IZN
Interdisziplinäres Zentrum für Neurowissenschaften der Ruprecht-Karls-Universität Heidelberg

Report 2003-2008
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Cover illustration by Simon Wiegert, Neurobiology, IZN: Depth-coded maximum z-projection of hippocampal CA1-neurons expressing Dronpa-labelled ERK1. The colour-spectrum from violet to red was used to artificially colour-code the position of neurons in z-direction.

Image Sources: Images were provided by the IZN Investigators and the Heidelberg University Hospital Media Center, the University of Heidelberg, the German Cancer Research Institute, Photolab/European Molecular Biology Laboratory, Max Planck Institute for Medical Research, and Central Institute for Mental Health Mannheim.

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## Boards

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IZN Investigators

University of Heidelberg

Faculty of Medicine Heidelberg

Department of Anatomy and Cell Biology

Uwe Ernsberger  
Development of nerve cells and generation of neuronal diversity

Joachim Kirsch  
Molecular cell biology of synapses

Thomas Kuner  
Structure and function of synapses

Siegfried Mense  
Neurobiological mechanisms of chronic muscle pain

Gerhard Schratt  
The role of microRNAs in synaptic development and plasticity

Horst Simon  
Differentiation and survival of mesencephalic dopaminergic neurons

Kerry Tucker  
Early events in neurogenesis and nerve development in the central and peripheral nervous systems

Klaus Unsicker  
TGF-β, FGF and neurotrophins in neural development and functions

Department of Physiology and Pathophysiology

Andreas Draguhn  
Functional analysis of cortical neuronal networks

Ulrich Misgeld  
Plasticity of GABAA receptor mediated inhibition

Department of Pharmacology

Rohini Kuner  
Molecular mechanisms underlying chronic pain

Stefan Offermanns  
Cellular signaling

Markus Schwaninger  
Gene regulation in cerebral ischemia

Department of Human Genetics

Gudrun Rappold  
Molecular pathogenesis of genetic disorders

Department of Neuropathology

Andreas von Deimling  
Molecular genetics of tumours of the central (CNS) and the peripheral nervous system (PNS)

Neurology

André Rupp  
Auditory evoked fields, auditory modelling, and psychoacoustics

Wolfgang Wick  
Biology and experimental therapy of malignant glioma

Faculty of Medicine Mannheim

Anaesthesiology

Martin Schmelz  
Translational pain research

Faculty of Biosciences

Centre for Biochemistry

Thomas Söllner  
Molecular mechanisms mediating regulated exocytosis
Research groups / IZN Investigators

**Department of Neurobiology**

**Hilmar Bading**
Nuclear calcium signaling in the dialogue between synapse and nucleus: Role in neuronal survival and memory

**Francesca Ciccolini**
Proliferation and differentiation of neural stem cells

**Christoph Schuster**
Mechanisms of experience-dependent synaptic plasticity, learning and memory, and memory extinction

**Department of Clinical Neurobiology**

**Hannah Monyer**
Neuronal synchrony and plasticity

**Andrei Rozov**
Mechanisms of short lasting synaptic plasticity

**Institute of Pharmacy and Molecular Biotechnology**

**Ulrike Müller**
Functional genomics of neurodegenerative diseases, Alzheimer’s disease, physiological and pathological function of APP family proteins

**Centre for Molecular Biology Heidelberg**

**Stefan Kins**
Alzheimer’s disease, APP function and transport

**Department of Zoology**

**G. Elisabeth Pollerberg**
Growth and orientation of axons in the developing nervous system

**Stephan Frings**
Signal transduction in sensory neurons

**Thomas Holstein**
The origin of the metazoan nervous system and body plan

**Joachim Wittbrodt**
Vertebrate retina development and differentiation

**Faculty of Behavioural and Cultural Studies**

**Institute for Psychology**

**Christian Fiebach**
Cognitive neuroscience: Neural mechanisms of higher cognitive functions

**Sabina Pauen**
Early childhood brain and cognitive development

**Faculty of Mathematics and Computer Science**

**Institute for Computer Science**

**Gabriel Wittum**
Computational neuroscience as part of the chair simulation in technology

**Central Institute for Mental Health Mannheim**

**Dusan Bartsch**
Molecular and cellular basis of normal and pathologic cognition, learning and memory, and mental retardation

**Martin Bohus**
Pain perception, learning and memory, and treatment development for patients with trauma-related disorders

**Herta Flor**
Learning and neuronal plasticity

**Peter Gass**
Animal models of psychiatric disorders

**Andreas Meyer-Lindenberg**
Translational neurogenetics of psychiatric disorders
Rainer Spanagel
The neurobiology of drug abuse

Max-Planck Institute for Medical Research

Winfried Denk
Structure of and activity in neuronal networks.

