active conformation and protects F-actin at the base of the spine against cofilin-induced severing. Caldendrin gene knockout results in higher synaptic actin turnover, altered nanoscale organization of spinous F-actin, defects in structural spine plasticity, LTP, and hippocampus dependent learning (Fig.2). Collectively our data indicate that caldendrin/cortactin directly couple $[Ca^{2+}]_i$ to preserve a minimal F-actin pool that is required for actin remodeling in the early phase of LTP.

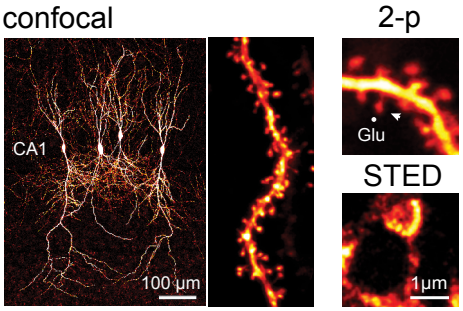

Figure 2. Investigating neuronal structure from cellular to nanoscale level: pyramidal neurons, dendritic branch, 2-p glutamate uncaging and STED imaging of F-actin.

Functional interplay of microtubule and actin motors in dendritic compartmentalization

Bas van Bommel, Anja Konietzny, Sergei Klykov

The highly complex and polarized morphology of principal cells in the brain is established by the neuronal cytoskeleton, a network of protein polymers, such as F-actin and microtubules (MT), and their associated proteins that determine cytoskeletal shape and stability. MT serve as tracks for long-range active transport driven by dynein and kinesin motor proteins, whereas short-range transport and tethering is mediated via actin-based motors - myosins. The stability of synaptic contacts depends on the transport of plasticity related products (mRNA and proteins) from the soma and on activity induced local protein synthesis from dendritic mRNAs (Fig.1). The latter mechanism relies on the proper positioning of secretory organelles, which are present along dendrites serve as a supply station for the building blocks needed to construct and maintain local dendritic arbors and spines. Live imaging experiments demonstrate the existence of both mobile and stationary pools for ERGIC, dendritic Golgi-satellites and various types of endosomes including Rab11 vesicles containing AMPA receptors. Most intracellular cargos are bound by multiple and different motors but how motor activity is controlled is not well understood. The aim of this project is to understand the interplay between motor proteins allowing controlled cargo delivery, retention or release in response to synaptic activity in specific dendritic segments and their role in establishment of dendritic compartmentalization. Specifically, we will address the following questions: i) is organelle positioning in dendrites determined by local organization of the microtubule and actin cytoskeleton; and ii) how local synapto-dendritic calcium signalling affects the activity of different motors on the same cargo.

Interactions between nearby synapses via sharing of synaptic proteins

Julia Bär, Michael Bucher

In this project we are asking whether sharing of synaptic proteins between neighbouring spines is essential for synaptic clustering and dendritic compartmentalization. What is the turnover rate of proteins in active vs. inactive spines? How does synaptic turnover correlate with spine size and morphology? Do these proteins exit spines and move as a cluster? How far do they travel? Do the proteins remain within a dendritic branch (Fig.1)? To address these questions we are tracing re-location of endogenous synaptic proteins labelled by a specific intrabody fused to photo-convertible fluorescent proteins. Currently we are using a readily existing FNIII-based intrabody against PSD95. We have generated an alpaca nanobody library against synaptosomes and performing phage display selections to identify specific binders for SHANK3, Homer1 and other synaptic scaffolds.

Colaborative projects performed in the lab:

- Concerted axon guidance between Draxin and Netrin-1 via the DCC Receptor. Collaborative project with Rob Maijers lab (EMBL-DESY, Hamburg). Yiqiong Liu, Sergei Klykov
- Molecular mechanisms of targeting the *spine apparatus* into dendritic spines. Collaborative project with Michael Frotscher and Thomas Oerner labs, ZMNH. Judit Gonzalez, Anja Konietzny, Bas van Bommel
- Mutations in SHANK3 gene linked to ASDs: proteomic approach for analysis of synaptic protein composition. Collaborative project with Michael Kreutz lab (LIN, Magdeburg), Daniela Dieterich lab (OvGU, Magdeburg) and Tobias Böckers lab (University Ulm, Ulm). Michael Bucher

Selected Publications

Katrukha EA*, Mikhaylova M*, van Brakel HX, van Bergen En Henegouwen PM, Akhmanova A, Hoogenraad CC, Kapitein LC (2017) Probing cytoskeletal modulation of passive and active intracellular dynamics using nanobody-functionalized quantum dots. Nat Commun 8:14772. * shared first authorship

Frese CK*, Mikhaylova M*, Stucchi R*, Gautier V, Liu Q, Mohammed S, Heck AJR, Altelaar AFM, Hoogenraad CC (2017) Quantitative map of proteome dynamics during neuronal differentiation. Cell Rep 18: 1527-1542.* shared first authorship

Bär J, Kobler O, van Bommel B, Mikhaylova M (2016) Periodic F-actin structures shape the neck of dendritic spines. Sci Rep 6:37136.

Mikhaylova M*, Bera S*, Kobler O, Frischknecht R, Kreutz MR (2016). A dendritic Golgi satellite in between ERGIC and retrome. Cell Rep 14:189-199. *shared first authorship

Mikhaylova M, Cloin BM, Finan K, van den Berg R, Teeuw J, Kijanka MM, Sokolowski M, Katrukha EA, Maidorn M, Opazo F, Moutel S, Vantard M, Perez F, van Bergen En Henegouwen PM, Hoogenraad CC, Ewers H, Kapitein LC (2015) Resolving bundled microtubules using anti-tubulin nanobodies. Nat Commun 6:7933.

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Collaborators

ZMNH:

Prof. Dr. Thomas Oertner
Prof. Dr. Matthias Kneussel
Prof. Dr. Dr. h. c. Michael Frotscher
Dr. Froylan Calderon de Anda
Dr. Peter Šoba
Dr. Michaela Schweizer
Priv.-Doz. Dr. Irm Hermans-Borgmeyer

Dr. Michael R. Kreutz
LIN, Magdeburg, Germany

Dr. Lukas C. Kapiten
UU, Utrecht, The Netherlands

Prof. Dr. Casper C. Hoogenraad
UU, Utrecht, The Netherlands

Dr. Jeroen Demmers
Erasmus MC, Rotterdam, The Netherlands

Dr. Virgilio Faila
UMIF, Hamburg, Germany

Dr. Sabine Windhorst
UKE, Hamburg, Germany

Dr. Rob Maijers
EMBL-DESY, Hamburg, Germany

Prof. Dr. Daniela C. Dieterich
OvGU, Magdeburg, Germany

Prof. Dr. Helge Ewers
FU, Berlin, Germany

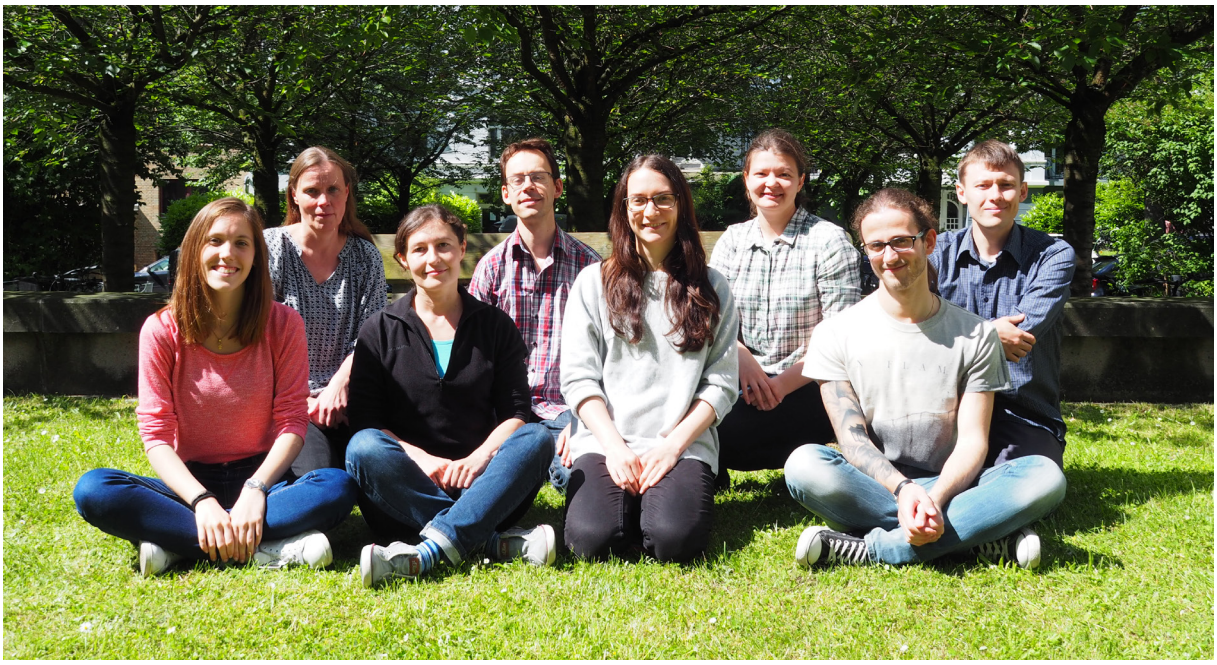
Dr. Egor Loktionov
BMSTU, Moscow, Russia

Dr. Dmitrii Sitnikov
JIHT, Moscow, Russia

Team

Head: Dr. Marina Mikhaylova
Postdoc:
Dr. Julia Bär
PhD students:
Bas van Bommel
Anja Konietzny
Sergei Klykov
Michael Bucher
(shared with Kreutz group)
HiWi: Judit Gonzales
Daniela Hacker

Technician:
Sabine Wehrmann
Secretary:
Dörte Claussen
Former students:
Irina Schäfer
(internship student)
Kim Dose
(internship student),
Yiqiong Liu
(guest scientist)



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Neuronal and Cellular Signal Transduction

Head: Prof. Dr. Meliha Karsak

The ZMNH Research Group "Neuronal and Cellular Signal Transduction" studies G-protein coupled receptors (GPCR) and interacting proteins to investigate signaling in physiological and selected pathophysiological conditions. Our main interest is to link specific disturbances in GPCR protein function to human diseases such as neurodegenerative, neurodevelopmental and skeletal disorders. To achieve this aim we are using interdisciplinary approaches including e.g. cell biological, human genetic and pharmacological studies. Together with collaboration partners from Human Genetics we investigate new disease causing mutations and variants in membrane receptors or their interacting proteins and examine molecular mechanisms of disease associated protein variants. In the past we have been successful with this approach in the investigation of the cannabinoid system and identified important functions in humans as well as in mouse models. We now want to extend our studies to a more general aspect of GPCRs and their interacting partners. Therefore, we are aiming to systematically analyze this protein superfamily with special emphasis on their role in severe neurodevelopmental disorders. For future pharmacological treatment studies, the research group is also using disease models in cell systems and transgenic mice. The long-term aim is to understand the mechanism of receptor signaling in healthy and diseased status and to identify new therapeutic approaches.

Identification of cannabinoid receptor interacting proteins

Christina Kroos, Ahmed Sharaf, Leonore Mensching, Sebastian Rading, Simge Yilmaz

Our main focus is the function of the G-protein cannabinoid receptors. The known functions of cannabinoid receptors are mainly related to modulation of neuronal activity and the immune system. Cannabinoid CB2 receptors are activated by lipophilic substances like phyto-, dietary and endo-cannabinoids. Increased CB2 receptor expression is associated with a wide range of human diseases and it has been shown to contribute to various pathological states in animal models of e.g. neurodegenerative diseases (Pacher and Mechoulam, 2011). Whereas CB2 receptors are absent in healthy brain microglia (Stella, 2004), microglial expression levels of CB2 were found to be increased in Alzheimer´s brain tissue as well as in models of neuropathic pain (Atwood and Mackie, 2010). In the past, our multidisciplinary approach led us into the investigation of the cannabinoid system in bone remodeling, skin contact hypersensitivity and amyotrophic lateral sclerosis amongst others (Karsak et al., 2005, Ofek et al., 2006, Karsak et

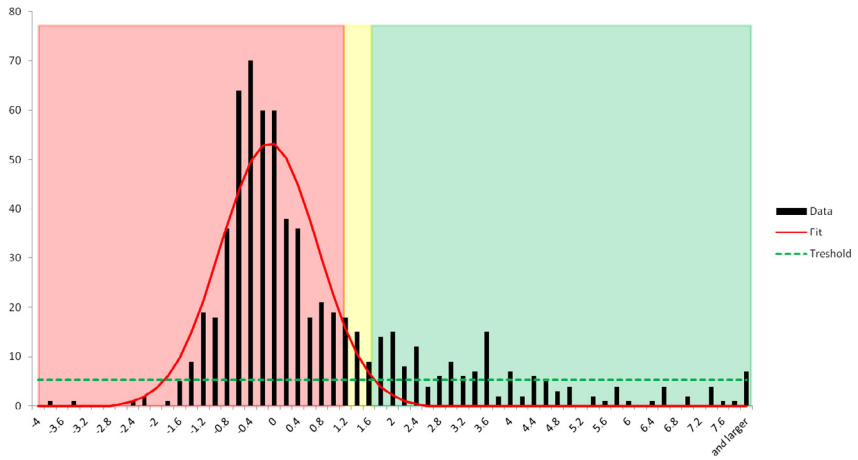

Figure 1. Background filtering of CB2 affinity purification: Histogram of enrichment factors (CB2 / control) of identifications to determine threshold of enrichment for specific interactors. Red area represents Gaussian distribution of unspecific interactors, yellow area is in the border and in the green area are the specific interactors (threshold as 10 % of max. peak height).

al., 2007, Karsak et al., 2009, Pasquarelli et al., 2017). In our current projects, we are especially seeking to identify new protein interaction partners of cannabinoid receptors and other GPCRs. To achieve this aim, we performed a protein-protein interaction screen for cannabinoid receptor protein complexes. For the identification of putative interaction partners of CB2 we used a method, which is specifically applicable for membrane receptors consisting of systematic affinity purification and mass spectrometric analysis of precipitated protein complexes (Glatter et al., 2009). After subtraction of background interactions and protein frequency library assessment several putative interaction partners of CB2 could be identified by this method (Fig. 1, unpublished data). Among the putative interaction partners, an important signaling protein was present. It was one of the proteins with the highest probability of interaction, based on six specific tryptic peptides. Because this interactor is known to be associated with both neurodegenerative diseases and bone cell function, which nicely overlaps with the known functions of CB2 receptors, we decided to study this interacting protein and the kind of interaction in more detail. Therefore, we are currently analyzing the crosstalk of both proteins as regarding their signaling and function. To this end, we are using already existing knockout mouse models to study *in vivo* cannabinoid effects and to isolate primary cells and investigate cellular responses in more detail. Therefore, we are treating KO mouse models of the newly identified interacting protein with cannabinoid receptor agonist and antagonists and investigate if neurogenesis and bone remodeling (in collaboration with Thorsten Schinke) are affected.

GPCRs and intracellular protein-complexes

Leonore Mensching, Ahmed Sharaf, Sebastian Rading, Christina Kroos, Jeremy Krohn

In a novel project, we are investigating new mechanisms concerning the ‘communication’ of different GPCRs and their modulation by intracellular signaling complexes. GPCRs belong to a group of proteins with a high therapeutic

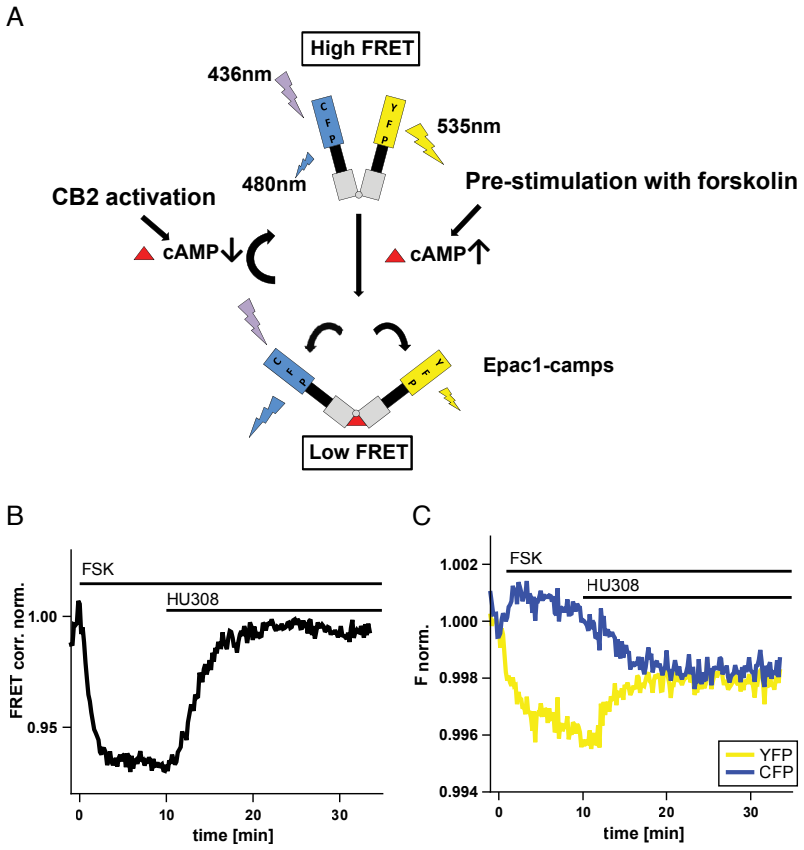

Figure 2. A) FRET-based Epac1-camps biosensor. Scheme of the cAMP biosensor showing its cAMP unbound and bound conformation as well as the orientation of the two fluorophores CFP and YFP. Figure modified from Calebiro et al., 2010. B&C) Representative live-cell FRET recording of Epac1-camps-hCB2-FLAG HEK293 cells. Cells were subsequently stimulated with 1 µM of the adenylyl cyclase activator forskolin (FSK) and 1 µM of CB2 agonist HU308. B) FRET Ratio (FYFP/FCFP) over time normalized to pre-stimulation baseline and corrected for spectral bleedthrough and photobleaching. C) Fluorescence intensity in the YFP (yellow) and CFP (blue) emission spectrum over time normalized to pre-stimulation baseline and corrected for photobleaching.

relevance, indeed more than 30% of available drugs are targeting this class of proteins. It is therefore important to understand the regulation, signaling and function of these membrane receptors in more detail especially to further explore their pharmaceutical potential. The signaling of GPCRs is influenced by a variety of processes and mechanisms like the heterodimerization of receptors (that can change the efficacy and specificity of ligands to their receptors) or receptors can couple to different Gα and β subunits. Regulators of G-protein signaling (RGS) (Zhong and Neubig, 2001) and activators of G-protein signaling (AGS) (Blumer et al., 2007) modulate G-proteins. Recently, we have shown that the CB2 receptor and AGS2 (dynein light chain 1) compete for the binding of Gβ proteins (Nagler et al., 2016), which we are investigating in more detail. Fluorescence-resonance energy transfer (FRET) has already been used in the past to discover GPCR signaling events on the molecular level (Lohse et al., 2012). We have now established - in collaboration with Viacheslav Nikolaev - FRET-technology in my group to study signaling cascades in real-time on the single cell level (Fig. 2, unpublished data). By the usage of specific biosensors we are now able to measure second messengers and by the development of new FRET-pairs we will be able to investigate protein-complexes microscopically in direct response to receptor activation or blocking in single cells. Further, we investigate second messengers in primary cells like macrophages /osteoclast and microglial cells derived of transgenic mice expressing a cAMP-biosensor. Furthermore, in collaboration with Christian Kubisch we have recently identified novel mutations in GPCRs and G-proteins in neurodevelopmental disorders and autism. We will therefore apply FRET-based methods and further tools to study the pathophysiological consequences of these mutated proteins and prove that the mutations are disease causative.

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Support

Deutsche Forschungsgemeinschaft (DFG)
DFG KA2306/3 to MK

Collaborators

Dr. Laura Bindila
Institut für Physiologische Chemie,
Universitätsmedizin Mainz
Germany

Dr. Jean-Pierre David
Institut für Osteologie und Biomechanik, UKE

Prof. Dr. Linda Diehl
Institut für Experimentelle Immunologie und
Hepatologie, UKE Hamburg, Germany

Dr. Claudia Dumitru
Prof. Dr. Erol Sandalcioglu
KRH Klinikum Nordstadt
Neurochirurgische Klinik, Hannover, Germany

Priv.-Doz. Dr. Lars Fester
Prof. Dr. Gabriele Rune, Institut für
Neuroanatomie, UKE Hamburg, Germany

Priv.-Doz. Dr. Irm Hermanns-Borgmeyer
Core Facility Transgene Tiere, ZMNH, UKE
Hamburg, Germany

Prof. Dr. Christian Kubisch
Institut für Humangenetik, UKE Hamburg,
Germany

Prof. Dr. Katrin Lamszus
Klinik und Poliklinik für Neurochirurgie
UKE Hamburg

Prof. Dr. Barbara Möpps
Institut für Pharmakologie und Toxikologie,
Universitätsklinikum Ulm, Germany

Dr. Fabio Morellini
Forschungsgruppe Verhaltensbiologie, ZMNH,
UKE Hamburg, Germany

Prof. Dr. Viacheslav Nikolaev
Instititut für Experimentelle Herz-
Kreislaufforschung, UKE Hamburg

Dr. Ora Ohana
Prof. Dr. Dietmar Kuhl
ZMNH, UKE Hamburg, Germany

Priv.-Doz. Dr. Alfredo Ramirez
Klinik für Psychiatrie und Psychotherapie,
Universität Bonn, Germany

Prof. Dr. Thorsten Schinke
Institut für Osteologie und Biomechanik, UKE
Hamburg, Germany

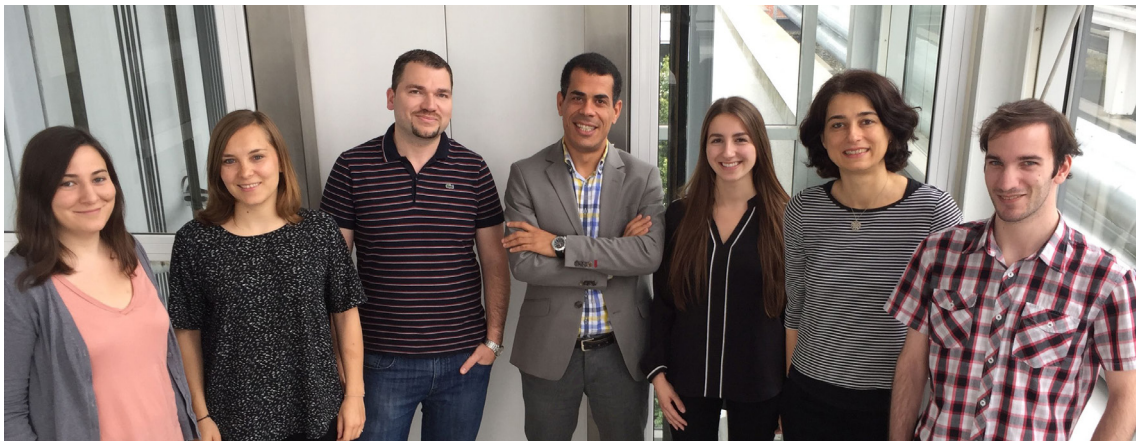
Prof. Dr. Jochen Walter
Klinik für Neurologie, Universität Bonn,
Germany

Priv.-Doz. Dr. Anke Witting
Experimentelle Neurologie,
Universitätsklinikum Ulm, Germany

Team

Head: Prof. Dr. Meliha Karsak
Postdoc: Dr. Ahmed Sharaf
PhD students:
Christina Kroos
Leonore Mensching
Technician:
Sebastian Rading
Bachelor students:
Jeremy Krohn
Simge Yilmaz
Secretary:
Dörte Clausen

Alumni: Dr. Nevena Djogo
Dr. Marina Nagler



Behavioral Biology

Head: Dr. Fabio Morellini

Our group was founded at the end of 2013 to strengthen and support system neurosciences at the ZMNH and UKE by investigating how behavior develops, is controlled and finally degenerates under pathological conditions. 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 causations by means of transgenic, pharmacological and optogenetic approaches in collaborations with our colleagues at the ZMNH and UKE.

Animal models for perturbation of perinatal neurodevelopment: long-term effects on behavior and possible therapeutic approaches

Ronja Dörk, Vanessa Kraus, Fabio Morellini

Perturbations of early brain development (such as gene mutations or viral infection) can have long-term effects on brain function. In collaboration with D. Isbrandt we showed that pharmacological intervention during a vulnerable neonatal period of cortical development prevents pathology in a genetic epilepsy model. In transgenic mice with dysfunctional Kv7 voltage-gated K+ channels, which are mutated in human neonatal epilepsy syndromes, transient bumetanide treatment during the first two postnatal weeks restored wild-type adult behavioral phenotypes in adulthood (Marguet et al., 2015). In a separate study we showed that neurodegenerative diseases can also be caused by perturbations during a critical period of brain development. Namely, we identified a pre-symptomatic period during which enhanced protein synthesis results in progressive loss of neuronal function and motor deficits in mice deficient for UCH-L1. UCH-L1 belongs to the UCH family of deubiquitinating enzymes and its loss results in neurodegeneration and ataxia. In collaboration with C. Meyer-Schwesinger, we found that UCH-L1 deficiency causes an accelerated development of sensorimotor reflexes in the first postnatal week followed by degeneration of motor function starting at periadolescence. Biochemical experiments showed an increased protein turnover characterized by enhanced protein synthesis and energy requirement under UCH-L1 deficiency. Dampening protein synthesis by rapamycin treatment during the first 8 postnatal days ameliorated the neurological phenotype of UCH-L1-deficient mice up to 16 weeks. In addition to genetic insults, we showed that also external perturbations like viral infections can impair perinatal developomnet with long-lasting effects on brain function. Maternal Zika virus (ZIKV) infection is associated with serious neurological defects in about 1% of affected newborns. However, it is yet unclear whether the remaining majority of newborns might suffer from long-term effects on CNS function. In collaboration with G. Gülsah we analyzed the impact of ZIKV infection at early gestation on the offspring. Adult offspring born to ZIKV infected mothers showed altered performances in cognitive tests compared to uninfected controls. Our data are the first evidence of long-term behavioral changes resulting from maternal ZiKV infection.

Validation of mice models for autism spectrum disorders (ASD)

Ronja Dörk, Vanessa Kraus, Julia Mienert, Fabio Morellini, Eva Romswinkel

SAPAPs constitute a family of scaffold proteins promoting the assembly of signalling complexes within the postsynaptic density. In collaboration with S. Kindler we showed that functional loss of SAPAP4 triggers profound behavioural changes in mice, including severe learning and memory deficits as well as impaired social interest, alterations also found in patients with ASD. In collaboration with the group of F. Calderon de Anda we investigated the behavior of mice dedicient for TAO2. TAO2 is one of several genes located in the ASD-associated 16p11.2 deletion region. Mice lacking TAO2 display deficits in learning, memory, anxiety and social interaction. Our data, thus, validate the link between TAO2 and ASD. Another molecule that has been associated with neuropsychiatric disorders is the serine protease inhibitor neuroserpin. In collaboration with G.

Galliciotti and M. Glatzel we showed that spatial learning, contextual emotional memory and social behavior are impaired in neuroserpin-deficient mice (Reumann et al., in press).

Role of L-type VDCCS and dopanine in extinction of conditioned fear

Fabio Morellini, Alper Yüksel

We reported that administration of L-DOPA boosts extinction of fear memories in mice and humans (Haaker et al., 2013). We further investigated the role of the dopaminergic system in extinction and consolidation of fear memory by testing the effects of specific D3 and D2 receptors agonist and antagonist. Our data suggest that dopamine facilitates consolidation of new memories through the D2 receptor and extinction through the D3 receptor. Moreover, in collaboration with A. Dityatev we found that extinction of fear memory is impaired in mice deficient for the extracellular matrix protein tenascin-C, while other cognitive functions are unaffected. By means of pharmacological and electrophysiological studies we showed that impaired extinction of TNC-deficient mice is caused by reduced function of L-type voltage gated calcium channels (Morellini et al., in press).

Role of entorhinal cortex and different hippocampal subregions in spatial learning and memory

Kolja Meier, Fabio Morellini

Within the SFB-936 on multi-site communication we found that ablation of I_h in entorhinal cortex affects hippocampus-dependent spatial learning and memory Moreover, by means of electrophysiological recordings in behaving mice we showed that dentate network activity plays an important role in memory consolidation during slow-wave sleep. Based on these findings, we have been collaborating with T. Oertner to reveal, by optogenetics approaches, how complex spatial information is stored and updated in the different hippocampal and cortical subregions.

Effects of psychological stress on the immune system and progression of multiple sclerosis: a study in a mouse model for high and low trait anxiety

Ronja Dörk, Fabio *Morellini*

In the last years we identified C57BL/6J mice with both enhanced or reduced trait anxiety and activity of the stress response. In collaboration with E. Tolosa and M. Friese we started a project to analyze the effects of chronic stress on the immune system with the long-term goal to test whether individual trait anxiety and activity of the stress response predicts the susceptibility to develop multiple sclerosis and the progression of the disease.

Behavioral characterization of transgenic mice

Ronja Dörk, Jakob Hellmann, Vanessa Kraus, Julia Mienert, Fabio Morellini, Eva Romswinkel, Sarah Scharf, Lynn Schau

Since 2015, we have performed throughout behavioral analyses of twelve different transgenic lines generated by colleagues at the ZMNH and UKE to test possible roles of specific molecules of interest in CNS function (Hochgräfe et al., 2015).

Selected Publications

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Federal State of Hamburg
(Landesforschungsförderung)

Collaborators

ZMNH:
Dr. Froylan Calderon de Anda
Dr. Kent Duncan
Prof. Dr. Manuel Friese
Priv.-Doz. Guido Hermey
Prof. Dr. Dr. h. c. Melitta Schachner
Dr. Simon Wiegert
Prof. Dr. Thomas Oertner

UKE:
Prof. Dr. Christian Büchel
Dr. Chi-un Choe
Dr. Kerstin Cornils
Dr. Giovanna Galliciotti
Prof. Dr. Markus Glatzel
Prof. Dr. Stefan Kindler
Prof. Dr. Hans-Jürgen Kreienkamp
Dr. Axel Neu
Dr. Catherine Meyer-Schwesinger
Dr. Diego Sepulveda-Falla
Prof. Dr. Tobias Sommer
Prof. Dr. Eva Tolosa
Dr. Sabine Windhorst

Germany:
Prof. Dr. Alexander Dityatev
(DZNE, Magdeburg)
Prof. Dr. Dirk Isbrandt (DZNE, Bonn)
Prof. Dr. Eckard (DZNE, Bonn)
Dr. Eva-Maria Mandelkow (DZNE, Bonn)

Team

Leader: Dr. Fabio Morellini
Medical student:
Kolja Meier
Diploma/Master students:
Ronja Dörk
Vanessa Kraus
Eda Doenmez
Lynn Schau
Student assistants:
Jakob Hellmann
Julia Mienert
Eva Romswinkel
Sarah Scharf
Alper Yüksel
Secretary:
Dörte Clausen

Neuronal Development

Head: Dr. Froylan Calderon de Anda

The ZMNH Research Group is 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.

Cortical neurons gradually attain a post-mitotic state.

Once generated, neurons are thought to permanently exit the cell cycle and become irreversibly differentiated. However, neither the precise point at which this post-mitotic state is attained nor the extent of its irreversibility is clearly defined. Here we report that newly born neurons from the upper layers of the mouse cortex, despite initiating axon and dendrite elongation, continue to drive gene expression from the neurogenic intermediate neural progenitor tubulin √1 promoter (Tα1p). These observations suggest an ambiguous post-mitotic neuronal state. Whole transcriptome analysis of sorted upper cortical neurons further revealed that neurons continue to express genes related to cell cycle progression long after mitotic exit until at least post-natal day 3 (P3). These genes are, however, downregulated thereafter and are associated with a concomitant upregulation of tumor suppressors at P5. Interestingly, newly born neurons located in the cortical plate (CP) at embryonic day 18-19 (E18-E19) and P3 challenged with calcium influx are found in S/G2/M phases of the cell cycle, and still able to undergo division at E18-E19 but not at P3. At P5 however, calcium influx becomes neurotoxic and leads instead to neuronal loss. Our data delineate an unexpected flexibility of cell cycle control in early born neurons, and describes how neurons transit to a post-mitotic state.

Autism spectrum disorder susceptibility gene TAO2 kinase regulates neuronal migration in the developing cortex in an isoform specific manner.

The development of the mammalian neocortex is responsible for higher cognitive and associative functions. However our understanding of cortex development is limited. Here we show that TAO2 is essential for neuronal migration and cortex development. Mice lacking TAO2 develop gross cortex and upper cortex layers cytoarchitecture abnormalities. Moreover, acute TAO2 down regulation or analysis of know-out TAO2 cortices show delayed neuronal migration of upper layer cortical neurons. Cultured neurons lacking *TAOK2* have unstable microtubules with reduced levels of acetylated tubulin and phosphorylated JNK1, Importantly, expression of constitutive active JNK1 rescued neuronal migration in the developing cortex. Finally, one *de novo* mutation from Autism Spectrum Disorder (ASD) patient, which decrease phosphorylation of TAO2 in its kinase domain, affects neuronal migration in an isoform specific manner. Mutated TAO2α, which localized with microtubules, but not TAO2β impaired neuronal migration. These results delineate the important role of TAO2 in cortex development.

Altered TAOK2 activity causes neurodevelopmental and cognitive abnormalities through RhoA signaling.

Atypical brain connectivity is a major contributor to the pathophysiology of neurodevelopmental disorders (NDDs) including Autism spectrum disorders (ASD). *TAOK2* is one of several genes in the 16p11.2 microdeletion region, but whether it contributes to NDDs is unknown. Here we performed behavioral analysis on a *Taok2* knockout (KO) mouse and found impairments in cognition, anxiety and social interaction.

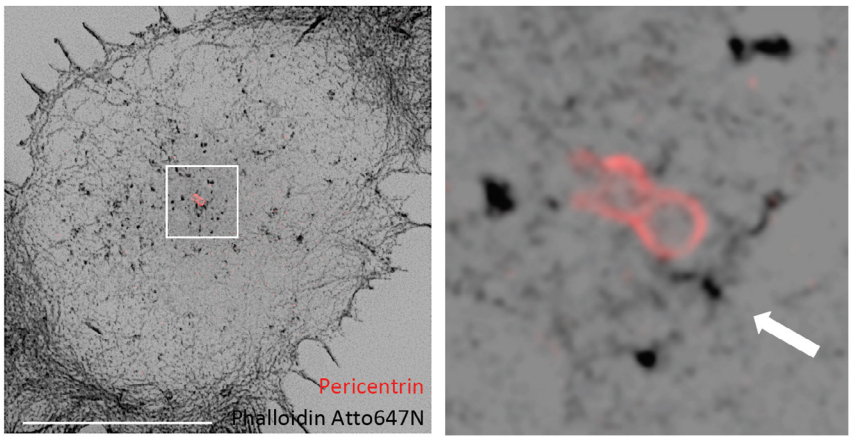

Figure 1. Super-resolution microscopy (STED) of cytosolic F-actin dots around the centrosome in developing neurons. F-actin dots (aster-like structures) localize near the centrosome (red; white square, Max projection) and bear F-actin fibers (inset, white arrow). Scale bar: 5 µm

Taok2 KO mice have abnormal brain size and neural connectivity in multiple regions, deficits in dendrite and synapse formation, and reduced excitatory neurotransmission. Whole genome and exome sequencing of ASD families identified three *de novo* mutations in *TAOK2* and functional analysis in mice and human cells revealed that the mutations impair protein stability, and differentially impact kinase activity, dendrite growth and spine/synapse development. Mechanistically, loss of *Taok2* activity causes a reduction in RhoA activation, and pharmacological enhancement of RhoA activity rescues synaptic phenotypes. Together, these data provide evidence that *TAOK2* is a neurodevelopmental disorder risk gene and identify RhoA as a potential therapeutic target.

Microtubules Instruct F-actin Dynamics during Neuronal Polarization.

Neuronal polarization is reflected by different dynamics of microtubule and filamentous actin (F-actin). Axonal microtubules are more stable than those in the remaining neurites, while dynamics of F-actin in axonal growth cones clearly exceed those in their dendritic counterparts. However, whether a functional interplay exists between microtubules and F-actin dynamics in growing axons and whether this interplay is instrumental to break cellular symmetry is currently unknown. Here, we show a negative correlation between microtubules and F-actin dynamics, where an increment on microtubules stability or number of microtubules is associated with increased F-actin dynamics. Moreover, we show that drebrin E, which binds F-actin and plus ends microtubules, mediates this cross talk. Drebrin E segregates to more dynamic growth cones where more plus end microtubules are found. Interruption of the interaction of drebrin E with microtubules decreases F-actin dynamics and arrests neuronal polarization. Collectively the data show that microtubules instruct F-actin dynamics for initial axon extension during neuronal development.

Radial Organization of F-actin During Early Neuronal Development.

Breaking cell symmetry during neuronal development is reflected by changes in microtubules and filamentous actin (F-actin) dynamics. The Centrosome is thought to be the major neuronal microtubule-organizing center (MTOC) in early neuronal development. However, whether F-actin has the same radial organization during early neuronal development is currently unknown. Here we report, using high-resolution microscopy, unexpected F-actin organization around the centrosome (Fig. 1) with dynamic F-actin aster-like structures, which extend and retract actively. Moreover, F-actin photo-conversion or molecular manipulation of F-actin stability revealed that somatic F-actin is delivered towards the cell periphery. Finally, we show that somatic F-actin intermingles with centrosomal PCM-1 satellites. Knockdown of PCM-1 and disruption of centrosomal activity not only affect F-actin dynamics near the centrosome, but also in distant growth cones. Collectively our results show a radial F-actin organization during early neuronal development, which may be a cellular mechanism to provide peripheral regions with a fast and continuous source of actin polymers; hence sustaining initial neuronal development.

Publications 2015 – 6/2017

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Kwan V, Meka DP, White SH, Hung CL, Holzapfel NT, Walker S, Murtaza N, Unda BK, Schwanke B, Yuen RK, Habing K, Milsom C, Hope KJ, Truant R, Scherer SW, Calderon de Anda F, Singh KK (2016) DIXDC1 phosphorylation and control of dendritic morphology are impaired by rare genetic variants. Cell Rep 17:1892-1904.

Rudenko A, Seo J, Hu J, Su SC, de Anda FC, Durak O, Ericsson M, Carlen M, Tsai LH (2015) Loss of Cdk5 from parvalbumin-interneurons leads to hyperinhibition, decreased anxiety, and memory impairment. J Neurosci 35:2372-2383.

Durak O*, de Anda FC*, Singh KK, Leussis MP, Petryshen TL, Sklar P, Tsai LH (2015) Ankyrin-G regulates neurogenesis and Wnt signaling by altering the subcellular localization of beta-catenin. Mol Psychiatry 20:388-397. *Equal contribution.

Book chapter: Richter M, Calderon de Anda F (2015) Control of axon selection. In: eLS. 1-7.

Doctoral/PhD Theses

Anne Naumann (2017) Mechanistic insights: ASD risk factor TAO2 controls neuronal migration and spine formation. Department Biology, Universität Hamburg.

Master Theses

Bianka Bedürftig (2015) GTPase-activity depending on the ASD risk factor TaoK2 - Methodical optimization and analysis. Department Biology, Universität Hamburg.

Ole Johanns (2017) GTPase activity and alterations in spine formation in neuronal cells after introducing ASD related human variants of TAOK2 Kinase. Department Biology, Universität Hamburg

Bachelor Thesis

Robin Scharrenberg (2016) ASD risk factor TAOK2 influences basal dendrite formation. Department Biology, Universität Hamburg.

Collaborators

ZMNH:
Dr. Marina Mikhaylova
Dr. Fabio Morellini
Dr. Ileana Hanganu-Opatz
Dr. Matthias Kneussel
Dr. Kent Duncan
Dr. Peter Šoba

Germany:
Dr. Michael Kreutz
Leibniz Institute of Neurobiology (LIN), Magdeburg

Prof. Dr. Gülsah Gabriel
Heinrich Pette Institute, Leibniz Institute of Experimental Virology

Priv.-Doz. Dr. Sabine Windhorst
Department of Biochemistry and Signal Transduction, University Medical Center Hamburg-Eppendorf, Hamburg

Canada:
Dr. Karun Singh
Stem Cell and Cancer Research Institute, McMaster University

Prof. Dr Stephen Scherer
The Center for Applied Genomics Hospital for Sick Children, University of Toronto

Switzerland:
Prof. Dr. Claudia Bagni
Department of Fundamental Neuroscience, University of Lausanne, Lausanne, Switzerland

Prof. Dr. Johannes Graff
Brain Mind Institute School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, EPFL, Lausanne

France:
Dr. Mireille Montcouquiol; INSERM, University of Bordeaux, Bordeaux

Spain:
Dr. Carlos Dotti; Centro de Biología Molecular Severo Ochoa (CBMSO), Madrid

Support

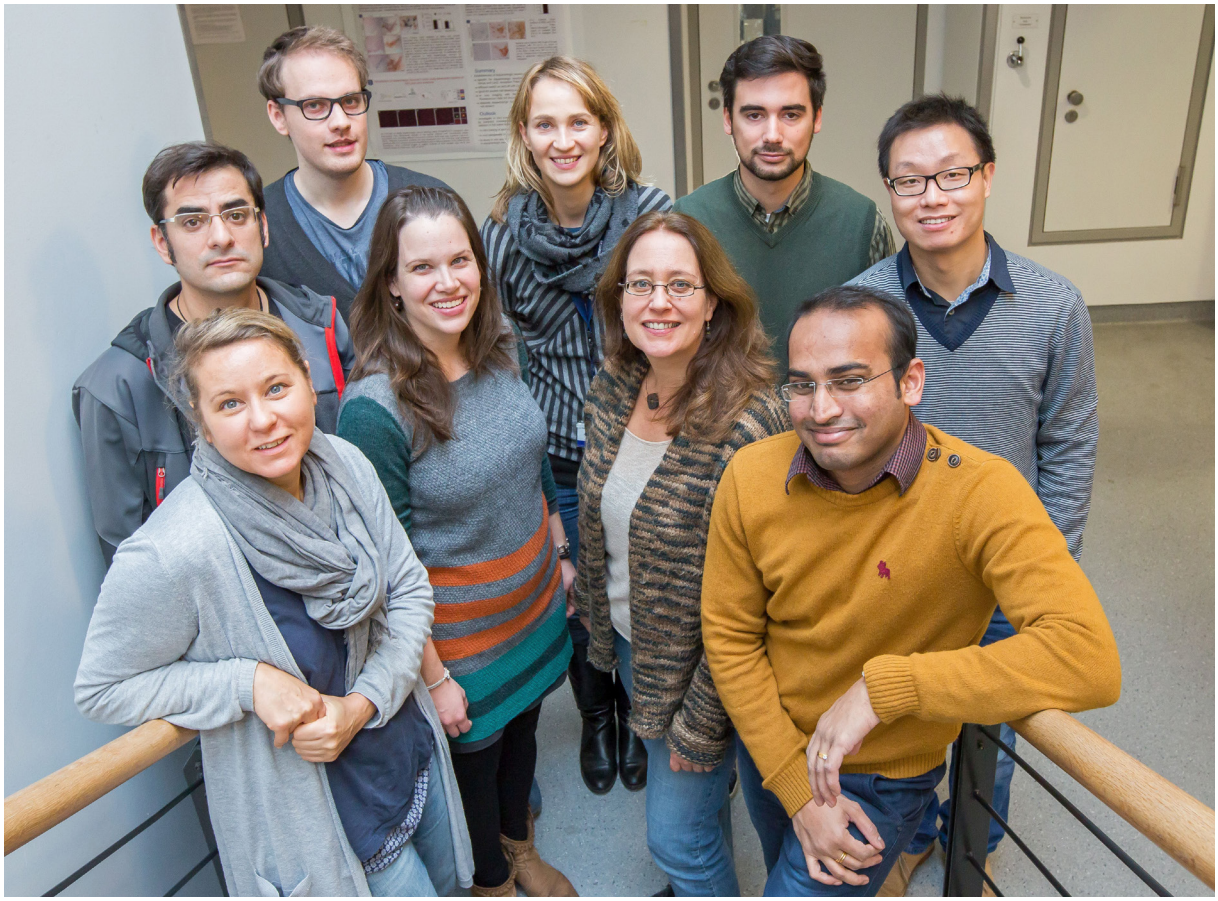
ERA-NET NEURON, Calderon (PI/ Coordinator) (The role of TAO2 in Autism Spectrum Disorders) 2014-2017.

FOR 2419, Calderon (PI) (DFG; The role of TAO2 in synapse formation and plasticity) 2015-2018.

Landesforschungsförderung Hamburg (LFF-FV27/P2), Calderon (PI) (Regulation of dendritic plasticity by Tao kinase) 2014-2017.