Thomas Euler
Signal processing in the retina

Georg Köhr
Cross talk between excitatory and inhibitory synapses and ion channel and signalling function of NMDA receptors

Peter Seeburg
Fast excitatory neurotransmission, synaptic plasticity and learning

Hartwig Spors
Spatio-temporal patterns of neuronal activity in the healthy and diseased brain

Rolf Sprengel
The role of glutamate receptors in hippocampus mediated learning, emotional behaviors and mood disorders

Veit Witzemann
Molecular anatomy of the developing neuromuscular junction

German Cancer Research Center

Christof Niehrs
Molecular embryology

Günther Schütz
Molecular genetics of signal-dependent gene expression

Otmar D. Wiestler
Molecular neuropathology of human brain tumors / surgical neuropathology of CNS tumors

European Molecular Biology Laboratory

Detlev Arendt
The evolution of the animal central nervous system

Darren Gilmour
The role of chemokine-mediated tissue migration in generating mechanosensory organs in the zebrafish lateral line
Concept and Structure of the IZN
Concept and Mission of the IZN

The Interdisciplinary Center for Neurosciences (IZN) was founded in 2000 as a research network incorporating neuroscientists from all faculties and local research institutions in Heidelberg. Its mission is to enhance brain research, to coordinate technology transfer and to improve graduate and post-graduate education in the neurosciences. Originally consisting of three ‘core’ institutes, including the Departments of Neurobiology, Neuroanatomy, and Clinical Neurobiology, the IZN has been joined by groups from the Departments of Physiology and Pathophysiology, Anatomy and Medical Cell Biology, as well as by various other research units both within and external to the University of Heidelberg that collectively formed the IZN’s ‘ring’ structure.

At present, the IZN encompasses all research activities in the neurosciences in the Heidelberg/Mannheim area, providing a forum for scientific exchange at all levels. Our weekly seminar series brings together junior and senior scientists with diverse neuroscience backgrounds. Annual retreats foster extensive communication and planning of common projects, and are complemented by regular, informal exchanges between group leaders and the IZN Board.
Introduction

Concept and Mission of the IZN

Basic Sciences

Developmental Neuroscience and Genetics
Behavioural Neuroscience
Computational Neuroscience
Molecular Physiology and Imaging

Applications

Neurogenetic Diseases
Cognitive Disorders and Addiction
Stroke
Aging
Neurodegenerative Diseases
AD, PD, ...

Perspectives

Gene Therapy
Pharmacology and Drug Design
Behavior Therapy
Stem Cell Therapy
Regeneration and Repair
Pain Therapy
Pain Therapy

Aging

Brain Tumors

Pain

Developmental Neuroscience and Genetics
Behavioural Neuroscience
Computational Neuroscience
Molecular Physiology and Imaging

Neurogenetic Diseases
Cognitive Disorders and Addiction
Stroke
Aging
Neurodegenerative Diseases
AD, PD, ...

Gene Therapy
Pharmacology and Drug Design
Behavior Therapy
Stem Cell Therapy
Regeneration and Repair
Pain Therapy
Pain Therapy
of Directors. The IZN facilitates the common usage of specialized equipment and access to resources, and supports joint funding schemes such as Sonderforschungsbereiche, Forschergruppen, and Graduierten Kollegien. It shapes the future of the local neuroscience community by participating in search committees for new junior and senior scientists as well as by helping to decide upon new directions of research in the University of Heidelberg’s molecular life sciences. The IZN runs a graduate program leading to the degree ‘MSc Molecular Bioscience, Major Neuroscience’, and a PhD program. The IZN also plays a very active role in the university’s Cluster of Excellence ‘Cellular Networks: From Molecular Mechanisms to a Quantitative Understanding of Complex Functions’ (CellNetworks) and in the research network for the ‘Quantitative Analysis of Molecular and Cellular Biological Systems’ (BIOQUANT).