Team

Head: Dr. Froylan Calderon de Anda
Postdocs:
Dr. Melanie Richter
Dr. Durga Praveen Meka
PhD students:
Bing Zhao
Anne Naumann
Melad Henis
Master students:
Bianca Bedurftig
Ole Johanns
Robin Scharrenberg
Technician:
Birgit Schwanke



RG Neuronal Patterning and Connectivity

Head: Dr. Peter Šoba

The development and maintenance of neuronal networks forms the basis for brain function, which requires precise spatial and temporal regulation of wiring to properly connect our estimated 86 billion neurons. How neurons find the right partners and maintain functional connectivity is to date little understood. To get insight in these questions we use the somatosensory network of *Drosophila* larvae as a model by investigating how functional connections are established, maintained during juvenile development, and allow generation of robust and specific behaviors throughout life.

The larval somatosensory system consists of regularly arranged sensory neurons lining the body wall, with each sensory neuron class featuring stereotyped morphology and specific functions, ranging from mechanosensation to nociception. Recent efforts in electron microscopy based reconstruction of the larval connectome and genetic tool development have opened novel avenues to understand network connectivity and function. The approximately 10.000 larval neurons form a simple yet sufficiently complex nervous system to produce a range of behaviors supporting growth and survival, which we can study with high precision and allows us to extrapolate the results to higher organisms.

In recent years, we have expanded our methodological approaches to understand neuronal connectivity in this system, in particular the nociceptive network (Fig.1), and deduce general principles of network formation and function. We employ techniques and tools that allow visualization of cell type specific synapses *in vivo* at the light microscopic and ultrastructural level. Furthermore, we combine structural circuit analysis with functional calcium imaging and behavior to get in depth insight into network connectivity and function on all levels. Lastly, we use optogenetic approaches and CRISPR/Cas9-mediated genome editing to functionally and molecularly dissect the somatosensory network in an effort to understand the basis of its form and function.

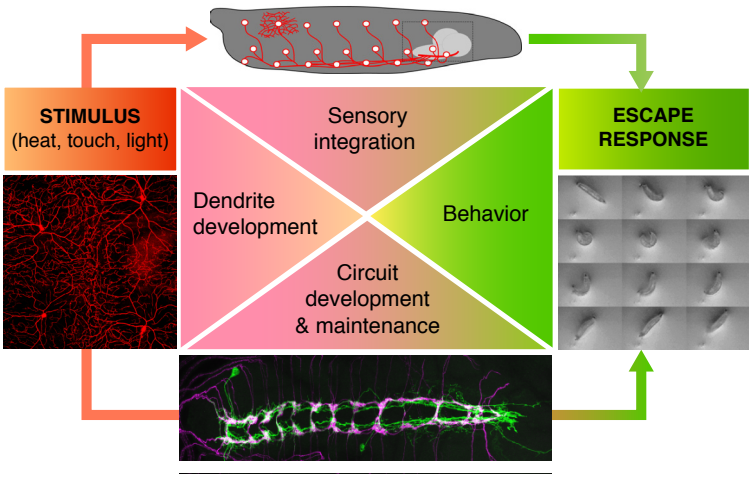


Figure 1. Analysis of Drosophila larval nociceptive network function.

Molecular mechanisms of space filling dendrite growth and tiling

Nina Hoyer, Philip Zielke, Meike Petersen, Chun Hu

Certain cell types including retinal ganglion cells in mammals as well as nociceptive neurons in *Drosophila* larvae feature mosaic-like arrangement of their dendrites and complete receptive field coverage with minimum overlap, a phenomenon termed tiling. The molecular cues mediating these patterning mechanisms remain elusive so far. We have identified a dendrite spreading mechanism required for formation of space-filling dendritic fields of *Drosophila* nociceptive neurons, which requires the neuronal receptor tyrosine kinase Ret and a novel TGFβ ligand. The substrate derived ligand acts as a developmental short-range signal promoting dendrite growth within not yet covered areas of the receptive field (Fig. 2). We propose that such a mechanism enables radial spreading

of dendrites to establish complete receptive field coverage. These studies allow us to gain mechanistic insight into the basis of dendritic field development and patterning, which is essential for neuronal network function.

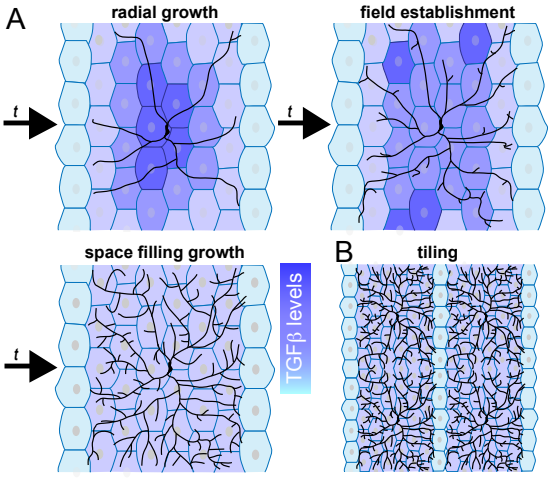


Figure 2. (A) Space filling growth of dendrites is regulated by a substrate derived ligand via Ret, which contributes to (B) tiling.

Maintenance of dendritic growth and synaptic specificity during juvenile development

Federico Tenedini, Chun Hu, Maria Saéz, Meike Petersen, Kathrin Sauter

Juvenile organisms like *Drosophila* larvae maintain functional connectivity through all stages while increasing their body surface 100-fold within few days. This requires immense growth of dendrites and specific synapse addition to maintain receptive field coverage and circuit output, respectively (Fig. 3). By now, we have identified several genes including the conserved Tao kinase (with F. Calderon de Anda), which are required for maintaining functional network integrity. Tao activity keeps neuronal and synaptic growth rates in sync and is required for circuit specific addition of synapses. We are investigating the underlying signaling machinery to gain mechanistic insight into how Tao activity confers growth synchronization and synaptic specificity. These findings and further analyses are of particular relevance as Tao kinase dysfunction is strongly linked to neurodevelopmental disorders including autism and schizophrenia.

We have identified a second class of regulators including the SLC36 transporter pathetic, which is required to sustain neuronal morphology and synaptic connectivity of nociceptive class IV da neurons (with Prof. Jay Parrish). Interestingly, degeneration of synapses and circuit dysfunction can be reversed even at late developmental time-points showing that functional connectivity can be restored. We have identified additional genes suggesting a general mechanism underlying maintenance of neuronal morphology and synaptic connectivity, which we investigate to gain conceptual understanding of circuit maintainance, degeneration and its reversal.

Encoding of modality specific and internal state dependent behavior

Chun Hu, Meike Petersen, Nina Hoyer, Bettina Spitzweck, Federico Tenedini, Denan Wang, Nusreen Imambocus, Alisa Gruschka, Kathrin Sauter, Janine Tutas

Nociception is an evolutionary conserved mechanism to detect and avoid noxious stimuli. Similarly to vertebrates, *Drosophila* larval nociceptors are able to detect different modalities including nociceptive touch and heat. How behavioral responses to these distinct modalities are encoded at the network level has so far not been elucidated. We have uncovered a circuit and

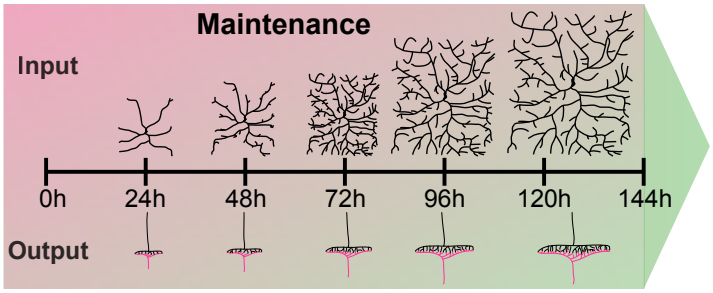


Figure 3. Receptive fields and synaptic output of nociceptive neurons scale with larval size and development.

neuromodulatory mechanism encoding mechano-nociceptive escape behavior (Hu et al., Nat. Neurosci. 2017), which relies on the *Drosophila* Neuropeptide Y homolog sNPF. We investigate how neuromodulation regulates action selection at the circuit level using electron microscopy reconstruction of larval circuits (with Dr. A. Cardona), and by developing novel tools to visualize, measure, and optogenetically manipulate neuropeptide-mediated actions required for modality specific and internal state dependent behavior *in vivo*. Our studies shed light on poorly understood neuropeptide action, which should provide answers to fundamental questions of network function and behavioral action selection.

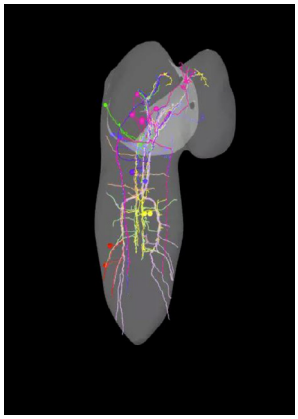


Figure 4. Video: Nociceptive circuit subset in *Drosophila* larvae.

Selected Publications

Almeida-Carvalho MJ, Berh D, Braun A, Chen Yc, Eichler K, Eschbach C, Fritsch PMJ, Gerber B, Hoyer N, JiangnX, Kleber J, Klämbt C, König C, Louis M, Michels B, Miroschnikow A, Mirth C, Miura D, Niewalda T, Otto N, Paisios E, Pankratz MJ, Petersen M, Ramsperger N, Randel N, Risse B, Saumweber T, Schlegel P, Schleyer M, Šoba P, Sprecher SG, Tanimura T, Thum AS, Toshima N, Truman JW, Yarali A, Zlatic M (2017). The Ol1mpiad: Concordance of behavioural faculties of stage 1 and stage 3 *Drosophila* larvae. J Exp Biol 220: 2452-2475.

Hu C*, Petersen M*, Hoyer N*, Spitzweck B, Tenedini F, Wang D, Gruschka A, Burchardt LS, Szpotowicz E, Schweizer M, Guntur AR, Yang CH, Šoba P (2017) Sensory integration and neuromodulatory feedback facilitate *Drosophila* mechanonociceptive behavior. Nat Neurosci Jun 12. doi: 10.1038/nn.4580. (*equal contribution)

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Šoba P*, Han C, Zheng Y, Perea D, Miguel-Aliaga I, Jan LY, Jan YN* (2015) The Ret receptor regulates sensory neuron dendrite growth and integrin mediated adhesion. Elife 4:e05491. (*co-corresponding author)

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

Doctoral/PhD Theses

Nina Hoyer (2016) The Ret receptor mediates sensory neuron dendrite growth through TGFβ. Department Biology, Universität Hamburg.

Chun Hu (2016) The role of tao kinase in cytoskeletal regulation of dendrite plasticity and function in *drosophila melanogaster*. Department Biology, Universität Hamburg.

Master Theses

Philip Zielke (2016) The role of the TGF-ß ligand maverick in sensory dendrite development and its link to the receptor tyrosine kinase Ret in *Drosophila melanogaster*. Department Biology, Universität Hamburg.

Alisa Gruschka (2015) Investigating the role of the receptor tyrosine kinase Ret in the *Drosophila melanogaster* larval light avoidance circuit. Department Biology, Universität Hamburg.

Collaborators

ZMNH:
Dr. Froylan C. de Anda
Dr. Kent Duncan
Prof. Dr. Manuel Friese
Dr. Marina Mikhaylova
Prof. Dr. Thomas Oertner
Dr. Michaela Schweizer
Dr. Simon Wiegert

Germany:
Prof. Dr. Daniela Dieterich
University of Magdeburg, Magdeburg

Dr. Christoph Metzendorf
BZH, University of Heidelberg, Heidelberg

Dr. Gaia Tavosanis
DZNE, Bonn

Priv.-Doz. Dr. Sabine Windhorst
University Medical Center Hamburg-Eppendorf, Hamburg

USA:
Dr. Albert Cardona
Janelia Research Campus, Ashburn

Prof. Dr. Chun Han
Cornell University, Ithaca

Prof. Dr. Yuh Nung Jan
University of California, San Francisco

Prof. DR. Jay Parrish
University of Washington, Seattle

Prof. Dr. Chung-Hui Yang
Duke University, Durham

Dr. Marta Zlatic
Janelia Research Campus, Ashburn

Japan:
Prof. Dr. Kazuo Emoto
Tokyo University, Tokyo

Austria:
Dr. Harald Janovjak
IST, Vienna

UK:
Prof. Dr. Irene Miguel-Aliaga
MRC, Imperial College London

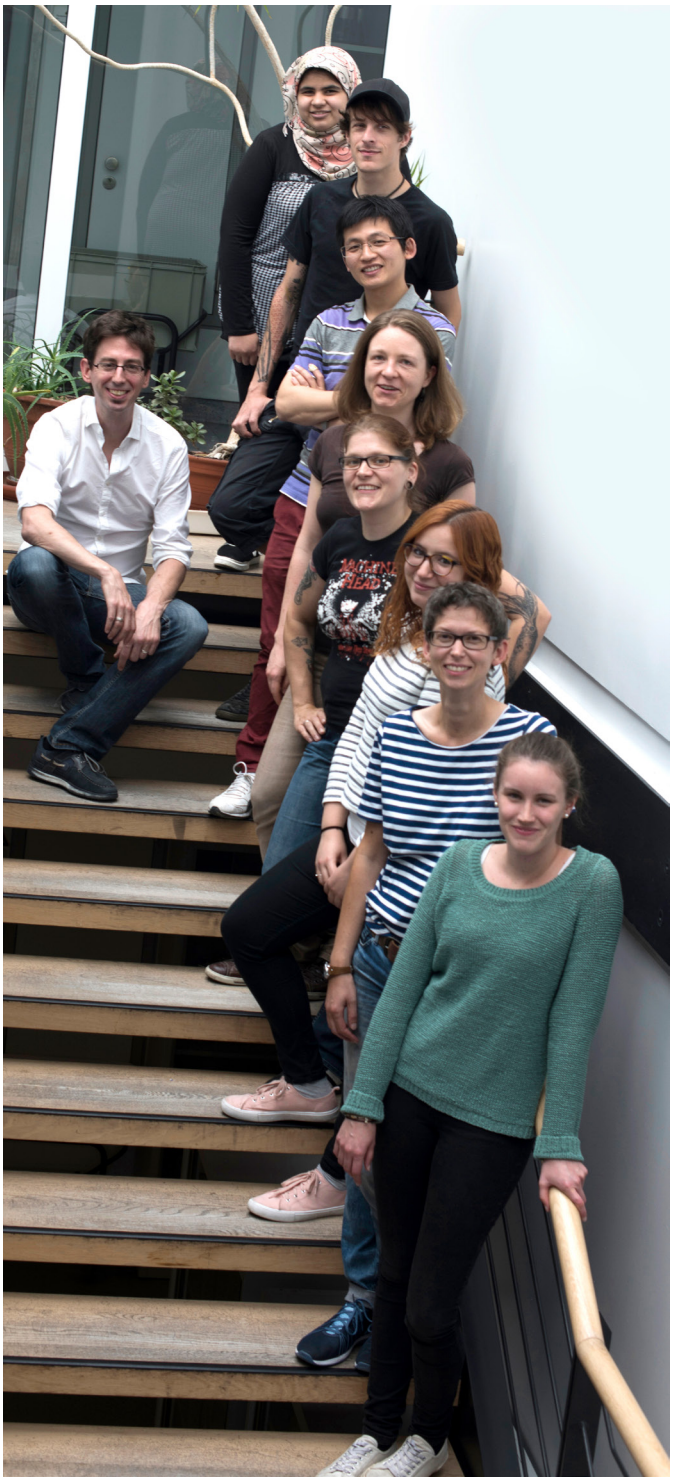
Support

Landesforschungsförderung Hamburg (LFF-FV27/P2) Peter Šoba (PI) 1/10/2014-31/12/2017 “Regulation of dendritic plasticity by Tao kinase” (with Dr. F. Calderon de Anda).

DFG priority program SPP1926 “Next generation optogenetics” (SO1337/2-1), Peter Šoba (PI) 08/2016-07/2019 “Development of next-generation light-gated inhibitory ion channels to probe somatosensory integration in the *Drosophila* nociceptive circuit *in vivo*” (with Dr. S. Wiegert).

Team

Head: Dr. Peter Šoba
Postdocs:
Dr. Nina Hoyer
Dr. Chun Hu
Dr. Bettina Spitzweck
PhD students:
Federico Tenedini
Nusreen Imambocus
Technicians:
Meike Petersen
Kathrin Sauter
(shared with J. Simon Wiegert)
Guest Scientist:
Dr. Denan Wang
Master students:
Alisa Gruschka
Philip Zielke
Fatma Ibrahim
Bachelor students:
Janine Tutas
Maria Saéz Gonzales



Neuronal Translational Control

Head: Dr. Kent Duncan

The ZMNH Neuronal Translational Control Research Group studies the mechanisms through which translational control contributes to cell-specific functions, with a major emphasis on the nervous system. We want to understand how regulated translation serves cell-specific functions *in vivo* in animals and how alterations to these cell-specific regulatory functions contribute to human disease. Our current focus is on two classes of translational regulators: non-canonical translation factors and RNA-binding proteins.

We seek mainly to answer the following questions:

- How do 'non-canonical' translation factors work and what are their cellular functions *in vivo?*
- What is the role of RNA-binding proteins in nervous system development and memory?
- How does altered RNA-binding protein function cause neurodegenerative disease?

Our approach is multi-level and interdisciplinary inasmuch as it 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 to take advantage of powerful genetic approaches available for studying development, neurobiology, and for modeling aspects of human diseases. A common goal is to identify specific mRNAs regulated by the factors we study at the translational level. For this purpose, we use methods to study translational control such as polysome profiling and translating ribosome affinity purification (TRAP) in both genome-wide and directed configurations.

Non-canonical translation factors: biological functions, mRNA targets, molecular mechanisms

In vitro biochemical studies described a group of non-canonical translation factors, but nothing was known about their *in vivo* biological functions or mRNA targets prior to our work. Together with the Teleman group, we showed that the DENR-MCT-1 complex selectively promotes translation reinitiation downstream of upstream Open Reading Frames (uORFs) to promote tissue growth (Schleich et al., Nature 2014). Subsequently, de novo mutations in DENR were identified in patients with neurodevelopmental disorders and mouse studies reveal that these mutations affect neocortical development, although the exact mechanism and target mRNAs remain to be determined. Our future goals include gaining a better understanding of conserved DENR functions in mammals. We are also pursuing *in vitro* biochemical experiments in collaboration with the Teleman lab to understand how exactly the DENR-MCT-1 complex functions to influence the fate of post-termination ribosomes (Fig. 1).

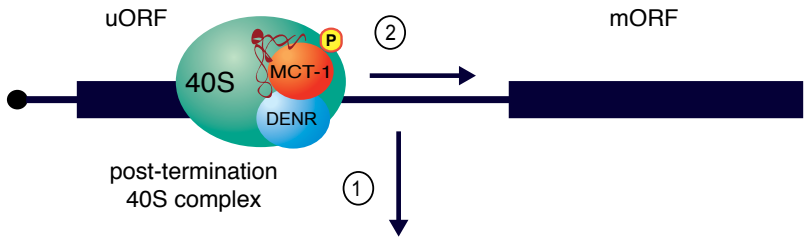


Figure 1. *How does DENR-MCT-1 control the Recycle-or-Reinitiate Decision?* Post-termination ribosomes that have translated a uORF have two possible fates: (1) recycle off the mRNA or (2) reinitiate on a downstream ORF. We are investigating how DENR-MCT-1 functions with other factors to influence this "recycle-or-reinitate decision". Failure to properly control this decision may lead to neurodevelopmental disorders.

We also identified the first *in vivo* functions and mRNA targets of the DENR ortholog, Ligatin/eIF2D in animals. *eIF2D*^{KO} flies that we generated have no gross developmental or morphological defects, but display striking deficits in locomotory behavior and synaptic transmission at Neuromuscular Junctions (NMJs). A major goal for this project during the reporting period was to determine how this relates to altered translation. To identify mRNAs whose translation is modulated by eIF2D *in vivo*, PhD student Aida Cardona-Alberich combined polysome profiling with genome-wide RNA-seq (Fig. 2). Strikingly, it was possible to rationalize the synaptic functional deficits based on the specific mRNAs that we found to be deregulated in *eIF2D*^{KO} by Poly-Seq. Our goals now are to understand exactly how eIF2D coordinates translation of these specific mRNAs to tune synaptic function.

RNA-binding protein function in nervous system development and memory

To gain insight into how translational control contributes to memory, we focus on the role of the RNA-binding protein Pumilio-2 in mice. The *Drosophila* Pum2 ortholog is a translational repressor selectively affecting long-term memory. However, it has remained unclear whether Pum2 affects mammalian memory. We generated Pum2 conditional knockout mice with the Transgenic Mouse Facility. Behavioral analysis with Fabio Morellini revealed striking effects on long-term memory performance when Pum2 is missing in forebrain principle neurons. We also found changes in both dendritic spine structure and the molecular composition of post-synaptic densities in neocortex. Polysome profiling revealed altered translation of a specific mRNA encoding a key protein for synaptic transmission in neocortices of mice lacking Pum2. This highlights a potential molecular mechanism by which Pum2 could modulate cortical memory processes. We plan to investigate this mechanism in more detail in the future. We have also asked whether Pum2 has a role in neocortical development *in vivo*. Dr. Kawssar Harb, who recently joined the group as an Alexander von Humboldt Fellow, has found extremely interesting phenotypes related to neuronal specification in developing neocortex of mice lacking Pum2. We are using polysome profiling to relate these cortical phenotypes to altered translational control.

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, particularly amyotrophic lateral sclerosis (ALS). How exactly TDP-43 contributes to disease remains unclear. We found that TDP-43 associates with polyribosomes and therefore hypothesize that it promotes disease by affecting translation of specific mRNAs. To identify these mRNAs we have used *in vitro* and *in vivo* approaches. Ribosome "footprint" profiling with cellular models of TDP-43-caused ALS revealed candidates for mRNA-specific translational control by patient mutant TDP-43. We are currently investigating potential mechanistic links to disease. Using mouse models of ALS caused by TDP-43 and Translating Ribosome Affinity Purification (TRAP) with genome-wide RNA-Seq, we have

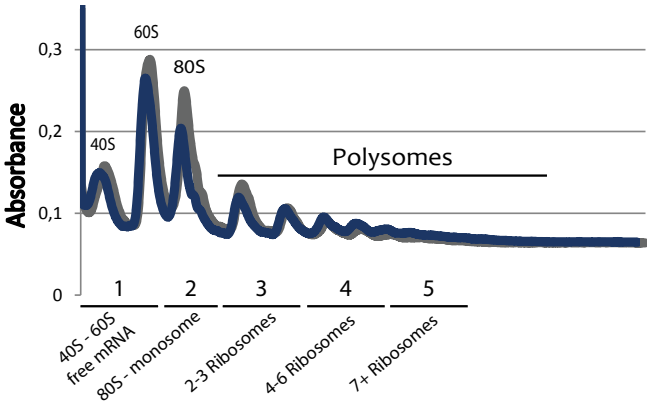


Figure 2. *Polysome profiling with RNA-Seq-(Poly-Seq) identifies in vivo regulatory targets of eIF2D in synaptic transmission*
Polysomes from *eIF2D*^{KO} and isogenic WT larvae were separated by sucrose-density gradient sedimentation and RNA from indicated fractions was used for RNA-Seq. This identified specific mRNAs with altered translation when eIF2D is missing *in vivo*. Many encode proteins involved in synaptic function and locomotion behavior, consistent with *eIF2D*^{KO}-phenotypes. We also use this approach to study translation in the mouse brain and degenerating spinal cord in neurodegenerative disease models.

identified new molecules whose levels are specifically altered in motor neurons when disease begins. These are candidates to be new "disease drivers". An important goal now is to validate these candidates in additional ALS models and patients. We are also developing an extension of this method that should be more sensitive for detecting translational changes than traditional TRAP.

Selected Publications

Haas MA, Ngo L, Li SS, Schleich S, Qu Z, Vanyai HK, Cullen HD, Cardona-Alberich A, Gladwyn-Ng IE, Pagnamenta AT, Taylor JC, Stewart H, Kini U, Duncan KE, Teleman AA, Keays DA, Heng JI (2016) De novo mutations in denr disrupt neuronal development and link congenital neurological disorders to faulty mRNA translation re-initiation. Cell Rep 15:2251-2265.

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Bachelor Thesis

David Schumacher (2016) Establishment of a polyribosome profiling assay for Drosophila larvae and assessment of eIF2D function in translation. Department of Chemistry, Universität Hamburg

Support

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Collaborators

ZMNH:
Dr. Froylan Calderon de Anda
Prof. Dr. Manuel Friese (INIMS)
Dr. Fabio Morellini
Dr. Irm Hermans-Borgmeyer
Prof. Dr. Matthias Kneussel
Prof. Dr. Jürgen Schwarz

Germany:
Dr. Aurelio Teleman
DKFZ, Heidelberg

Prof. Dr. Adam Grundhoff
Heinrich Pette Insitute, Hamburg

Prof. Dr. Stefan Kurtz
Center for Bioinformatics, Hamburg University

Dr. Gabriela Salinas-Riester
University Medical Center- Göttingen

Dr. Thomas Lindner
University Medical Center- Göttingen

Prof. Dr. Uwe Ohler
Berlin Institute of Systems Biology, Berlin

Prof. Dr. Stefan Bonn
DZNE, Göttingen

Dr. Virgilio Faila
UMIF, Hamburg

USA:
Prof. Dr. Myriam Heiman
Picower Institute of Learning and Memory, MIT

Prof. Dr. Jay Parrish
Department of Biochemistry, University of Washington, Seattle

Switzerland:
Dr. Martin Müller
Institute of Molecular Life Sciences, University of Zurich

Austria:
Dr. Gaia Novarino
Institute of Technology, Vienna

UK:
Dr. Jernej Ule
Francis Crick Institute

Japan:
Prof. Dr. Toshinobu Fujiwara
Kindai University, Osaka

Australia:
Prof. Dr. Julian Heng
Perkins Institute of Medical Research, University of Western Australia

Team

Head: Dr. Kent Duncan
Postdoc: Dr. Kawssar Harb
PhD students:
Aida Cardona-Alberich
Nagammal Neelagandan
Rita Francisco-Marques
Bachelor student:
David Schumacher
(thesis completed, Spring 2016)
Technicians:
Katrin Küchler
Christoph Janiesch

Development and Maintenance of the Nervous System

Head: Priv.-Doz. Dr. Edgar Kramer

The ZMNH Research Group headed by Edgar Kramer is working on the development and maintenance of the nervous system with a focus on cell surface proteins of neurons in the midbrain dopaminergic system of the mouse. This is of special interest concerning Parkinson disease (PD), a devastating neurodegenerative disorder with currently no cure that is characterized by a premature death of dopaminergic neurons.

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 signalling have been implicated in the pathogenesis of neurodegenerative disorders such as motoneuron diseases, PD and Alzheimer disease (AD) 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 signalling and regulatory pathways. So far our knowledge about neuronal cell surface protein interaction, signalling 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

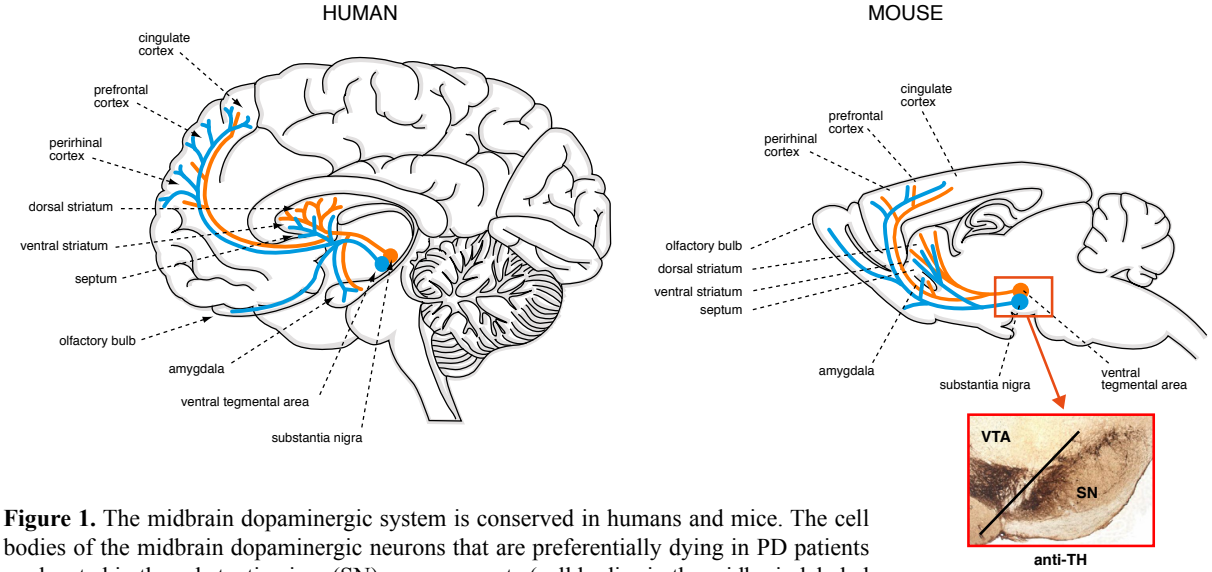

Figure 1. The midbrain dopaminergic system is conserved in humans and mice. The cell bodies of the midbrain dopaminergic neurons that are preferentially dying in PD patients are located in the substantia nigra (SN) pars compacta (cell bodies in the midbrain labeled in blue). They innervate with their axons mainly the dorsal striatum - a subcortical telencephalon region – and make up the mesostriatal pathway. Addiction affects DA neurons of the ventral tegmental area (VTA) mainly innervate the ventral striatum, cortex, amygdala and olfactory tubercle compacta (cell bodies in the midbrain labeled in red). They from the meocorticolimbic pathway. Dopaminergic neurons of the mouse can be visualized by immunohistochemistry using antibodies against tyrosine hydroxylase (TH).

dopaminergic system altered in PD patients and drug addicts and in motoneurons innervating the skeletal muscles. In addition, we analyse the function of different intracellular proteins encoded by genes mutated or linked to PD. We study their signalling 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 behavioural 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.

Our research supports ongoing clinical trials using GDNF and other Ret ligands in PD patients. So far their results are not conclusive. The results from my laboratory suggest that this approach strictly depends on the Ret receptor being expressed on dopaminergic neurons and can only be beneficial in the early phase of PD when still many dopaminergic neurons are present in these patients.

After completion of 8-year generous support at the ZMNH in spring 2016, I continued my research short-term at Ulm University. Currently I am re-establishing my laboratory at University of Plymouth, UK.

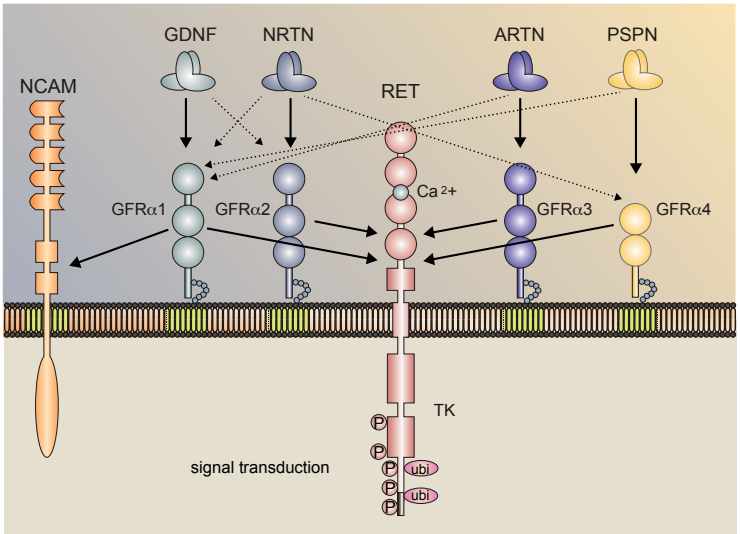

Figure 2. GDNF family of ligands and their receptors. The four members of the glial cell line-derived neurotrophic factor (GDNF) family of ligands, which include GDNF, neurturin, artemin, and persephin, are homodimers which bind with high affinity to one of the four members of the GDNF receptor α family (GFRα1-4). These receptor-ligand complexes can interact with and activate the canonical GDNF receptor Ret, a receptor tyrosine kinase. GDNF can also activate alternative GDNF receptors, such as the neuronal cell adhesion molecule (NCAM). The intracellular domain of Ret can be phosphorylated and ubiquitinylated.

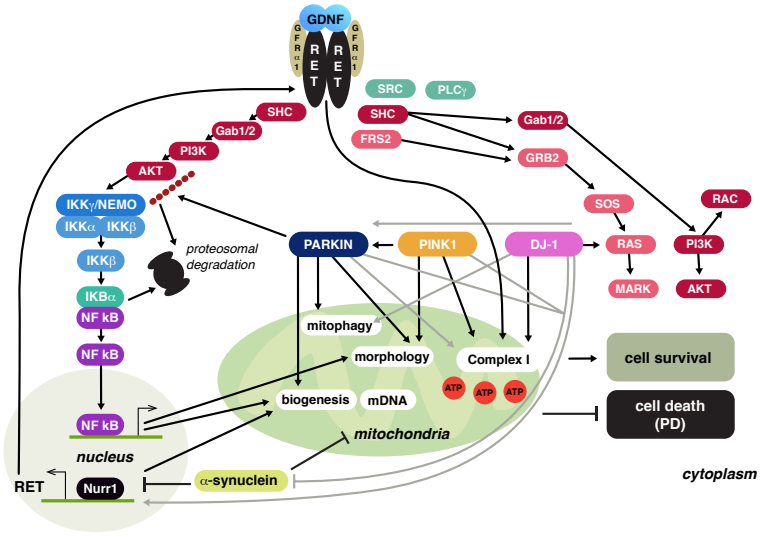

Figure 3. Signaling network of GDNF/Ret with proteins encoded by genes mutated in some familial forms of Parkinson disease. DJ-1 (PARK7) is involved in GDNF/Ret cell survival signaling through the RAS/MAPK pathway and stimulates Ret expression. α-synuclein (PARK1 and 4) inhibits Nurr1 and Ret expression. PINK1 (PARK6) and GDNF/Ret together control mitochondrial morphology and complex I activity. GDNF/Ret and parkin (PARK 2) signaling converges on mitochondrial morphology and complex I regulation. GDNF/Ret and parkin (PARK2) signaling also converges on mitochondrial morphology and complex I regulation by stimulating complex I activity and interacting with the NF-κB pathway to preserve mitochondrial integrity (see text for further details).

Publications 2015 - 6/2017

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Doctoral/PhD Theses

Helia Aboutalebi (2016) Establishing and using the new Tet system to study Parkinson's disease in mice. Department Biology, Universität Hamburg.

Collaborators

Prof. Dr. Heiko Braak
Medical Faculty, Ulm University, Germany

Prof. Dr. Nils Brose (Dr. Hiroshi Kawabe)
MPI for Experimental Medicine, Göttingen, Germany

Prof. Dr. Andreas Engel (Dr. Christian Moll)
UKE, Hamburg, Germany

Prof. Dr. Dirk Isbrandt
DZNE Bonn / University Hospital of Cologne, Germany

Dr. Sebastian Kügler, University of Göttingen, Germany

Prof. Dr. Christian Lohr, University of Hamburg, Hamburg, Germany

Prof. Dr. Sven Schröder (Dr. Thomas Friedemann)
UKE, Hamburg, Germany

Prof. Dr. Jörg Schulz
RWTH Aachen, Germany

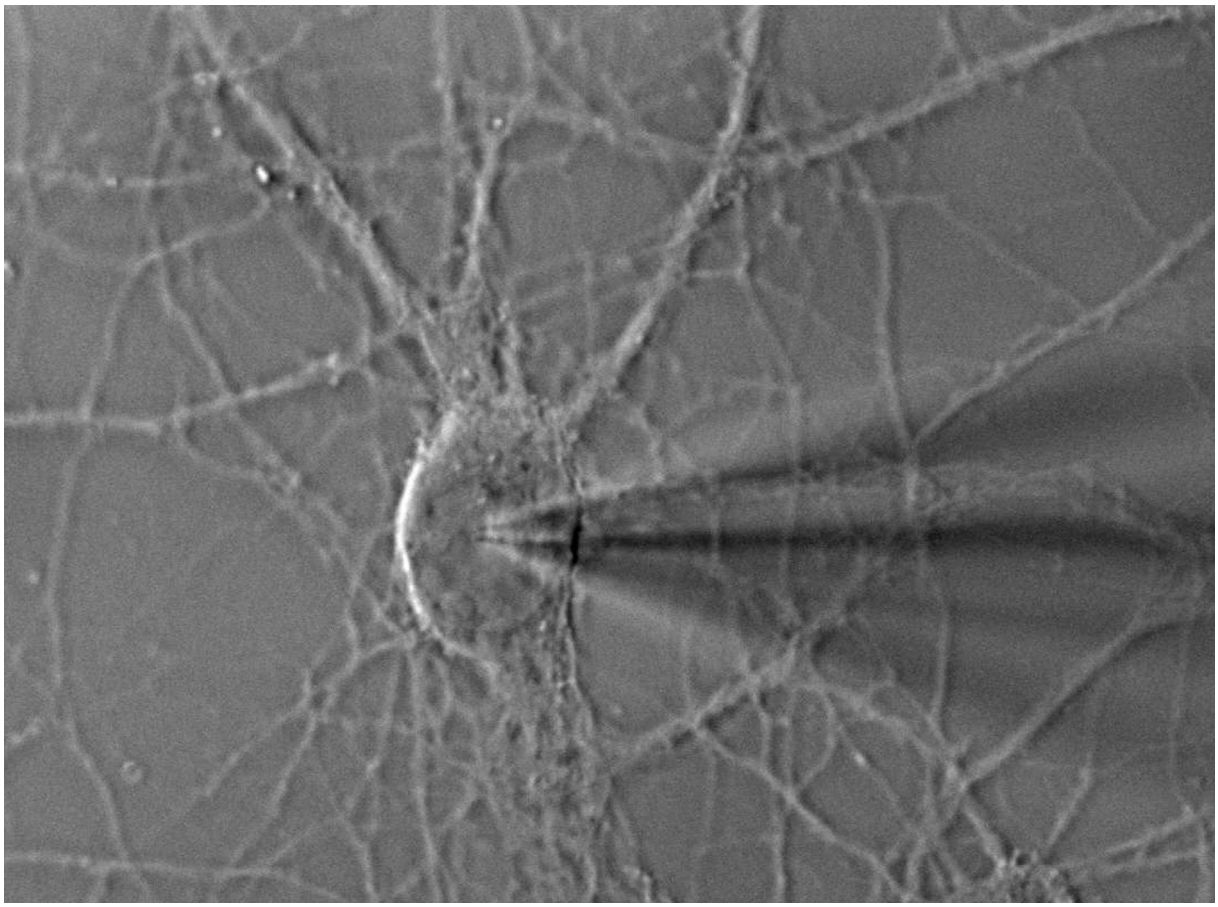
Prof. Dr. Jörg Tatzelt
University of Bochum, Bochum, Germany

Prof. Dr. Konstanze Winklhofer
University of Bochum, Germany

Team

Head: Edgar Kramer
Phd students:
- Helia Aboutalebi
- Prakash Nidadavolu
- Behnam Mohammadi
- Mahmoud Bassal

Technicians:
- Jenniver Koch
- Peggy Putthoff



Emeritus Group
Biosynthesis of Neural Structures

Head: Prof. Dr. Dr. h.c. Melitta Schachner

Cell adhesion molecules at the cell surface and in the extracellular matrix play important developmental roles in neural cell proliferation, migration, differentiation and survival, neuritogenesis, and synaptic targeting. Not only the protein backbones and their subdomains, but also the attached glycans have become of previously underestimated relevance. In the adult, they are involved in synaptic plasticity and promote regeneration after central and peripheral nervous system injuries. Our research is focused on the investigation of adhesion molecules that are crucial in these diverse functions: NCAM, L1, CHL1 and cellular prion protein and their associated glycans called polysialic acid (PSA), HNK-1 and LewisX, which are regulated in their expression independently of the protein backbones, thus introducing another dimension on the function of the proteins which display a multiplicity of functions by alternative splicing and by their processing via distinct proteolytic enzymes. We also search for interaction partners of adhesion molecules which modulate the adhesion molecules' functions. We expect that knowledge of these parameters will help to develop new therapies for treatment of acute and chronic nervous system disorders.

Novel CHL1 interaction partners

Mehrnaz Azami-Movahed, Patricia García-Jareño, Jelena Katic, Ralf Kleene, Agnieszka Kotarska, Gabriele Loers

We identified as CHL1 interaction partners vitronectin (VN), plasminogen activator inhibitor 2 (PAI-2), hedgehog receptor patched-1 (PTCH1) and serotonin 2c receptor (5-HT2c). CHL1 interacts with VN, PAI-2 and PTCH1 via its extracellular domain and with 5-HT2c through its intracellular domain. The trans-interactions with VN and PAI-2 regulate neuritogenesis and migration of cerebellar granule cells via integrins and PAI-2, and with PTCH1 it promotes survival of these cells via the PTCH1-regulated hedgehog signal transducer smoothened, RhoA and Rho-associated kinase. The cis-interaction of CHL1 with the constitutively active receptor isoforms of 5-HT2c regulates signaling pathways in subclasses of neurons via phosphatase and tensin homolog and β-arrestin.

Proteolysis of L1, localization and functions of novel L1 fragments and of L1 agonists

Gaston Castillo, Maria Girbes-Mínguez, Kristina Kraus, Gabriele Loers, Ralf Kleene, Volodymyr Serdyuk

Signals from the cell-surface are related to signal transducers in the cell interior not only by the intact molecules but also by fragments generated by different types of proteolytic cleavage. We identified myelin basic protein (MBP) as a serine protease that cleaves L1 and generates a transmembrane fragment which is essential for L1-dependent functions, such as neurite outgrowth, neuronal cell migration and survival, myelination by Schwann cells as well as Schwann cell proliferation, migration, and process formation. Ablation and blocking of MBP or disruption of its proteolytic activity abolish L1-dependent cellular responses. In utero injection of adeno-associated virus encoding proteolytically active, but not proteolytically inactive MBP into MBP-deficient shiverer mice normalized these functions. Also, application of purified active MBP promotes functional recovery after mouse spinal cord injury and, similarly, virus-mediated expression of active MBP resulted in improved functional recovery, indicating an important role of L1 proteolysis by MBP and here not mentioned other proteases in an injured adult mammalian nervous system.

Lack of permissive mechanisms and abundance of inhibitory molecules in the lesioned mammalian central nervous system contribute to impaired functional recovery. To identify agents that can mimic the functions of beneficial adhesion molecules for clinical translation we screened libraries of small molecules for agonists of regeneration-permissive L1 and identified L1

agonists that stimulated the known beneficial L1 functions *in vitro* and *in vivo* in femoral nerve and spinal cord injury mouse models. Small L1 mimicking molecules improved recovery of motor functions, being paralleled by enhanced remyelination, neuronal survival, and monoaminergic innervation, reduced astrogliosis, and activation of microglia, thus raising hopes that these drugs may be valuable additions to treatments of nervous system injuries.

Identification and functional characterization of PSA mimetics and nuclear PSA-NCAM fragments

Ralf Kleene, Gabriele Loers, Vedangana Saini, Nina Westphal, Mina Yakoub

PSA-NCAM is important for recovery after spinal cord injury. Transgenic mice lacking PSA-NCAM showed reduced locomotor recovery in parallel with decreased monoaminergic and cholinergic spinal cord re-innervation caudal to the injury, with decreased axonal regrowth/sprouting and decreased scar formation. Based on these findings we searched for small molecule mimetics of PSA and identified tegaserod, 5-nonyloxytryptamine, vinorelbine, epirubicin, idarubicin and irinotecan by using a competition ELISA. All six compounds stimulated neurite outgrowth and survival of cultured neurons via signaling pathways involving fibroblast growth factor receptor, myristoylated alanine-rich C kinase substrate and Erk. Furthermore, these compounds enhanced *in vitro* process formation of Schwann cells and neuronal migration and reduced aversive astrogliosis after spinal cord injury. 5-nonyloxytryptamine and vinorelbine enhanced the regain of motor functions in parallel with axonal regrowth, motor neuron survival and remyelination, raising the possibility to re-target these drugs used in treatment of cancers to nervous system repair.

PSA-NCAM plays a crucial role in regulation of the circadian rhythm. Interestingly, a PSA-carrying transmembrane NCAM fragment can enter the cell nucleus. The nuclear import of the PSA-carrying NCAM fragment is associated with altered expression of clock-related genes. *In vivo*, levels of nuclear PSA in different mouse brain regions depend on the circadian rhythm and clock-related gene expression in the suprachiasmatic nucleus and cerebellum are affected by the presence of a PSA-carrying nuclear NCAM fragment. These unexpected observations show that PSA attached to a transmembrane proteolytic NCAM fragment containing part of the extracellular domain enters the nucleus, where PSA-carrying NCAM contributes to the regulation of clock-related gene expression and of the circadian rhythm.