In 2007, the Directors of the IZN have, together with the IZN Scientific Advisory Board, reorganized the structure of the IZN to further improve its presence and impact in the international scientific community. Strategic planning, coordinating future, high-profile faculty appointments, and establishing new funding initiatives in Heidelberg and Mannheim all require the active participation of a broad and diverse group of neuroscientists extending beyond traditional institutional boundaries. To this end, a new Board of Directors has been selected, representing most of the institutions and faculties that participate in the IZN.

These institutions are: the University of Heidelberg, the University Hospital, the Max Planck Institute for Medical Research, the German Cancer Research Center (DKFZ), the European Molecular Biology Laboratory (EMBL), and the Central Institute of Mental Health (ZI) in Mannheim. Additionally, the distinction between members of the IZN’s ‘core’ and ‘ring’ structures has been abolished in favor of a minimal hierarchy currently comprised of 51 ‘IZN Investigators’ selected on the basis of their scientific merits. The IZN Investigators are introduced in the Research Profiles (pp 35).

Such organizational modifications acknowledge two recent developments in the neurosciences. First, conceptual and methodological innovations have meant that the border between molecular and cellular neurosciences, on one hand, and behavioral/systems neurosciences, on the other, is becoming progressively more permeable. Secondly, translational neurosciences are becoming more significant and powerful insofar as investigators are increasingly able to transfer knowledge from the basic neurosciences into clinical contexts. The IZN is actively involved in both of these promising advancements. Prominent examples of this involvement include the Collaborative Research Center ‘SFB 636’ in which clinical and basic scientists are jointly investigating the phenomena of learning and memory in the context of psychopathological processes. Additionally, the SFB 636 has initiated a graduate school for translational neurosciences, which will foster cooperative research and interaction between clinical and basic neuroscientists. While Heidelberg has traditionally been regarded as a leading center in molecular and cellular biology, the IZN now includes several groups working on transgenic animal models, in vivo recording and imaging, and behavioral testing. This systems-based approach has already been expanded to include new groups from the ZI in Mannheim and will be further improved by the creation of a new research group for behavioral/systems neuroscience.

In summary, the IZN has extended its scope of enquiry while simultaneously improving its capacity to conduct research in particular behavioral/systems and translational neurosciences. Its new structure is efficient as well as modern, and will assist both junior and senior investigators in the Heidelberg/Mannheim area in addressing future challenges in the neurosciences.
Appointments

Developments in the IZN since 2003:

During the period 2003 to 2008, the IZN has further consolidated and gained international visibility. Scientists at the IZN have been very successful with major discoveries from the molecular to the systems level. Several IZN scientists have been appointed to positions outside Heidelberg, and a number of new recruitments to the Heidelberg neuroscience community could be made. Various members of the IZN have received honourable prizes and awards.

Detlev Arendt
was appointed to a professorship in Zoology at the University of Heidelberg in 2008.

Martin Bohus
was appointed to a chair in Psychosomatics and Psychotherapy, University of Heidelberg, and Director of the Dept. of Psychosomatics and Psychotherapy, Central Institute of Mental Health.

Andreas von Deimling
became chair of the Department of Neuropathology, Institute of Pathology, University of Heidelberg, in 2007.

Thomas Euler
became Research Group Leader at the Max Planck Institute for Medical Research in 2006.

Dirk Feldmeyer
took a professorship at the Federal Research Centre Jülich.

Rainer Friedrich
MPI for Medical Research, in 2005 was offered a leading position at the Miescher Institute Basel.

Peter Gass
became extraordinary professor of Psychiatry at the Med. Faculty Mannheim, consultant and research group leader at the Central Institute of Mental Health in 2004.

Darren Gilmour
came to the European Molecular Biology Laboratory (EMBL) Heidelberg as a Group Leader in 2004.

Hans-Hermann Gerdes
took a professorship at the University of Bergen, Norway, Department of Biomedicine.

Thomas Holstein
was appointed to a professorship at the Department of Molecular Evolution and Genomics, Zoological Institute, University of Heidelberg in 2004.

Harald Hutter
left the Max Planck Institute for Medical Research in 2005 to become an associate professor at the Simon Fraser University, Department of Biological Sciences, Burnaby, Canada.