Prion protein and oxidative stress

Kathrin Guitart, Ralf Kleene, Gabriele Loers

Astrocytes provide trophic support for neurons in the nervous system and are important for neurotransmission, protection against cellular stress, metabolite and electrolyte homeostasis, inflammation, and synapse modulation. Prion protein (PrP) plays crucial roles in regulating antioxidant systems to improve cell defenses against cellular stress like oxidative stress, hypoxia, ischemia, and hypoglycemia. We could show that the interactions of PrP with the excitatory amino acid transporter 3 (EAAT3), γ-glutamyl transpeptidase, and multi-drug resistance protein 1 in astrocytes and the interaction between PrP and EAAT3 in neurons regulate the astroglial and neuronal metabolism of the anti-oxidant glutathione. Ablation of PrP in astrocytes and cerebellar neurons leads to dysregulation of EAAT3-mediated uptake of glutamate and cysteine, which are precursors for the synthesis of glutathione. PrP-deficient cerebellar neurons are more sensitive to oxidative stress and glutamate excitotoxicity than wild-type neurons. Furthermore, wild-type, but not PrP-deficient astrocytes protect wild-type cerebellar neurons against oxidative stress and exosomes released from stressed wild-type, but not from stressed PrP-deficient astrocytes reduce neuronal cell death. Upon hypoxic or ischemic conditions PrP levels in exosomes from wild-type astrocytes are increased as well as levels of the 37/67 kDa laminin receptor, apolipoprotein E and the ribosomal proteins S3 and P0, whereas levels of clusterin/apolipoprotein J are reduced. The levels of these proteins were not altered in exosomes from stressed PrP-deficient

astrocytes. The results indicate that PrP in astrocytes is a sensor for oxidative stress and mediates beneficial cellular responses, e.g. release of exosomes carrying PrP and other molecules that are taken up by neurons resulting in improved survival of neurons under hypoxic and ischemic conditions.

Future perspectives

The focus of our research will remain on L1, CHL1 and NCAM as well as on PSA, HNK-1 and LewisX with the goal to fully unravel the functions of these proteins and glycans in a developing, adult and regenerating mammalian nervous systems. A new line of research will characterize the functions of the nuclear L1 and PSA-NCAM fragments with and without their glycans. Furthermore, we will continue to work on improving our PSA- and L1-based drugs to translate them for treatment of patients.

Team

Head: Prof. Dr. Dr. h. c. Melitta Schachner

Scientists:

Dr. Kathrin Guitart
Dr. habil. Ralf Kleene
Dr. Gabriele Loers

PhD students:

Mehrnaz Azami-Movahed
Gaston Castillo
Patricia García-Jareño
Maria Girbés-Mínguez
Jelena Katic
Agnieszka Kotarska
Kristina Kraus
Vedangana Saini
Volodymyr Serdyuk
Nina Westphal

Master student:

Mina Yakoub

Technician:

Ute Bork

Selected Publications

Guitart K, Loers G, Buck F, Bork U, Schachner M, Kleene R (2016) Improvement of neuronal cell survival by astrocyte-derived exosomes under hypoxic and ischemic conditions depends on prion protein. Glia 64:896-910.

Lutz D, Kataria H, Kleene R, Loers G, Chaudhary H, Guseva D, Wu B, Jakovcevski I, Schachner M (2016) Myelin basic protein cleaves cell adhesion molecule L1 and improves regeneration after injury. Mol Neurobiol 53:3360-3376.

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Kataria H, Lutz D, Chaudhary H, Schachner M, Loers G (2016) Small molecule agonists of cell adhesion molecule L1 mimic L1 functions *in vivo*. Mol Neurobiol 53:4461-4483.

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Ma L, Shen HF, Shen YQ, Schachner M (2016) The adhesion molecule-characteristic HNK-1 carbohydrate contributes to functional recovery after spinal cord injury in adult zebrafish. Mol Neurobiol 2016 Apr 16. [Epub ahead of print]

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Guitart K, Loers G, Schachner M, Kleene R (2015) Prion protein regulates glutathione metabolism and neural glutamate and cysteine uptake via excitatory amino acid transporter 3. J Neurochem 133:558-571.

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Papastefanaki F, Jakovcevski I, Poulia N, Djogo N, Schulz F, Martinovic T, Ciric D, Loers G, Vossmeyer T, Weller H, Schachner M, Matsas R (2015)Intraspinal delivery of polyethylene glycol-coated gold nanoparticles promotes functional recovery after spinal cord injury. Mol Ther 23:993-1002.

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Schmalbach B, Lepsveridze E, Djogo N, Papashvili G, Kuang F, Leshchyns'ka I, Sytnyk V, Nikonenko AG, Dityatev A, Jakovcevski I, Schachner M (2015) Age-dependent loss of parvalbumin-expressing hippocampal interneurons in mice deficient in CHL1, a mental retardation and schizophrenia susceptibility gene. J Neurochem 135:830-844.

Tang DY, Yu Y, Zhao XJ, Schachner M, Zhao WJ. (2015) Single chain fragment variable antibodies developed by using as target the 3rd fibronectin type III homologous repeat fragment of human neural cell adhesion molecule L1 promote cell migration and neuritogenesis. Exp Cell Res 330:336-345.

Wobst H, Schmitz B, Schachner M, Diestel S, Leshchyns'ka I, Sytnyk V (2015) Kinesin-1 promotes post-Golgi trafficking of NCAM140 and NCAM180 to the cell surface. J Cell Sci 128:2816-2829.

Doctoral/PhD Theses

Mehrnaz Azami Movahed (2017) Identification of novel cytosolic binding partners of the cell recognition molecule CHL1 and study their functional interactions. Department Biology, Universität Hamburg.

Nina Westphal (2017) Functional role of a polysialic acid-carrying proteolytic fragment of the neural cell adhesion molecule NCAM in the nervous system. Department Biology, Universität Hamburg.

Jelena Katic (2016) The role of the cell adhesion molecule CHL1 and its interaction partners in cerebellar development. Department Biology, Universität Hamburg.

Master Thesis

Mina G. Yakoub (2016) Investigation of the interaction of TRPCs and NCAM proteins, and the functional consequences. Department Biology, Martin-Luther-Universität Halle-Wittenberg.

Awards and Distinctions

30/11/2015

Honorary doctorate degree of Universität Heidelberg

Prof. Dr. Melitta Schachner Camartin, ZMNH Emeritus Group Biosynthesis of Neural Structures

Emeritus Group Cell Biochemistry and Clinical Neurobiology

Head: Prof. Dr. Dietmar Richter, Founding Director of ZMNH

Due to my retirement in 2005 the Institute of 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 of 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 ZMNH Research Report 2009-2014 85 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

Thyssen Stiftung
Dr. Hans Ritz und Lieselotte Ritz Stiftung

Collaborators

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

Prof. Dr. Fernando G. Noriega
Dept. Biology Sciences, Florida International University, Miami, USA

Prof. Dr. Wolfgang Meyerhof
Department of Molecular Genetics, German Institute of Human Nutrition, Potsdam, Germany. (Topic: allatostatin receptors in insects)

Leibniz Group Dendritic Organelles and Synaptic Function

Head: Dr. Michael R. Kreutz

The Leibniz Group investigates how microsecretory systems and organelles in neurites are involved in synaptic function. In recent work we identified a satellite Golgi-related microsecretory system (GS) that exists in all principal neurons (Mikhaylova et al., 2016). GS contain glycosylation machinery but lack many matrix components of Golgi cisternae. We found that a broad spectrum of synaptic transmembrane proteins might pass and even recycle through these organelles. We currently investigate whether GS is indeed involved in re-cycling and glycosylation of synaptic transmembrane proteins and we test the hypothesis that the presence of an ER-ERGIC-GS-retromer microsecretory system in all neuronal dendrites enables autonomous local control of transmembrane protein synthesis and processing.

Some reports have indicated that hybrid organelles might exist in neurons but very little is known about their assembly and their functional role. In very recent work we found evidence for an amphisome that allows for TrkB signaling at mossy fiber synapses. The RapGAP SPAR2/SIPA1L2 associates with TrkB receptors and links TrkB to a dynein motor as well as to autophagosomes. This ride on service seems to impact on the retrograde transport of a signalling amphisome that trafficks between presynaptic boutons. RapGAP signaling regulates the motility of the complex and LC3 binding to the RapGAP domain slows down the velocity of the amphisome and enables TrkB signaling at presynaptic sites, which in turn facilitates neurotransmitter release.

For additional information please refer to
http://www.kreutzlab.com/

Selected Publications in Collaboration with ZMNH 2015 – 6/2017

Mikhaylova M, Bera S, Kobler O, Frischknecht R, Kreutz MR (2016) A widespread satellite Golgi micro-secretory system in between ERGIC and retromer in neuronal dendrites. Cell Rep 14:189-199.

Spilker C*, Nullmeier S*, Grochowska KM*, Schumacher A, Butnaru I, Macharadze T, Yuanxiang P, Gomes GM, Bayraktar G, Rodenstein C, Kolodziej A, Montag D, Angenstein F, Bär J, D'Hanis W, Roskoden T, Mikhaylova M, Budinger E, Ohl FW, Stork O, Karpova A, Zenclussen AC, Schwegler H, Kreutz MR (2016) A jacob/nsmf gene knock-out results in hippocampal dysplasia and impaired BDNF signalling in dendritogenesis. PLoS Genet 12:e1005907. *Equal contribution

Grochowska KM, Yuanxiang P, Bär J, Raman R, Brugal G, Sahu G, Schweizer M, Bikbaev A, Schilling S, Demuth HU, Kreutz MR (2017) Posttranslational modification impact on the mechanism by which amyloid-β induces synaptic dysfunction. EMBO Rep pii: e201643519

Team

Head: Dr. Michael R. Kreutz
Postdoc:
Dr. Maria Andres-Alonso
PhD students:
Maximillian Borgmeyer
Michael Bucher

Publications with ZMNH Affiliation of Michael Kreutz 2015 – 6/2017

Grochowska KM, Yuanxiang P, Bär J, Raman R, Brugal G, Sahu G, Schweizer M, Bikbaev A, Schilling S, Demuth HU, Kreutz MR (2017) Posttranslational modification impact on the mechanism by which amyloid-beta induces synaptic dysfunction. EMBO Rep 18:962-981.

Bera S, Raghuram V, Mikhaylova M, Kreutz MR (2016) A plasmid-based expression system to study protein-protein interactions at the Golgi *in vivo*. Anal Biochem 502:50-52.

Hrdinka M, Sudan K, Just S, Drobek A, Stepanek O, Schluter D, Reinhold D, Jordan BA, Gintschel P, Schraven B, Kreutz MR (2016) Normal development and function of T cells in proline rich 7 (Prr7) deficient mice. PLoS One 11:e0162863.

Kravchick DO, Karpova A, Hrdinka M, Lopez-Rojas J, Iacobas S, Carbonell AU, Iacobas DA, Kreutz MR, Jordan BA (2016) Synaptonuclear messenger PRR7 inhibits c-Jun ubiquitination and regulates NMDA-mediated excitotoxicity. EMBO J 35:1923-1934.

Lopez-Rojas J, Heine M, Kreutz MR (2016) Plasticity of intrinsic excitability in mature granule cells of the dentate gyrus. Sci Rep 6:21615.

Lopez-Rojas J, Kreutz MR (2016) Mature granule cells of the dentate gyrus--Passive bystanders or principal performers in hippocampal function? Neurosci Biobehav Rev 64:167-174.

Melgarejo da Rosa M, Yuanxiang P, Brambilla R, Kreutz MR, Karpova A (2016) Synaptic-GluN2B/CaMKII-alpha signaling induces synapto-nuclear transport of ERK and Jacob. Front Mol Neurosci 9:66.

Mikhaylova M, Bera S, Kobler O, Frischknecht R, Kreutz MR (2016) A Dendritic Golgi Satellite between ERGIC and Retromer. Cell Rep 14:189-199.

Spilker C, Grochowska KM, Kreutz MR (2016) What do we learn from the murine Jacob/Nsmf gene knockout for human disease? Rare Dis 4:e1241361. eCollection 2016.

Spilker C, Nullmeier S, Grochowska KM, Schumacher A, Butnaru I, Macharadze T, Gomes GM, Yuanxiang P, Bayraktar G, Rodenstein C, Geiseler C, Kolodziej A, Lopez-Rojas J, Montag D, Angenstein F, Bär J, D'Hanis W, Roskoden T, Mikhaylova M, Budinger E, Ohl FW, Stork O, Zenclussen AC, Karpova A, Schwegler H, Kreutz MR (2016) A Jacob/Nsmf gene knockout results in hippocampal dysplasia and impaired BDNF signaling in edendritogenesis. PLoS Genet 12:e1005907.

Xiang PY, Janc O, Grochowska KM, Kreutz MR, Reymann KG (2016) Dopamine agonists rescue Aβ-induced LTP impairment by Src-family tyrosine kinases. Neurobiol Aging 40:98-102.

Guest Group
Experimental Neuropediatrics

Head: Priv.-Doz. Dr. Axel Neu

The research group of Experimental Neuropediatrics is involved in translational research in the field of neurobiology and neurology. Our main research interests are genetic epilepsies and creatine deficiency syndromes. Our lab is located at the Center for Molecular Neurobiology (ZMNH) which allows us to interact closely with basic research groups. As a clinical research group, we have direct access to patients of the Departments of Pediatrics and Neurology.

The majority of childhood onset epilepsies are considered to be of genetic origin, in many cases due to mutations in ion channels. Our major goal is to identify basic mechanisms of epileptogenesis in the immature brain to develop novel therapeutic strategies. In cooperation with the Department of human genetics, we analyze functional consequences of mutations in ion channel genes identified in pediatric patients, e.g. SCN8A, KCNT1 or KCNB1. In addition, we generate mouse models to perform behavioral, neurophysiological and pharmacological studies. Our second research focus is the creatine metabolism, especially the consequences of impaired creatine synthesis and transport on CNS function. Creatine deficiency syndromes in humans are associated with mutations in genes coding for AGAT, GAMT or CrT and characterized by epilepsy and mental retardation. We use different mouse models of creatine deficiency syndromes to examine the pathophysiological aspects on molecular, cellular and systemic levels. For example, we could show that AGAT is also involved in the synthesis of homoarginine, a non-proteinogenic amino acid without clearly defined role. Using our mouse models, homoarginine could be identified as a modifiable cardiovascular risk factor, offering a high translational potential e.g. for stroke prevention.

Publications in Collaboration with ZMNH

Stockebrand M, Nejad AS, Neu A, Kharbanda KK, Sauter K, Schillemeit S, Isbrandt D, Choe CU (2016) Transcriptomic and metabolic analyses reveal salvage pathways in creatine-deficient AGAT(-/-) mice. Amino Acids 48:2025-39

Stockebrand M, Hornig S, Neu A, Atzler D, Cordts K, Böger RH, Isbrandt D, Schwedhelm E, Choe CU (2015) Homoarginine supplementation improves blood glucose in diet-induced obese mice. Amino Acids 47:1921-9

Marguet SL, Le-Schulte VT, Merseburg A, Neu A, Eichler R, Jakovcevski I, Ivanov A, Hanganu-Opatz IL, Bernard C, Morellini F, Isbrandt D (2015). Treatment during a vulnerable developmental period rescues a genetic epilepsy. Nat Med 21:1436-44

Team

Head: Priv.-Doz. Dr. Axel Neu
Co-Investigator:
Priv.-Doz. Dr. Chi-un Choe
Postdoc:
Dr. Sönke Hornig
PhD students:
Janna Gellermann
Schabira Habib
Technician:
Stefan Schillemeit

Guest Group Developmental Neurophysiology

Head: Prof. Dr. Ileana Hanganu-Opatz

The guest research group Developmental Neurophysiology elucidates 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:

Development of neuronal networks accounting for cognitive processing

We recently identified the cellular substrate of long-range coupling in developing prefrontal-hippocampal networks using a novel optogenetic approach (Bitzenhofer et al., 2017 – Nature Comm.)

Uni- and multisensory processing and ontogeny

Optimal perception of environment requires the convergence of different senses. We identified the cortical mechanisms of multisensory processing and its ontogeny (Sieben et al., 2015 – PLOS Biol.)

Dysfunction of network ontogeny in mental illness

Schizophrenia is a miswiring disorder. We showed that this miswiring results from a developmental switch from a neonatal shortage to a juvenile surge of functional coupling between prefrontal cortex and hippocampus (Hartung et al., 2016 – Cereb Cortex).

Olfactory control of limbic development

We investigate how a specific spatiotemporal organization of activity patterns in the olfactory bulb during neonatal development facilitates the entrainment and refinement of downstream entorhinal-prefrontal-hippocampal networks.

For additional information please refer to:
www.uke.de/entwicklungsneurophysiologie

Publication in Collaboration with ZMNH 2015 – 06/2017

Bitzenhofer SH, Ahlbeck J, Wolff A, Wiegert JS, Gee CE, Oertner TG, Hanganu-Opatz IL (2017) Layer-specific optogenetic activation of pyramidal neurons causes beta-gamma entrainment of neonatal networks. Nature Comm 8:14563.

Support

ERC Consolidator Grant (681577)
DFG (SPP 1665, SFB 936, Ha4466/10-1, Ha4466/12-1)
NSF (IPAN)

Team

Head: Prof. Dr. Ileana Hanganu-Opatz
Postdocs:
Dr. Henrike Hartung
Dr. Christoph Lindemann
Dr. Sabine Gretenkord
Dr. Xiaxia Xu
Dr. Kay Sieben
PhD students:
Joachim Ahlbeck
Sebastian Bitzenhofer
Malte Bieler
Mattia Chini
Antonio Candela
Johanna Kostka
Steven Schepanski
Technicians:
Annette Marquardt
Achim Dahlmann
Peggy Putthoff

Guest Group
Fraunhofer IME ScreeningPort

Head: Dr. Ole Pless

The ScreeningPort of the Fraunhofer Institute of Molecular Biology and Applied Ecology IME in Hamburg has substantial expertise in assay development and high-throughput screening as well as structure-based drug design. The ScreeningPort is a division within the IME, which is headquartered in Aachen and has around 650 scientists working across eight sites in Germany, Chile and the United States. The IME operates in the applied life sciences from the molecular to the ecosystem level in the areas of pharmacy, medicine, chemistry, and agriculture. Within IME, the ScreeningPort works in four main areas: Drug discovery, life sciences informatics using "Big Data" approaches, clinical trial support / *in vitro* diagnostic development, and development of novel life science technologies.

Ongoing work in the BMBF-funded biomarker group located at the Center for Molecular Neurobiology Hamburg (*Zentrum für Molekulare Neurobiologie Hamburg*, ZMNH) involves support for several clinical trials for neurodegenerative diseases using profiling of markers of inflammation. Furthermore, the group aims at identifying and validating biomarkers for neurodegeneration based on proteins, small non-coding RNAs and metabolites in patient specimen.

For additional information please refer to
http://www.ime.fraunhofer.de/en/businessareasMB/screeningport.html.

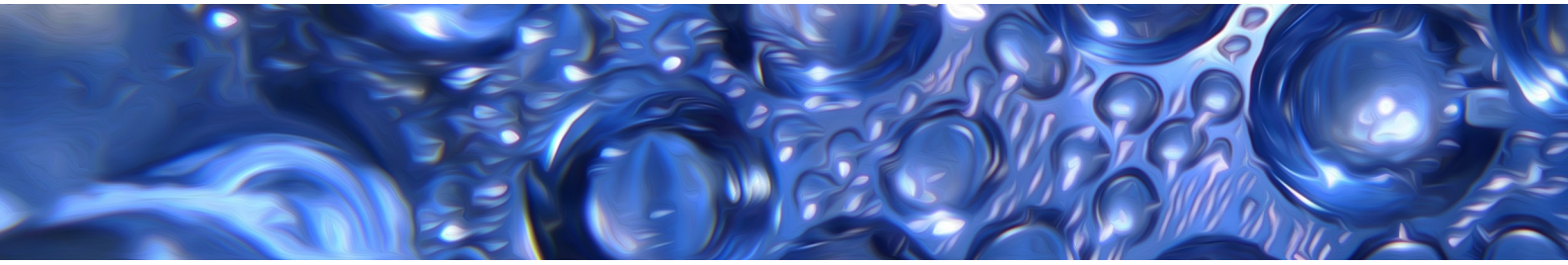
Publications in Collaboration with ZMNH 2015 – 06/2017

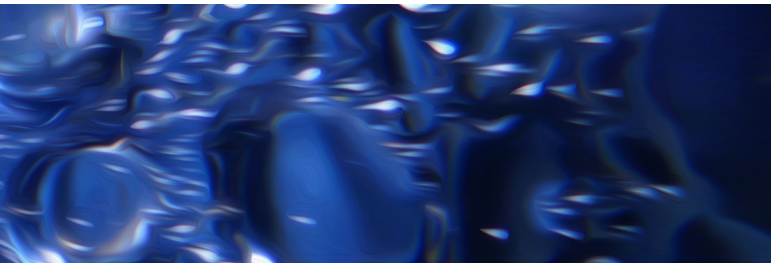
Ufer F, Vargas P*, Engler JB*, Tintelnot J, Schattling B, Winkler H, Bauer S, Kursawe N, Willing A, Keminer O, Ohana O, Salinas-Riester G, Pless O, Kuhl D, Friese MA (* equal contribution) (2016) Arc/Arg3.1 governs inflammatory dendritic cell migration from the skin and thereby controls T cell activation. Science Immunol 1: eaaf8665

Briken S*, Rosenkranz SC*, Keminer O, Patra S, Ketels G, Heesen C, Hellweg R, Pless O, Schulz KH*, Gold SM* (* equal contribution) (2016) Effects of exercise on Irisin, BDNF and IL-6 serum levels in patients with progressive multiple sclerosis. J Neuroimmunol 299:53-58

Team

Head: Dr. Ole Pless
Research Associate:
Oliver Keminer
PhD student:
Undine Haferkamp
Research Assistants:
Dan Nguyen Luong
Jeanette Reinshagen
Tobias Schäfer
Felix Uecker
Technicians:
Birte Behrens
Jennifer Leu





Research Reports of the ZMNH Core Facilities

Core Facility Bioanalytics

Head: Priv.-Doz. Dr. Sabine Hoffmeister-Ullerich

The Core facility Bioanalytics, 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 2015 until June 2017 approximately 15,000 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, together with the ZMNH Transgenic Mouse Core Facility, we also developed several assays which are applicable for genotyping of genetically altered mice. These assays are High Resolution Melting assays which were established by our group for use with our instruments, as well as Copy Number Variation assays. These assays are performed on demand.

Team

Group leader:

Priv.-Doz. Dr. Sabine Hoffmeister-Ullerich

Technician:

Marion Hohlbaum

Core Facility Electron Microscopy and Morphology

Head: Dr. 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 immunolocalisation of proteins, ultrastructural analysis, and data processing.

We advise 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.

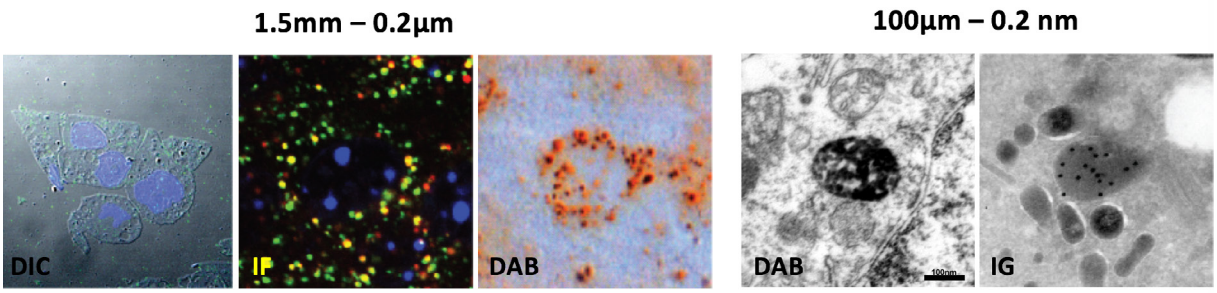
Offered services

- 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)

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.



Using our equipment (CLSM and TEM) and different protocols, we cover the whole range from light- to electron microscopical resolution, e.g.the localisation of lysosomal proteins with DIC, fluorescent markers (IF), DAB and postembedding immunogold (IG).

Selected Publications

Hu C, Petersen M, Hoyer N, Spitzweck B, Tenedini F, Wang D, Gruschka A, Burchardt LS, Szpotowicz E, Schweizer M, Guntur AR, Yang CH, Šoba P (2017) Sensory integration and neuromodulatory feedback facilitate Drosophila mechanonociceptive behavior. Nat Neurosci Jun 12. doi: 10.1038/nn.4580.

Schneppenheim J, Loock AC, Hüttl S, Schweizer M, Lüllmann-Rauch R, Oberg HH, Arnold P, Lehmann CHK, Dudziak D, Kabelitz D, Lucius R, Lennon-Duménil AM, Saftig P, Schröder B (2017) The influence of MHC class II on B cell defects induced by invariant chain/CD74 N-terminal fragments. J Immunol May 26. doi: 10.4049/jimmunol.1601533. PMID:28550201

Kuhn PH, Colombo AV, Schusser B, Dreymueller D, Wetzel S, Schepers U, Herber J, Ludwig A, Kremmer E, Montag D, Müller U, Schweizer M, Saftig P, Bräse S, Lichtenthaler SF (2016) Systematic substrate identification indicates a central role for the metalloprotease ADAM10 in axon targeting and synapse function. Elife 5:e12748.

Petar M, Zimmermann EA, vom Scheidt A, Hoffmann B, Sarau G, Yorgan T, Schweizer M, Amling M, Christiansen S, Busse B (2017) The formation of calcified nanospherites during micropetrosis represents a unique mineralization mechanism in aged human bone. Small 13(3)

Köster JD, Leggewie B, Blechner C, Brandt N, Fester L, Rune G, Schweizer M, Kindler S, Windhorst S (2016) Inositol-1,4,5-trisphosphate-3-kinase-A controls morphology of hippocampal dendritic spines. Cell Signal 28:83-90.

Team

Group leader:

Dr. Michaela Schweizer

Technicians:

Chudamani Raithore

Emanuela Szpotowicz

Publications 2015 – 6/2017

Grochowska KM, Yuanxiang P, Bär J, Raman R, Brugal G, Sahu G, Schweizer M, Bikbaev A, Schilling S, Demuth HU, Kreutz MR (2017) Posttranslational modification impact on the mechanism by which amyloid-beta induces synaptic dysfunction. EMBO Rep 18:962-981.

Hu C, Petersen M, Hoyer N, Spitzweck B, Tenedini F, Wang D, Gruschka A, Burchardt LS, Szpotowicz E, Schweizer M, Guntur AR, Yang CH, Šoba P (2017) Sensory integration and neuromodulatory feedback facilitate Drosophila mechanonociceptive behavior. Nat Neurosci Jun 12. doi: 10.1038/nn.4580.

Milovanovic P, Zimmermann EA, Vom Scheidt A, Hoffmann B, Sarau G, Yorgan T, Schweizer M, Amling M, Christiansen S, Busse B (2017) The formation of calcified nanospherites during micropetrosis represents a unique mineralization mechanism in aged human bone. Small 13:1602215.

Schmiesing J, Lohmoller B, Schweizer M, Tidow H, Gersting SW, Muntau AC, Braulke T, Muhlhausen C (2017) Disease-causing mutations affecting surface residues of mitochondrial glutaryl-CoA dehydrogenase impair stability, heteromeric complex formation and mitochondria architecture. Hum Mol Genet 2017 Jan 5. pii: ddw411. doi: 10.1093/hmg/ddw411. [Epub ahead of print]

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Transgenic Mouse Facility

Head: Priv.-Doz. Dr. Irm Hermans-Borgmeyer

The ZMNH Transgenic Mouse Facility supports scientists in all aspects of transgenic mouse production and maintenance of mouse lines. Due to growing demand in spring 2017 we extended our services to the support of gene editing in cells. Techniques available include pronuclear and ES cell injection, preparing constructs for injection and gene targeting in embryos and ES cells, ES cell culture, *in vitro* transcription, embryo transfer of complex lines, genotyping by PCR and Southern blot, cryopreservation of sperm and embryos. Collections of mouse lines of general interest, vectors, embryonic stem cells (ES) and mouse embryonic fibroblasts (MEF) are available. We help with the design and cloning of constructs for generation of transgenes and gene targeting in mice and cells, the design of genotyping strategies. We inform scientist about new developments in the field and establish new techniques as fast as possible. In addition, we teach and train students and interested scientists and offer training courses for animal care takers.

Irm Hermans-Borgmeyer is a member of the *Kommission für Tierversuche* according to §15 of the *Tierschutzgesetz* and the *Tierschutzausschuss* of the UKE as well as of the cage contigent commission of the UKE and serves as representative of the ZMNH for mouse issues.

Publications 2015 – 6/2017

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Team

Priv.-Doz. Dr. Uwe Borgmeyer
(since April 2017)

Priv.-Doz. Dr. Irm Hermans-Borgmeyer

Sarah Homann

Ute Eicke-Kohlmorgen
(since January 2017)

Peggy Putthoff
(until January 2017)

Core Facility
IT Service and Development

Head: Dr. Hans-Martin Ziethen

The ZMNH IT Service Group is dedicated to provide each research group with the resources and technologies relevant to their work. That includes the purchase and installation of software and hardware, supporting and consulting the scientists in all IT matters as well as the assembly of specialized computer and software systems tailored to perform specific tasks. Currently there are about 700 clients in the ZMNH, each of them having an individual configuration of components. Windows, Mac-OS and Linux are used, depending on the intended purpose of the machine. Nearly 100 computers are provided for the operation of technical equipment, such as microscopes, sequencing instruments or PCR thermal cyclers.

We provide all the important network services for the center, including access to the intranet, internet, VPNs, Wi-Fi and roughly 200 TB of storage space. In our data center we operate about 50 servers, mostly equipped with Linux and open source components. Approximately 50% of them are virtualized, running on a VMware cluster. 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.

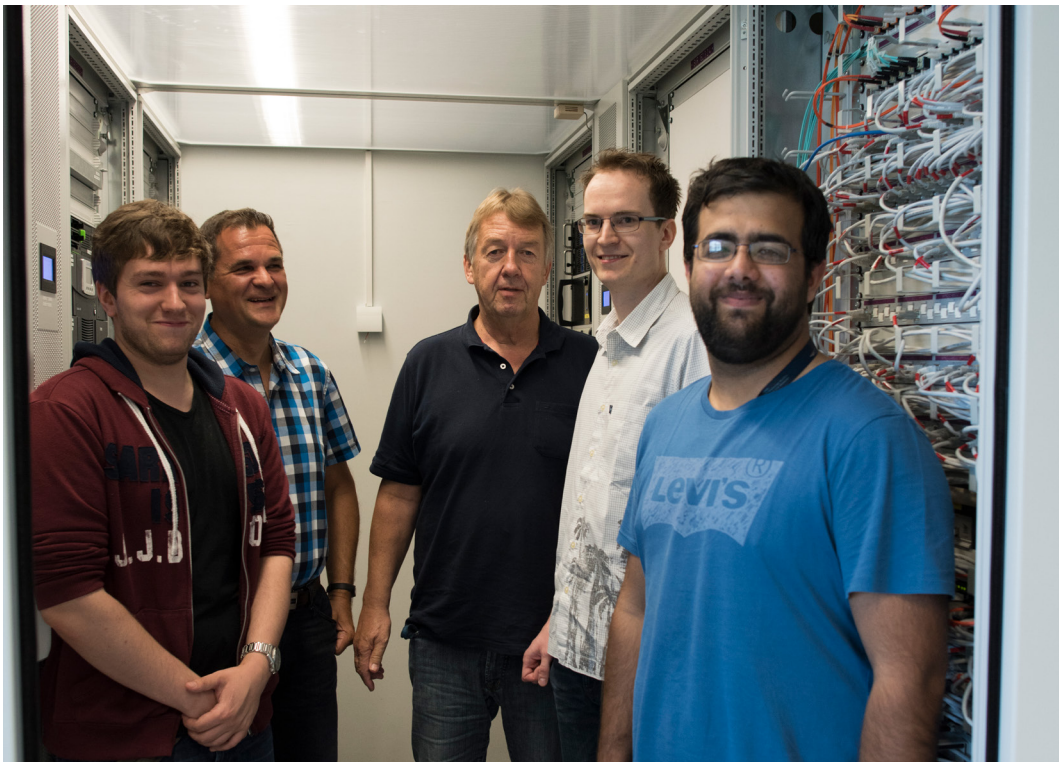
Another part of our expertise is the integration and adaptation of the Open Source technology and the development of customized applications. We provide assistance in data evaluation, archiving and software development. This includes the development of tools and programs for the analysis, visualization 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 framework based on GNU R 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
- Programming in Java, C/C++, PHP, Perl, MATLAB, ImageJ and GNU R
- Procurement of hard- and software equipment
- Web design and development

Team

Group Leader:
Dr. Hans-Martin Ziethen
IT specialists:
Siegfried Koloschin
Stephan Rattai
Apprentices:
Lorenz Wellmer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Financial Report of the ZMNH Administration

ZMNH Administration

Managing Director: Katja Husen

The ZMNH was founded in 1987 as an independent research center of Universität Hamburg and became part of the University Medical Center Hamburg-Eppendorf (UKE) in 2001. It is composed of five institutes, seven research groups, four core facilities and the central administration.

The central ZMNH administration is headed by the administrative director and consists of a team organizing human resources, accounting, budgeting and external funding. Other responsibilities include the scientific workshop and the library. In total nine employees share 6.8 full-time positions. The administrative director and her assistant also lead the Center for Dental and Oral Medicine of the UKE, thus only 50% of their positions are financially covered by the ZMNH.

The independent administration was maintained when the ZMNH became part of the UKE. Although the ZMNH institutes have been integrated in the UKE's performance-based funding system (LOM), central administration receives in addition a core budget by the deanery to finance the administration department, the junior research groups and the ZMNH core facilities.

Each institute receives a basic funding budget (*Grundausstattung* 2015: 305.500 €; 2017: 310.700 €), which is supplemented by LOM based on the impact of publications and the amount of external funds. In 2015, LOM ranged from 51.164 € to 412.387 € per institute; in 2017 from 44.790 € to 478.307 €. The ZMNH is also granted a budget for small investments (*Kleingeräteetat, KGE*) of 73.158 € in 2015. Large equipment can be covered by the UKE invest board based on competitive applications or is covered by start-up funds, external grants or overheads.

The development of all annual appropriations within the financial model for funding research and teaching (*Forschung und Lehre, FuL*) by the UKE Dean's office are depicted in the following table. It also shows the expenses for personnel costs, material costs, investments for small equipment as well as disbursed grants:

Expenses/Investments	*2013*	*2014*	*2015*	*2016*	*2017*
Research and teaching (*Forschung und Lehre*, FuL)	6.449.513	6.422.848	6.477.436	6.284.735	6.496.451
Personnel	5.377.254	5.522.921	5.961.828	5.759.739	5.736.842
Material costs	2.482.694	2.250.257	1.954.736	1.966.763	
External grants	3.453.634	3.589.201	4.309.237	3.886.705	
Small investments (*Kleingeräte*, KGE)	141.192	97.951	95.118	45.267	

The basic budget for central ZMNH matters, which is supplemented by resources for additional demand, covers personnel costs of the central administration, the ZMNH core facilities and the budget-funded junior research groups, as well as the running costs.

The budget for additional demand also finances overdrafts of individual institutes, if tolerated by the Dean's office, for instance when contractual agreements in the framework of new appointments (*Berufungszusagen*) are not fully covered by LOM. Moreover, these supplements cover personnel costs for employees, whose positions are not or only partially connected to specific institutes or research groups, respectively.

For the year 2018, the Dean's office has announced a budget cut of the FuL supplements by almost 40%, which will be an extreme burden for the ZMNH. Taking into account that many employment contracts are permanent and long-term, this would be an extreme challenge and a risk for the ZMNH scientific output. Obviously, this issue will need to be discussed at the ZMNH budget's negotiations in September 2017.

Team

Managing director:
Katja Husen

ZMNH office:
Katrin Wenning

Budget and external funds administration:
Uwe Csizmadia

Accounting:
Herma Dörnbrack
Heike Pehlke

Human Resources:
Rolf Maronde

Library: Heiko Pump

Scientific Workshop:
Torsten Renz
Fritz Kutschera

ZMNH Research Funding in the Framework of Coordinated Programs

Research Funding by the Hamburg Ministry of Science and Research

Identification of Immune Mechanisms in Diseases with Sex-Specific Differences
Coordinator: Prof. Dr. Manuel Friese, ZMNH
Funding period: 04/2017-09/2020

Project and Principal Investigators at ZMNH:
Sex-specific microbiome variation determines Mucosal-associated-invariant T- cell development and thereby modifies the pathogenesis of multiple sclerosis
Manuel Friese, Stefan Gold, Anne Willing
ZMNH Institute of Neuroimmunology and Multiple Sclerosis

BMBF-VIP+ project

Validation of Small Molecules that Inhibit the Ion Channel TRPM4 for Treatment of Neurodegeneration in Multiple Sclerosis – TRPM4-VIP
Coordinator: Dr. Philipp Gribbon, Fraunhofer IME
and Prof. Dr. Manuel Friese, ZMNH
Funding period: 01/2017 – 12/2019

Project and Principal Investigators at ZMNH:
Targetvalidation, development of pharmacodynamics biomarkers and functional characterisation of lead substances for the validation of neuroprotective drugs
Manuel Friese, ZMNH Institute of Neuroimmunology and Multiple sclerosis

DFG Priority Programme SPP 1665

Resolving and Manipulating Neuronal Networks in the Mammalian Brain – from Correlative to Causal Analysis
Coordinator: Prof. Dr. Ileana Hanganu-Opatz,
Institute of Neuroanatomy, Universitätsklinikum Hamburg-Eppendorf (UKE)
Funding period: 09/2013 – 08/2019

Project and Principal Investigators at ZMNH:
Cognitive performance as result of coordinated neuronal activity within developing prefrontal-hippocampal circuits
Thomas Oerter, ZMNH Institute of Synaptic Physiology
Dr. Michael Denker, Jülich
Prof. Dr. Ileana Hanganu-Opatz, UKE
Prof. Dr. Peter Hegemann, Berlin
Funding period: 09/2016 – 08/2019

DFG Priority Programme SPP 1926

Next Generation Optogenetics: Tool Development and Application

Speaker: Prof. Dr. Alexander Gottschalk, Goethe-Universität Frankfurt am Main
Funding period: 07/2016 - 06/2019

Project and Principal Investigators at ZMNH:
Development of Next-Generation Light-gated Inhibitory Ion Channels to Probe Somatosensory Integration in the Drosophila Nociceptive Circuit *in vivo*
Peter Šoba, Research Group Neuronal Patterning and Connectivity
Simon Wiegert, ZMNH Institute of Synaptic Physiology

BMBF Competence Network Multiple Sclerosis

Interdisciplinary Network

Spokesperson: Prof. Dr. Bernhard Hemmer, TU Munich
Funding period 04/2016 - 03/2019

Project and Principal Investigators at ZMNH:
Modeling CD8+ T cell responses in multiple sclerosis
Manuel Friese, ZMNH Institute of Neuroimmunology and Multiple Sclerosis
Funding period: 04/2016 - 03/2019

DECIMS: Coaching the decision making process for immunotherapy
Christoph Heesen, ZMNH Institute of Neuroimmunology and Multiple Sclerosis
Funding period: 12/2012 – 05/2017

REGIMS – A register for patients with multiple sclerosis undergoing immunotherapy
Christoph Heesen, ZMNH Institute of Neuroimmunology and Multiple Sclerosis
Funding period: 04/2016 - 03/2019

2.2 NationNMO: Similarities, differences and connections between multiple sclerosis and neuromyelitis spectrum disorders – adaption of the IT-platform/ concept of data security and transfer of patient data from existing cohorts (NEMOS-DAB)
Patrick Stellmann, ZMNH Institute of Neuroimmunology and Multiple Sclerosis
Funding period: 08/2016 - 07/2019

National Multiple Sclerosis Society (NMSS)

International Deprexis Trial in Multiple Sclerosis (IDEMS) – a Multicenter Randomized Controlled Trial
Coordinator: Stefan Gold, Charité, Berlin and ZMNH Institute of Neuroimmunology and MS
Funding period: 04/2016 - 03/2020

Project and Prinicpal Investigator at ZMNH:
An international multicenter study to test the effectiveness of an online program to reduce depressive symptoms in Multiple Sclerosis
Stefan Gold and Christoph Heesen, ZMNH Institute of Neuroimmunology and Multiple Sclerosis

DFG Research Unit FOR 2419

Plasticity versus Stability: Molecular Mechanisms of Synaptic Strength
Speaker: Prof. Dr. Matthias Kneussel, ZMNH Institute of Molecular Neurogenetics
Funding period: 01/2016 - 12/2018

Project and Prinicpal Investigator at ZMNH:

P1 Delivery of Plasticity-Related Proteins (PRPs) in Synaptic Consolidation
Matthias Kneussel, ZMNH Institute of Molecular Neurogenetics

P2 Functional Interplay of Microtubule and Actin Motors in Dendritic Compartmentalization
Marina Mikhaylova, ZMNH Research Group Neuronal Protein Transport

P3 Mechanisms of Actomyosin-Dependent Regulation of Postsynaptic Function and Plasticity in Purkinje Cells
Wolfgang Wagner, ZMNH Institute of Molecular Neurogenetics

P4 Impact of Spine Endoplasmic Reticulum on Synaptic Function and Plasticity
Thomas Oertner, ZMNH Institute of Synaptic Physiology

P5 Role of TAO2 in Synapse Formation and Plasticity
Froylan Calderon de Anda, ZMNH Research Group Neuronal Development

P6 Structural Plasticity of Hippocampal Mossy Fiber Synapses
Michael Frotscher, ZMNH Institute of Structural Neurobiology

P7 Dynamic Rewiring of Hippocampal Circuits Following Synaptic Plasticity
Christine E. Gee and J. Simon Wiegert, ZMNH Institute of Synaptic Physiology

DFG Research Unit FOR 2289

Calcium Homeostasis in Neuroinflammation and -degeneration: New Targets for Therapy of MS?

Speakers: Prof. Dr. Ricarda Diem, University Heidelberg and Prof. Dr. Veit Flockerzi, Saarland University
Funding period: 11/2015 - 10/2018

Project and Prinicpal Investigator at ZMNH:
The Role of Transient Receptor Potential Channels in Neuroinflammation
Manuel Friese, ZMNH Institute of Neuroimmunology and Multiple Sclerosis

DFG Priority Programme SPP 1775

Functional Specializations of Neuroglia as Critical Determinants of Brain Activity

Coordinators: Christine R. Rose, University of Düsseldorf and Frank Kirchhoff, University of Saarland
Funding period: 09/2015 - 08/2018

Project and Prinicpal Investigator at ZMNH:
Role of Reelin in the Functional Specialization of Radial Glia Cells
Michael Frotscher and Bianka Brunne, ZMNH Institute of Structural Neurobiology

DFG Collaborative Research Center SFB 936

Multi-site Interactions during Development, Plasticity and Learning

Coordinators: Prof. Dr. Andreas K. Engel and Prof. Dr. Christian Gerloff, UKE

Second Funding period: 07/2015 - 06/2019

Project and Prinicpal Investigator at ZMNH:
B7: Emergence and plasticity of architectures underlying multi-site communication
Fabio Morellini, ZMNH Behavioral Biology Unit and Thomas Oertner, Institute of Synaptic Physiology

First Funding period: 07/2011 - 06/2015

Project and Prinicpal Investigator at ZMNH:
B3: Network mechanisms underlying information transfer in the entorhinal cortex-hippocampus circuitry during learning and memory
Fabio Morellini, Research Group Behavioral Biology

B4: Dependence of memory consolidation on synaptic consolidation in the cortico-hippocampal network
Dietmar Kuhl, Institute of Molecular and Cellular Cognition

DFG Clinical Research Unit KFO 296

Feto-maternal Immune Cross Talk: Consequences for Maternal and Offspring's Health
Coordinator: Prof. Dr. Petra Clara Arck, Experimental Feto-Maternal-Medicine, UKE
Funding period: 06/2015 - 05/2018

Project and Prinicpal Investigator at ZMNH:
Antigen-specific immune modulation during pregnancy as a mechanism for establishing tolerance in multiple sclerosis
Manuel Friese, Stefan Gold, ZMNH Institute of Neuroimmunology and Multiple Sclerosis

Start-up grant from the Hamburg Ministry of Science and Research (Landesforschungsförderung)

Molecular Mechanisms of Circuit Modification: Tuning Synapses and Networks for Plasticity (Collaborative research project LFF-FV 27)
Coordinator: Matthias Kneussel, ZMNH Institute of Molecular Neurogenetics
Funding period: 10/2014 - 09/2017

Project and Prinicpal Investigator at ZMNH:
P2: The role of TAO kinases in regulation of dendritic plasticity
Froylan Calderon de Anda, ZMNH Research Group Neuronal Development and Peter Šoba, ZMNH Research Group Neuronal Patterning and Connectivity

P3: Structural modification of hippocampal synapses
Michael Frotscher, ZMNH Institute of Structural Neurobiology and Gabriele Rune, UKE Institute of Neuroanatomy

P4: The effect of the interaction of estradiol and dopamine on the synaptic and network-activity underlying cognitive functions in mice and human beings
Christian Büchel, Tobias Sommer, UKE Dept. of Systems Neuroscience and Fabio Morellini, ZMNH Behavioral Biology Unit

P5: Arc/Arg3.1 interactions with a transmembrane protein of the endoplasmatic reticulum in synaptic plasticity and memory consolidation
Dietmar Kuhl, Ora Ohana. ZMNH Institute of Molecular and Cellular Cognition and Jackie Schiller, Technion Israel Institute of Technology, Haifa, Israel

P6: Local regulation of the cytoskeleton and the function of motor proteins in synaptic activity and plasticity
Matthias Kneussel and Wolfgang Wagner, ZMNH Institute of Molecular Neurogenetics

P7: Modulation of synaptic signal transduction and integrity by the calcium-activated TRPM4 ion channel
Manuel Friese, ZMNH Institute of Neuroimmunology and Multiple Sclerosis and Christine Gee, Thomas Oertner, ZMNH Institute of Synaptic Physiology

P9: Control of neuronal translation by RNA-binding proteins and uORFs
Kent Duncan, ZMNH Research Group Neuronal Translational Control and Hans-Jürgen Kreienkamp, Christian Kubisch, UKE Institute of Human Genetics

EU ERA-Net NEURON JTC2013

European Research Projects on Mental Disorders
Funding period: 06/2014 - 05/2017

Project and Prinicpal Investigator at ZMNH:
The role of TAO2 in Brain Connectivity and Autism Spectrum Disorders
Coordinator: Froylan Calderon de Anda, ZMNH Research Group Neuronal Development

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

Evaluation of miRNAs and Metabolites – Discovery of Biomarkers for Neurodegeneration in Multiple Sclerosis
Applicants and donnee: Manuel Friese, ZMNH, UKE; Ole Pless, ZMNH Guest Group Fraunhofer IME ScreeningPort; Nikolaus Schauer, Metabolomie Discoveries GmbH
Funding period 11/2014 - 10/2017

Project and Prinicpal Investigator at ZMNH:
Biomaterial Sampling and Identification of miRNA Profiles in Multiple Sclerosis
Manuel Friese, Institute of Neuroimmunology and Multiple Sclerosis

ASIC 1 inibitors for treatment of Multiple Sclerosis
Speaker: Timm Jessen, Bionamics GmbH
Applicant and donee: Merck KGaA, Evotec AG
Funding period: 04/2010 – 03/2015
Prinicpal Investigator at ZMNH:
Manuel Friese, Institute of Neuroimmunology and Multiple Sclerosis

MRI and clinical platforms and validation study SABA
Prinicpal Investigators at ZMNH:
Roland Martin and Christoph Heesen, ZMNH Institute of Neuroimmunology and MS
Funding period: 05/2010 – 10/2015

Treatment of Multiple Sclerosis with the monoclonal antibody BT-061
Applicant and donee: Biotest AG
Funding period: 2010 – 2015
Prinicpal Investigator at ZMNH:
Roland Martin, Institute of Neuroimmunology and Multiple Sclerosis

Relapse escalation treatment trial in Optic Neuritis (RESCON)
Prinicpal Investigator at ZMNH:
Christoph Heesen, ZMNH, Institute of Neuroimmunology and Multiple Sclerosis
Funding period: 11/2012 – 12/2015

Connectivity Platform: New approaches for the analysis of networks and their function in MS
Applicants and donees: Christoph Heesen and Stefan Gold, ZMNH, UKE; Andreas Engel, Dept. of Neurophysiology and Pathophysiology, UKE
Funding period: 01/2012 – 10/2016
Prinicpal Investigators at ZMNH:
Christoph Heesen and Stefan Gold, Institute of Neuroimmunology and Multiple Sclerosis

Nanodeliver: Optimization and clinical testing of a tolerance-inducing drug candidate for MS
Applicants: Johannes Herkel, I. Department of Internal Medicine, UKE; Christoph Heesen, ZMNH, UKE
Funding period: 08/2014 – 12/2017
Prinicpal Investigator at ZMNH:
Christoph Heesen, Institute of Neuroimmunology and Multiple Sclerosis

Identification of a small molecule inhibitor for ion channel TRPM4
Prinicpal Investigator at ZMNH:
Manuel Friese, Institute of Neuroimmunology and Multiple Sclerosis
Funding period: 08/2014 – 07/2016

DFG Priority Programme SPP 1665

Resolving and Manipiulating Neuronal Networks in the Mammalian Brain – from Correlative to Causal Analysis
Speaker: Prof. Dr. Ileana Hanganu-Opatz, UKE
Funding period: 08/2013 - 07/2016

Project and Prinicpal Investigators at ZMNH:
Optogenetic dissection of the developing prefrontal-hippocampal circuitry that gates mnemonic and executive maturation
Thomas Oerter, ZMNH Institute of Synaptic Physiology and Ileana Hanganu-Opatz, Dept. of Neuroanatomy, UKE

National MS Society (NMSS)

Development and Validation of Behavioral Interventions to Enhance Self Management in MS
Coordinator: Christoph Heesen, ZMNH Institute of Neuroimmunology and Multiple Sclerosis

Project and Prinicpal Investigator at ZMNH:
Development and validation of behavioral interventions to enhance self management in MS
Christoph Heesen, ZMNH Institute of Neuroimmunology and Multiple Sclerosis
Funding period: 07/2013 - 06/2018

DFG Research Training Group GRK 1459

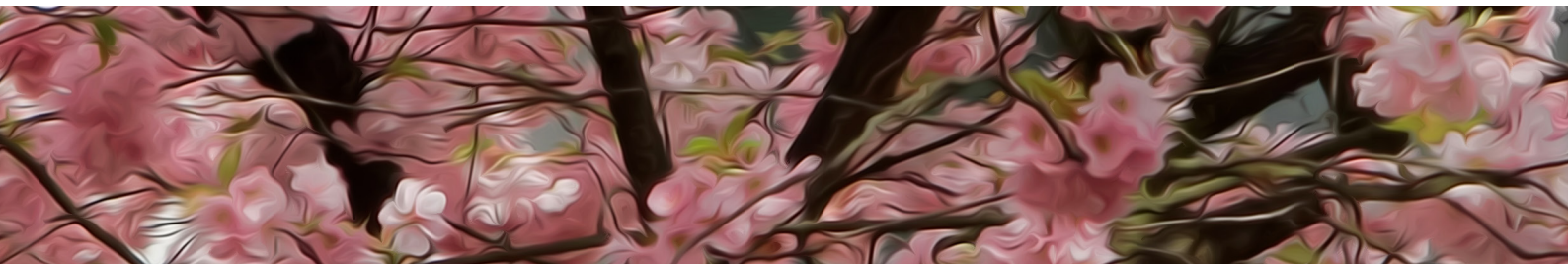
Sorting and Interaction between Proteins of the Subcellular Compartment
Speaker: Prof. Dr. Thomas Braulke, UKE
Funding period: 11/2012 - 04/2017

Project and Prinicpal Investigator at ZMNH:
Role of Microtubule Turnover in Cytoskeleton-Mediated Sorting and Transport of Synaptic Proteins
Matthias Kneussel, ZMNH Institute of Molecular Neurogenetics

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

Synaptopodin, calcium stores and neuronal plasticity
Applicants: Menahem Segal, Weizmann Institute of Science, Rehovot, Israel and Michael Frotscher, ZMNH, UKE
Funding period: 01/2012 – 12/2015

Prinicpal Investigator at ZMNH:
Michael Frotscher, Institute of Structural Neurobiology



Teaching & Training

ZMNH Doctoral Program

The ZMNH Doctoral Mentoring Program was established in 2013 to ensure that the doctoral candidates gain a broad knowledge and key competencies required for a successful scientific career and to assure the quality of dissertations. It offers cross-faculty continuing education and training in the fields of neuroscience and molecular biology that is designed to lead to the award of a doctoral degree in conformity with the regulations of the Faculty for Mathematics, Informatics, and Natural Sciences (MIN) or the Faculty of Medicine at Universität Hamburg. Joining the program is mandatory for all ZMNH doctoral students who are not enrolled in another structured doctoral program.

Each doctoral student concludes a Doctoral Supervision Agreement with a main supervisor (the so-called *Doktorvater*) and two independent mentors who constitute the Thesis Advisory Committee. This agreement serves to support the student in all questions regarding her/his research project, training and education, scientific career as well as the student's scientific independence. Priv.-Doz. Dr. Irm Hermans-Borgmeyer, ZMNH Transgenic Mouse Facility, and Dr. Sabine Fleischer, ZMNH Institute of Neuroimmunology and Multiple Sclerosis, were elected ombudspersons for the doctoral students by ZMNH's WIKO (ZMNH Scientists' conference). After their retirement, Priv.-Doz. Dr. Guido Hermey, Institute of Molecular and Cellular Cognition, and Dr. Anne Willing, Institute of Neuroimmunology and Multiple Sclerosis, were elected new ombudspersons on 28/02/2017.

To foster lively scientific exchange and to benefit from academic continuing education, the doctoral candidates may participate in various ZMNH seminar series including the ZMNH PhD-Seminars which are organized by the students themselves (see chapter Scientific Events at ZMNH, page 150) as well as the Graduate Study in Molecular Biology (see chapter ASMB, page 145). They may also attend external seminars such as those offered by the Hamburg Center of NeuroScience (HCNS) to broaden their knowledge in neuroscience. Moreover, the doctoral candidates may join the academic key skills courses of the Q*WIN career development program for young researchers of Universität Hamburg, the Career Center of Universität Hamburg, and the MIN Graduate School International.

13 natural science and 10 medical students completed their doctoral study between 2015 and June 2017.

In June 2017, 53 doctoral students worked on their thesis projects at ZMNH: 25 of the 43 doctoral students in natural sciences joined the ZMNH Doctoral Program. Eight students worked on their medical doctor theses, two joinded the PhD programme for medical doctors of Faculty of Medicine, Universität Hamburg.

Doctoral Students' Activities at ZMNH

Two doctoral student representatives are elected by the WIKO (ZMNH Scientists' conference) who coordinate students' activities at ZMNH such as student meetings and ZMNH PhD-Seminars. In the reporting period, Jelena Katic (11/2014–03/2016) and Urban Maier (08/2013–03/2016) were representatives followed by Brenna Fearey and Aida Cardona.

Internal ZMNH PhD Seminar Series

In addition to the formal talk given by the speaker open to the general public, the doctoral students have further opportunities to interact with the high-profile scientists in a relaxed yet stimulating setting. See chapter Scientific Events at ZMNH, page 150.

Biweekly Journal Club

organized by the PhD candidate Dr. med. Sergio Castro-Gomez, Institute of Molecular and Cellular Cognition until 09/2016, followed by Dr. Paul J. Lamothe-Molina, Institute of Synaptic Plasticity, and Jasper Grendel, Institute of Molecular and Cellular Cognition.

ZMNH-based ASMB – Graduate Program in Molecular Biology

The ZMNH-based ASMB (*Aufbaustudium Molekularbiologie*) was founded at the Faculty of Medicine, Universität Hamburg by Prof. Dr. Gebhard Koch in 1986 to promote in an interdisciplinary approach the skills for scientific thinking and working in molecular biology. It was permanently established at ZMNH as an advanced training program in molecular and cellular biology for graduates with a diploma/master or doctoral degree in natural or life sciences and for students of medicine and physicians.

Academic content

The ASMB is a four-semester training program with lectures, seminars and hands-on research methods courses. In parallel to the theoretical education, the students pursue a research project which can be done as part of their 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 research project. The third semester covering neurobiology and immunology is taught in collaboration with the Department of Immunology, UKE and the Bernhard Nocht Institute of 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. To put theory into practice, two hands-on research methods courses per semester 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 research project and optionally write a report in the style of a "Letter to Nature". Successful students are awarded a certificate.

The broad range of topics and interdisciplinary exchange during the ASMB training are given both by the lectures and research methods courses as well as by students' research projects discussed during the project presentations.

In 2015, 16 students successfully completed the ASMB with their final project presentation; four of them did their research work at the ZMNH, 11 at departments and institutes of the University Medical Center Hamburg-Eppendorf (UKE) and one student at the Department of Chemistry of Universität Hamburg. In 2016, we had 19 successful ASMB graduates, five of them came from the ZMNH, 13 from the UKE and one from the Heinrich Pette Institute Hamburg. In September 2017, 18 ASMB students, nine of them from ZMNH, eight from the UKE and one from the Bernhard-Nocht-Institute, will give their final presentations.

Lecturers from 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 of Tropical Medicine Hamburg:

Prof. Dr. Bernhard Fleischer, Priv.-Doz. Dr. Thomas Jacobs,
Prof. Dr. Friedrich Nolte, Dr. Anke Osterloh, Prof. Dr. Eva Tolosa

Department of Clinical Chemistry, UKE:
Priv.-Doz. Dr. Friedrich Buck, Dr. Benjamin Otto
Department of Experimental Pharmacology and Toxicology, UKE:
Priv.-Doz. Dr. Torsten Christ, Prof. Dr. Arne Hansen
Department of Human Genetics, UKE:
Prof. Dr. Hans-Jürgen Kreienkamp, Prof. Dr. Christian Kubisch
Department of Osteology and Biomechanics, UKE:
Dr. Jean-Pierre David, Prof. Dr. Thorsten Schinke
Center for Oncology, Bone Marrow Transplantation Unit, UKE:
Dr. Kerstin Cornils, Prof. Dr. Boris Fehse
Heinrich Pette Institute:
Prof. Dr. Adam Grundhoff
Department of Neuropathology, Center for Diagnostics, UKE:
Dr. Giovanna Galliciotti, Dr. Diego Sepulveda-Falla

ASMB scientific coordinators:
Priv.-Doz. Dr. Sabine Hoffmeister-Ullerich (since 01/2013)
Dr. Fabio Morellini (since 08/2014)
ASMB scientific committee:
Prof. Dr. Dr. h. c. Michael Frotscher (08/2015 – 05/2017)
Prof. Dr. Matthias Kneussel (since 08/2015)
Prof. Dr. Dietmar Kuhl (2008 - 07/2015)
ASMB office/ZMNH Library:
Heiko Pump

Module Neuronal Development for Students from the Department of Chemistry, Universität Hamburg

Module Title: Neuronal Development
Module Number: CHE 476 A/B
Semester: Winter
Module Type: M.Sc. MLS: Optional module, 3rd Semester

Content

The lectures cover the development of the central nervous system, functional properties of neuronal cells and brain connectivity as well as neuropathologies. The seminars are intended to prepare students for the practical part, explaining the background, the biological relevance and the methods of the planned experiments. In the practical class, topics of the lecture are taken up and methods are acquired which are routinely implemented in the three participating laboratories (for example, production of neuronal primary cell cultures, immunohistochemical staining, *in situ* / *in vivo* pictures of live cultures, RNA biology, biochemistry).

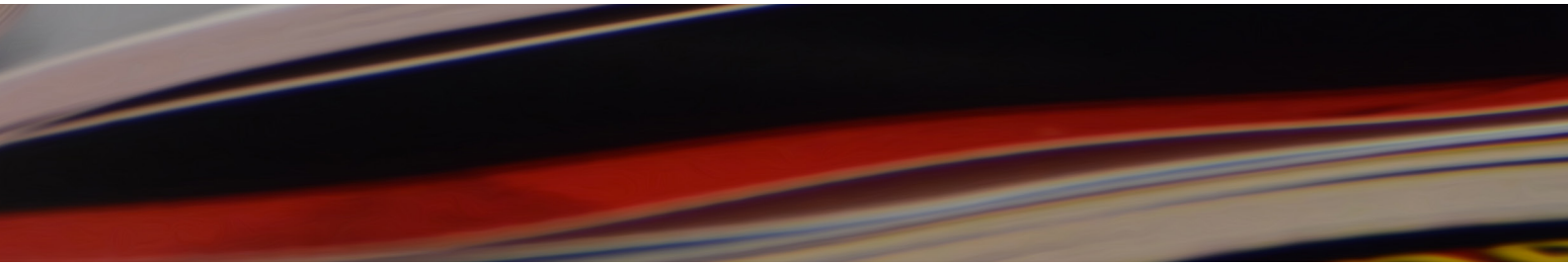
Learning outcome

The students acquire knowledge about the development, function and diseases of the central nervous system (CNS). Molecular, cell biology and anatomical aspects of neurobiological concepts are mediated, as well as new methods and findings are treated. Students should complete the module with a basic understanding of how these neurobiological concepts work in different model organisms *in vivo*. They are to learn current theories how deviations in the early neuronal development can lead to human pathological changes of the central nervous system. In the practical class, methods are presented to produce various neuronal preparations, as well as their analysis by means of imaging methods, immunohistochemical stains or biochemical investigations.

Internships for Apprentices from the School of Life Science (UKE) and the G13 Vocational School (State of Hamburg)

The School of Life Science for biological-technical assistants (BTAs) is a subsidiary of the University Medical Center Hamburg-Eppendorf (UKE) with the form of organization of a non-profit LLC (limited liability company). The vocational school G13 is a public school of the state of Hamburg offering education in the areas of chemistry, pharmacy and agriculture, including apprenticeship for BTAs.

BTA apprentices from both schools regularly pursue 4-months internships at the ZMNH during the practical year of the respective curriculum. They are integrated in the daily lab work and learn from technicians and scientist how to design, execute and troubleshoot experiments.
From January 2015 to June 2017, in total 56 BTA apprentices successfully completed an internship and 5 are currently working at the ZMNH.



Scientific Events & Public Relations

Seminars, Retreats and Conferences

To foster the scientific exchange between external and internal researchers there are several scientific events and seminar series at ZMNH.

In addition to cross-ZMNH seminars, the individual institutes and research groups have regularly their own internal group seminars.

ZMNH-Seminars

The ZMNH-Seminars hosted by a ZMNH institute director or research group leader are open to all researchers of the Hamburg Center of Neuroscience (HCNS) and doctoral students.

23/05/2017
Prof. Dr. Helge Ewers, Institute of Chemistry and Biochemistry, FU Berlin, Germany
Nanoscopic membrane compartmentalization in the axonal initial segment

14/04/2017
Prof. Haruhiko Bito. Dept. of Neurochemistry, University of Tokyo, Japan
Activity-dependent gene expression: mechanisms, functions and applications

13/04/2017
Dr. Harald Janovjak, Institute of Science and Technology Austria (IST Austria), Austria
Synthetic physiology - remote control of cellular signals

01/03/2017
Prof. Dr. Lothar Jänsch, Helmholtz Center for Infection Research Braunschweig, Germany
Proteome-aided characterization of novel mechanisms at immunological synapses

23/02/2017
Prof. Dr. Daniela C. Dieterich, Institute of Pharmacology and Toxicology, Magdeburg, Germany
Mechanosensitivity and neuronal protein synthesis

24/01/2017
Prof. Roderick MacKinnon, Laboratory of Molecular Neurobiology and Biophysics, The Rockefeller University, Howard Hughes Medical Institute, New York, USA
The incredible diversity of K+ channels

17/11/2016
Dr. Nicolas Gutierrez-Castellanos, Champalimaud Centre for the Unknown, Lisbon, Portugal Motor Learning Requires
Purkinje Cell Synaptic Potentiation through Activation of AMPA Receptor subunit GluA3

15/11/2016
Dr. Eugene Katrukha, Dept. of Cell Biology, Utrecht University, The Netherlands
Axonal cargo distribution and transport: role of motors composition

10/11/2016
Prof. Dr. H. Christian Pape, Instit. of Physiology I, Universitätsklinikum Münster, Germany
The extended amygdala: what it is and what it has to do with our fear to unpredictable threat

05/10/2016
Dr. Jack van Horssen, VU University Medical Center Amsterdam, The Netherlands
Mitochondrial dysfunction and free radicals contribute to neurodegeneration in multiple sclerosis

13/07/2016
Prof. Dr. Timothy Radstake, Radboud University in Nijmegen, The Netherlands
A Systems Medicine approach to disease understanding. Disease interception fact or fiction?

04/07/2016
Prof. Dr. Zoya Ignatova, Biochemistry, Universität Hamburg, Germany
Translational control: probing dimensionality beyond the linear sequence of mRNA

27/06/2016
Dr. Annika Herwig, Biozentrum Grindel, Universität Hamburg, Germany
A hibernating brain - why bother?

06/06/2016
Dr. Clemens Wülfing, Biozentrum Grindel, Universität Hamburg, Germany
Antigen presenting cells in lymphoid organs - new morphology and architecture of single cell innervation

27/05/2016
Prof. Dr. Thomas Schikorski, Universidad Central del Caribe, Bayamón, Puerto Rico, USA
Synaptic vesicle power spinning: a quick lottery

17/05/2016
Prof. Dion K. Dickman, PhD, University of Southern California, USA
Homeostatic control of synaptic strength and structure

12/05/2016
Prof. Dr. Peter Robin Hiesinger, Institute of Biology, FU Berlin, Germany
Brain wiring on the fly: simple rules in neural circuit assembly

11/02/2016
Petra van Bergeijk, Div. of Cell Biology, Utrecht University, Utrecht, The Netherlands
Optogenetic control of organelle transport and positioning

01/02/2016
Dr. Stefan Bonn, German Center for Neurodegenerative Diseases (DZNE) Göttingen, Germany
Taking a deeper look into the nature and nurture of health and disease

26/11/2015
Dr. Ingrid Ehrlich, Hertie-Institut für klinische Hirnforschung, Tübingen, Germany
Amygdala circuits and the control of fear memories

19/11/2015
Dr. Ivana Nikić, European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
Unravelling whole organism and single molecule physiology

07/09/2015
Prof. Dr. Martin Müller, Institute of Molecular Life Sciences, Zurich, Switzerland
Homeostatic modulation of presynaptic protein turnover and neurotransmitter release

18/06/2015
Prof. Dr. Robert Sloviter, Morehouse School of Medicine, Atlanta, USA
Hippocampal dentate hilar neuron loss and granule cell hyperexcitability as a primary epileptogenic mechanism

22/05/2015
Dr. Philipp Schönenberger, Institute of Science and Technology Austria
Activity-dependent modifications of hippocampal place fields

12/05/2015
Dr. Michael Kreutz, RG Neuroplasticity, Leibniz Institute of Neurobiology Magdeburg, Germany
Dendritic organelles and synaptic function

24/03/215
Dr. Andreas Görlich, Laboratory of Molecular Biology Rockefeller University New York, USA
Nicotine addiction: new insights into the role of the habenulo-interpeduncular pathway

27/02/2015
Dr. Shiva Tyagarajan, Institute of Pharmacology and Toxicology, University of Zurich, Switzerland
Organization of distal and proximal GABAergic synapses: A postsynaptic view into cellular mechanisms

19/02/2015
Dr. Gaia Tavosanis, German Center for Neurodegenerative Diseases (DZNE), Bonn, Germany
Sensory input-controlled synaptic organization in the fly brain: the photoreceptor case

09/02/2015
Dr. Pablo Vargas, Systems Biology of Cell Polarity and Cell Division, Institute Curie, Paris, France Innate control of actin nucleation machineries determines distinct migratory behaviors

ZMNH PhD Seminar

The ZMNH PhD Seminars are organized and hosted by the doctoral students of ZMNH. They are open to all HCNS researchers and doctoral students.

07/11/2016
Dr. Nicolas Gutierrez-Castellanos, Champalimaud Centre for the Unknown, Lisbon
Motor Learning Requires Purkinje Cell Synaptic Potentiation through Activation of AMPA Receptor subunit GluA3

FOR 2419 – Seminars

All scientists and doctoral students of the Hamburg Center of Neuroscience (HCNS) are invited to join the seminars of the DFG-funded Research Unit FOR 2419.

22/06/2017
Prof. Dr. Siegrid Löwel, Göttingen
The dynamic architecture of the adult visual cortex or how can I keep my brain young?

18/05/2017
Prof. Dr. Tobias Moser, InnerEarLab, Dept. of Otorhinolaryngology, Göttingen
How hearing happens: molecular physiology and optogenetic restoration

20/04/2017
Prof. Dr. Anthony Holtmaat, Geneva Neuroscience Center, Switzerland
Facilitation of synaptic plasticity in the mouse somatosensory cortex by paralemniscal circuits

16/03/2017
Dr. Frédéric Gambino, Interdisciplinary Institute of Neuroscience, Université Bordeaux
Dendritic mechanisms for associative learning in behaving animals

09/03/2017
Dr. Rajiv Mishra, Institute of Science and Technology Austria, Klosterneuburg
Cellular mechnisms of learning and memory: synaptic plasticity at CA3-CA3 synapses

16/02/2017
Prof. Dr. Imre Vida, Institute of Integrative Neuroanatomy, Charité, Berlin
Inhibiting inhibition:fast and slow inhibitory interactions among hippocampal GABAergic interneurons

19/01/2017
Dr. Benjamin Rost, Deutsches Zentrum für Neurodegenerative Erkrankungen e.V. Berlin
Optogenetics at the presynaptic terminal

15/12/2016
Prof. Dr. Victor Tarabykin, Institute of Cell Biology and Neurobiology, Charité, Berlin
Molecular control of the neocortex development

24/11/2016
Prof. Dr. Britta Qualmann, Institute of Biochemistry I, Medical School of Universität Jena
Actin nucleation and membrane remodelling in neuromorphogenesis and synaptic plasticity

03/11/2016
Dr. Nathalie Sans, INSERM, Pathophysiology of Neuroplasticity, University of Bordeaux
Planar cell polarity proteins and molecular mechanisms regulating exitatory synapses

04/10/2016
Prof. Dr. Guus Smit, Center for Neurogenomics and Cognitive Research, University Amsterdam,
Dissecting the role of auxiliary subunits in the regulation of AMPA-type glutamate receptors

01/09/2016
Prof. Dr. Martin Korte, Cellular Neurobiology, TU Braunschweig
Losing the balance between plasticity and stability: neuroinflammation and neurodegeneration

14/07/2016
Dr. Martin Fuhrmann, Deutsches Zentrum für Neurodegenerative Erkrankungen Bonn
Cellular and synaptic correlates of learning and memory

21/04/2016
Prof. Dr. Johann Helmut Brandstätter, Division of Animal Physiology, University of Erlangen,
Adaptation at a sensory synapse – the role of complexins

Joint Seminars

17/05/2016
Joint seminar of the ZMNH INIMS and Adaptive Biotechnologies
Enabling the power of immunosequencing

37th Blankenese Conference – Joint Meeting of FOR 2419 and Syn Signal

From 6 to 10 May 2017, the prestigious annual Blankenese Conference was held as joint scientific meeting of the ZMNH-based and DFG-funded FOR 2419 and Syn Signal. This shared conference entitled "Synaptic Plasticity versus Stability – Information Uptake, Processing and Coding" covered the focus of FOR 2419 complemented by aspects of the plasticity of cellular circuits in the olfactory and taste systems to illuminate the role of synapses in information processing in the central and peripheral nervous system. 43 talks including one of the Nobel Laureate Linda Buck on "Deconstructing smell" and 49 posters were presented.

Symposium "Advances in Molecular Neurobiology"

November 30, 2015

13 out of more than 150 applicants for the advertised FOR 2419 doctoral student positions were invited to present their research interest. Five candidates were selected for an employment in the DFG-funded Research Unit FOR 2419, one for a position in the INIMS.

PANOS Spring Meeting

April 14 – 15, 2016

The 2016 annual meeting of the work group PANOS (Preparation and Imaging of native organic systems) of the Deutsche Gesellschaft für Elektronenmikroskopie was organized by Michaela Schweizer, ZMNH Core Facility Morphology and Electron Microscopy. The topic was "Electron Microscopy in Pathology and Medicine". The scientific program included 12 talks and 8 posters.

Seasonal Cytoskeleton Meetings

The aim of those meetings is to bring together scientists from the ZMNH and UKE and to discuss questions related to cytoskeleton and protein trafficking in neuronal and non-neuronal cells. The initiative is coordinated by Marina Mikhaylova (ZMNH) and Sabine Windhorst (UKE).

30/03/2016
Cytoskeleton Kick-Off Meeting

11 research groups gave short overviews on their research topics.

25/05/2016
Spring Cytoskeleton Meeting

Dr. Sabine Windhorst, UKE, Hamburg.
Phenotype of itpka knock out mouse

Dr. Froylan Calderon de Anda, ZMNH,
Hamburg. Polarity before polarization

22/07/2016
Summer Cytoskeleton Meeting

Dr. Peter Šoba, ZMNH, Hamburg.
Tao kinase dependent regulation of cytoskeletal dynamics in dendrite growth

Prof. Stefan Linder, UKE, Hamburg.
Lymphocyte specific protein 1 (LSP1) is a myosin IIA binding regulator of podosome dynamics and macrophage migration and invasion

14/11/2016
Autumn Cytoskeleton Meeting

Dr. Wolfgan Wagner, ZMNH, Hamburg.
The role of myosin VI in AMPA receptor trafficking and cerebellar motor learning

Amol Aher, UU, Utrecht
Regulation of centriolar microtubule growth by CPAP/SAS-4

15/03/2017
Winter-Spring Cytoskeleton Meeting

Prof. Michael Schmeisser, OvGU, Magdeburg
Novel molecular pathways in model systems of autism and intellectual disability

Dr. Marina Mikhaylova, ZMNH, Hamburg.
Novel insights on the structural and function properties of F-actin in dendritic spine

Internal ZMNH-Seminars

In this seminar series the ZMNH institutes and research groups as well as the guest groups at ZMNH present their current research projects.

21/06/2017
Dr. Wolfgang Wagner, Institute of Molecular Neurogenetics
Regulation of postsynaptic long-term depression in cerebellar Purkinje cells by the 'reverse gear' motor myosin VI

07/06/2017
Dr. Melanie Richter, RG Neuronal Development
Altered TAOK2 activity causes autism-related neurodevelopmental and cognitive abnormalities through RhoA signaling

19/04/2017
Dr. Ole Pless, Guest Group Fraunhofer IME Screening Port
A screening and validation strategy for the discovery of drugs that show calorie restriction mimetic properties

15/03/2017
Dr. Marina Mikhaylova, RG Neuronal Protein Transport
Quantitative map of proteome dynamics during neuronal differentiation

15/02/2017
Alexander Drakew, Institute of Structural Neurobiology
Mossy fiber synapses tell their histories

18/01/2017
Dr. Dr. Jan Broder Engler, Institute of Neuroimmunology and Multiple Sclerosis
The glucocorticoid receptor in T cells mediates pregnancy protection from autoimmunity

07/12/2017
Dr. Ora Ohana, Institute of Molecular and Cellular Cognition
A critical period for learning and memory networks

09/11/2016
Dr. Christine Gee, Institute of Synaptic Physiology
Optogenetic manipulation of cyclic nucleotides and hippocampal synaptic plasticity

12/10/2016
Dr. Peter Šoba, RG Neuronal Patterning and Connectivity
No pain, no gain: modality specific encoding of nociceptive behavior in Drosophila

31/08/2016
Dr. Axel Neu, Guest Group Experimental Neuropediatrics
From bedside to bench – and back? Current projects of the ENP group

08/06/2016
Dr. Fabio Morellini, RG Behavioral Biology
Ongoing projects in our group: about cognition, coping strategies (and decision making)

14/04/2016
Prof. Dr. Meliha Karsak, RG Neuronal and Cellular Signal Transduction
Functional characterization of a novel TREM2 coding variant linked to familial Alzheimer´s disease

10/03/2016
Malte Bieler, Guest Group Developmental Neurophysiology
Combined senses: Multisensory processing in thalamo-cortical networks

21/01/2016
Dr. Kent Duncan, RG Neuronal Translational Control
Role of the RNA-binding protein Pum2 in memory

12/11/2015
Dr. Melanie Richter, RG Neuronal Development
P**athogenic inactivation of TAO2 causes autism-like cognitive and neurological abnormalities**

22/10/2015
Dr. Mary Muhia, Institute of Molecular Neurogenetics
Investigating the role of Muskelin (Mkln1) in behavioral and cognitive function

15/10/2015
Dr. Ole Pless, Guest Group Fraunhofer IME ScreeningPort
Treatment response biomarker studies in multiple sclerosis

10/09/2015
Dr. David Lutz, Institute of Structural Neurobiology
Reelin and cell adhesion molecule L1 interact to coordinate brain development

23/04/2015
Dr. Lars Binkle, Institute of Molecular and Cellular Cognition
Sorting nexin 7, a link between Arc/Arg3.1 and endosomal tubular sorting

19/03/2015 Dr. Stefan Gold, Institute of Neuroimmunology and Multiple Sclerosis
Pathobiological links between multiple sclerosis and depression

15/01/2015 Céline Dürst, Institute of Synaptic Physiology
Detecting release of individual transmitter vesicles in intact tissue

ZMNH Retreats

In the framework of the yearly ZMNH Retreats open for all ZMNH staff, current research projects of ZMNH scientists presented by talks and posters are discussed. Additionally, workshops of the ZMNH Core Facilities offer the opportunity to discuss the latest methodological developments. (Only the talks of oral sessions and the workshops are listed below, but not the titles of posters.)

03-04/04/2017
ZMNH Retreat in Timmendorf

Simon Wiegert, Research Group Synaptic Wiring and Information Processing
It's all about persistence

Kira Brune, Institute of Molecular Neurogenetics
Neurobeachin/KIF21B interactions regulate NMDA receptor endocytic recycling and participate in social behavior

Kent Duncan, Research Group Neuronal Translational Control
RNA-binding proteins Pum2 and TDP-43 modulate lamination of the developing neocortex

Meliha Karsak, Research Group Neuronal and Cellular Signal Transduction
Identification and functional characterization of a novel TREM2 coding variant linked to familial Alzheimer's disease

Guido Hermey, Institute of Molecular and Cellular Cognition
Profiling MAPK/ERK dependent and independent activity regulated transcriptional programs in the hippocampus *in vivo*

Manuel Friese, Institute of Neuroimmunology and Multiple Sclerosis
Shared mechanisms of the immune and nervous system

Sabine Gretenkord, Guest Group Developmental Neurophysiology
Olfactory control of entorhinal rhythms during postnatal development

Federico Tenedini, Research Group Neuronal Patterning and Connectivity
Synaptic maintenance and adaption during juvenile development: the SLC36 transporter Pathetic as a model for maintenance in larval development of Drosophila

Shu Ting Yin, Institute of Synaptic Physiology
Low resistance spince necks promote long-term potentiation of excitatory synapses

Praveen Meka, Research Group Neuronal Development
Radial organization of F-actin in developing neurons

Bianke Brunne, Institute of Structural Neurobiology
Radial glia-like cells and Reelin in development and adulthood

Fabio Morellini, Research Group Behavioral Biology
When behavioral analyses help generating hypotheses: an example from a study on mice deficient for ubiquitin C-Terminal hydrolase L1 (UCHL1)

Sabine Hoffmeister-Ullerich, ZMNH Core Facility Bioanalytics
Workshop DNA sequencing - different platforms - different applications

Irm Hermans-Borgmeyer and Uwe Borgmeyer, Core Facility Transgenic Mice
Workshop Gene Editing in Mice and Cells

56 posters were presented in two poster sessions.

05/09/2016
ZMNH Retreat in Hamburg

Michael Kreutz, Guest Group Dendritic Organelles and Synaptic Function
On a possible synaptic function of a dendritic Golgi satellite in between ERGIC and retromer

Frank Heisler, Institute of Molecular Neurogenetics
Muskelin regulates Prp^c trafficking and prion disease progression

David Lutz, Institute of Structural Neurobiology
Fragments of Reelin and the cell adhesion molecule L1 control cortical lamination

Simon Wiegert, Institute of Synaptic Physiology
Synaptic plasticity sets synaptic lifetime

Benjamin Schattling, Institute of Neuroimmunology and Multiple Sclerosis
Identification of neurodegenerative pathways during CNS inflammation by translatome sequencing

Ralf Scholz, Institute of Molecular and Cellular Cognition
Hippocampal Signaling Pathways Regulated by Sgk1

In addition to oral sessions, there was a poster session with 41 posters.

08/10/2015
ZMNH Retreat in Hamburg

Sergio Castro-Gomez and Xiaoyan Gao, Institute of Molecular and Cellular Cognition
Expression of Arg3.1 during development determines cognitive function in the adult brain

Céline Dürst, Institute of Synaptic Physiology
Detecting release of individual transmitter vesicles in intact tissue

Bas van Bommel, Research Group Neuronal Protein Transport
The molecular mechanisms of heterosynaptic plasticity

Shaobo Wang, Institute of Structural Neurobiology
Statistical analysis of migratory trajectories unveils Reelin's role for the lamination of the dentate gyrus

Nina Hoyer, Research Group Neuronal Patterning and Connectivity
Ret receptor mediates sensory dendrite growth through TGFß

Bing Zhao, Research Group Neuronal Development
Polarity before polarization: does centrosome/microtubules instruct actin nucleation?

43 posters were presented in the poster session after the oral sessions.

Internal ZMNH Research in Progress-Seminars / Internal ZMNH PhD Seminars

In 2013, the biweekly ZMNH Research in Progress-Seminar series hosted by the ZMNH Research Groups was established to provide a platform for students and postdocs to discuss their ongoing research and to enhance inter-lab interaction including exchange of techniques and expertise.

This seminar series was replaced by the biweekly Internal ZMNH PhD-Seminar series from 07/2016. Here the doctoral students have the opportunity to present their projects for getting feedback and to practice their presentation skills. To foster the scientific exchange and interdisciplinarity the ZMNH guest groups join also this internal seminar series.

Public Relations

In addition to its scientific seminar series, symposia and the ZMNH-based ASMB that address scientists and students, ZMNH communicates information about its neurobiological research to the public on its homepage www.uke.de/zmnh, by numerous internships for students and pupils as well as the events listed below.

Job Orientation Events for Students and Pupils

02/07/2015
Universität Hamburg-wide Job Orientation Day **"PhD finished – what next?"**organized on behalf of the ZMNH PhD Program with the following speakers:

Dr. Christiane Kummer
Nationale Kontaktstelle Lebenswissenschaften EU & Internationales

Dr. Isabel Veldkamp
Biogen (Medical Science Liaison Management)

Dr. Franziska Ahnert
Heinrich Pette Institute (Public Relations)

Dr. Jan Busch
VWR (Life Science Sales Management)

Dr. Ralf Krappa
UKE (Technology transfer)

Dr. André Guder
UEXKULL & STOLBERG, Hamburg (Patent Attorney)

Dr. Stephen Hess
Evotec (Research on Ion Channels)

Dr. Sandra Lubitz
Evotec (Research on Stem Cell Biology)

Dr. Barbara Ebert
MBA; University of Göttingen (Scientific Information Infrastructures)

Girls' and Boys' Day

In the framework of the nationwide Girls' and Boys' Day for pupils from class 5 the UKE offers activities and job information. ZMNH takes part with an introductory talk about neuroscience and lab visits.
28/04/2016 10 pupils
22/04/2015 12 pupils

Visit of School Classes

04/11/2016
Sophie-Barat-School Hamburg, class 11
22/09/2016
Gymnasium Süderelbe, class 12/S3
26/01/2017
Gymnasium Othmarschen, class 11

Visit of Groups of University Students

13/11/2015
TU Darmstadt (25 participants)

Night of Knowledge in Hamburg

The ZMNH offers lectures and workshops as part of the event „Nacht des Wissens" that is initiated by the City of Hamburg to promote the public understanding of science and research.

04/11/2017
The ZMNH will offer three lectures and six workshops (all in German).

07/11/2015
Lectures (in German)
Michael Frotscher, Institute of Structural
Neurobiology: The Structures of the Nervous System
Dietmar Kuhl, Institute of Molecular and
Cellular Cognition: Genes, Neurons and Memory

Workshops (in German)
Jasper Grendel, Institute of Molecular and
Cellular Cognition: Flowing Ions - an Easy Explanation for a Neuron
Iris Winkler and Caren Ramien, INIMS
The Nervous System as a Target of Endogenous Defence

Press and Press Releases

UKE Press Release of 03/01/2017:
"UKE-Studie zu Schutzmechanismen vor Multipler Sklerose während der Schwangerschaft" (in German)

Wissenschaftler des Universitätsklinikums Hamburg-Eppendorf (UKE) haben die Mechanismen untersucht, die während der Schwangerschaft zu einer Verminderung der Krankheitsaktivität der Multiplen Sklerose führen. Das Forscherteam konnte zeigen, dass die genetische Ausschaltung eines Hormonrezeptors in den T-Lymphozyten des Immunsystems zu einem Verlust jenes Schutzes vor Multipler Sklerose führt, der normalerweise während der Schwangerschaft besteht. Bei dem Hormonrezeptor handelt es sich um einen Sensor für das Steroidhormon Cortisol, der in den meisten Zellen des Körpers vorhanden ist. Diese in einem Krankheitsmodell gewonnenen Erkenntnisse haben die Forscher jetzt in der Fachzeitschrift Proceedings of the National Academy of Sciences of the USA (PNAS) veröffentlicht.

UKE Press Release of 20/12/2016:
"UKE und Fraunhofer IME wollen gemeinsam neue Wirkstoffe gegen MS entwickeln" (in German)

Das Universitätsklinikum Hamburg-Eppendorf (UKE) und das Fraunhofer-Institut für Molekularbiologie und Angewandte Oekologie IME wollen den Weg für neue Therapien gegen Multiple Sklerose ebnen. Ziel eines gemeinsamen Vorhabens ist es, Wirkstoffkandidaten weiterzuentwickeln, die gezielt den Nervenzelltod verhindern, der für den fortschreitenden Behinderungsgrad bei Multipler Sklerose verantwortlich ist. Das Projekt wird mit 1,5 Millionen Euro durch das Bundesministerium für Bildung und Forschung gefördert.

UKE Press Release of 13/12/2016:
"Landesforschungsförderung: Behörde unterstützt zwei UKE-Projekte mit mehr als 3,4 Millionen Euro" (in German)

Zwei neue Forschungsvorhaben des Universitätsklinikums Hamburg-Eppendorf (UKE) sind heute mit einer Landesforschungsförderung ausgezeichnet worden. Mit der "Anschubförderung kooperativer Forschungsverbünde" unterstützt die Behörde für Wissenschaft, Forschung und Gleichstellung zwei Projekte aus den Bereichen Infektiologie und Immunologie. Die Förderung beläuft sich in den kommenden drei Jahren auf rund 3,4 Millionen Euro. Darüber hinaus ging der Zuschlag an sechs weitere Projekte Hamburger Hochschulen und Forschungseinrichtungen.

UKE Press Release of 07/10/2016:
"Erneute Auszeichnung für Wissenschaftler des UKE durch Europäischen Forschungsrat" (in German)

Dr. J. Simon Wiegert, ZMNH Insitute for Synaptic Physiology, was awarded with an ERC Starting Grant from the European Research Council (ERC) for his project "LIFE synapses – Long-term Investigation of Functional Excitatory Synapses: Linking Plasticity, Network Wiring and Memory Storage". The grant amounts to € 1.5 million for a period of five years.

UKE Press Release of 26/09/2016:
"UKE-Wissenschaftler identifizieren "wandernde" Immunzellen" (in German)

Wissenschaftler des Universitätsklinikums Hamburg-Eppendorf (UKE) haben erstmalig ein Protein im Immunsystem beschrieben, das maßgeblich an Entzündungsvorgängen im Organismus beteiligt ist. Ihre Erkenntnisse haben die Forscher jetzt in der Fachzeitschrift Science Immunology veröffentlicht.

UKE Press Release of 12/02/2016:
"Drei Nachwuchswissenschaftler des UKE mit Dr. Martini-Preis 2016 ausgezeichnet" (in German)

Xuejun Chai from the ZMNH Institute of Structural Neurobiology is one of three junior scientists who were awarded with the Dr. Martini Prize 2016.

UKE Press Release of 30/11/2015:
"UKE-Professorin Melitta Schachner Camartin erhält Ehrendoktorwürde der Universität Heidelberg" (in German)

Prof. Dr. Melitta Schachner Camartin, ZMNH Emeritus Group Biosynthesis of Neural Structures received Honorary doctorate degree of Universität Heidelberg

Press Release of DFG of 01/10/2015:
"Sechs neue Forschergruppen, eine neue Kolleg-Forschergruppe" (in German)

Report on funding the Research Unit FOR 2419 "Plasticity versus Stability: Molecular Mechanisms of Synaptic Strength" by the German Research Foundation (DFG) as one of six Research Units from January 2016.

UKE news 02-03/2015:
"Molekulare Werkzeuge" (in German)

Article on the collaborative research project "Molecular mechanisms of circuit modification: tuning synapses and networks for plasticity" supported by start-up funding of the Federal State of Hamburg which is coordinated by the ZMNH researcher Prof. Matthias Kneussel (p. 18)

bild der wissenschaft – Themenheft 2015
"Power fürs Gehirn": „Bunter denken" (in German)

Article with report on research using optogenetics at the ZMNH Institute of Synaptic Physiology (p. 11-15).


Model
Developmental defines fun
stubby
mushroom
thin
filopodia