Stefan Kins
became Group Leader at the ZMBH in 2007; in 2008 he was appointed to a chair for Human Biology and Human Genetics at the TU Kaiserslautern.

Georg Köhr
became Research Group Leader at the Max Planck Institute for Medical Research in 2007.

Rohini Kuner
was appointed to a professorship in Pharmacology & Toxicology at the University of Heidelberg in 2006.

Thomas Kuner
in 2006 was appointed as full professor at the Institute for Anatomy and Cell Biology, University of Heidelberg.

Andreas Meyer-Lindenberg
was appointed to the chair in psychiatry at the Central Institute of Mental Health in Mannheim, as the successor of Fritz Henn.

Ulrike Müller
became a professor for Functional Genomics at the In-
stitute for Pharmacy and Molecular Biotechnology, IPMB, at the University of Heidelberg in 2005.

**Renato Paro**
left the ZMBH to the ETH Zürich to become founding director of the Center of Biosystems Science and Engineering of the ETH Zürich, located in Basel.

**Gudrun Rappold**
was appointed to a professorship and director of the newly established Department of Human Molecular Genetics, Institute of Human Genetics, University of Heidelberg.

**Andrei Rozov**
left Heidelberg to become a senior lecturer at the Centre for Neuroscience, University of Dundee, beginning of 2008.

**Gerhard Schratt and Kerry Tucker**
were appointed as DFG funded Junior Group Leaders in the Sonderforschungsbereich 488, University of Heidelberg, and established their groups.

**Christoph Schuster**
received a professorship of the Hertie Foundation within the Excellence Program in Neurosciences. He took a professorship in Developmental Neurobiology at the University of Heidelberg, Faculty of Biosciences, and established his group in Neurobiology.

**Markus Schwaninger**
moved from the Neurology Clinic of Heidelberg University Hospital to a professorship in Pharmacology at the Faculty of Biology and Pharmacy.

**Thomas Söllner**
was appointed as full professor at the Biochemistry Center, University of Heidelberg, in 2005.

**Hartwig Spors**
moved to the Max Planck Institute of Biophysics in Frankfurt/M. in 2008 as a Research Group Leader.

**Wolfgang Wick**
was appointed to a professorship at the Neurology Clinic of Heidelberg University Hospital, Department of Neurooncology, in 2007.

**Bill Wisden**
took a professorship in Neurobiology at the University of Aberdeen, Scotland.

**Gabriel Wittum**
Was appointed to a chair for Modelling and Simulation at the Institute for Informatics, Johann Wolfgang Goethe-University, Frankfurt/Main, in 2008.

**Jochen Wittbrodt**
Accepted offers from the Universities of Karlsruhe as director at the Research Center Karlsruhe, and Heidelberg as professor of Developmental Biology at the Heidelberg Institute of Zoology (HIZ).

We welcome all new group leaders and wish the leaving colleagues all the best with their new and challenging positions.
Awards

Hilmar Bading
- ERC Advanced Grant (2008)

Martin Bohus
- Established Investigator Award (2003)
  Borderline Personality Disorder Research Foundation, New York
- Research Award (2003)
  International Society for the Investigation and Teaching of Dialectical Behavioral Therapy, Boston
- Psychotherapy Award (2004)
  German Association of Psychiatry, Psychotherapy and Neurology
- Outstanding Research Award (2005)
  International Society for the Investigation and Teaching of Dialectical Behavioural Therapy, Washington

Winfried Denk
- Gottfried Wilhelm Leibniz Prize (2003)
  German Research Council
- Alden Spencer Award (2006)
  Columbia University, New York
- Kavli Lecture (2006)
  Society for Neuroscience
  Cornell University, Ithaca

Herta Flor
- Research Award (2003)
  German Society for Neurotraumatology and Clinical Neuropsychology
- Award for Basic Research (2004)
  State Baden-Württemberg
- ERC Advanced Grant (2008)
- Marsilius College Fellow (2008)
  University of Heidelberg

Member of the German Academy of Sciences Leopoldina (2008)

Stephan Frings

Thomas Holstein
- Member of the Heidelberg Academy of Sciences and Humanities (2007)

Rohini Kuner
- Rudolf-Buchheim Annual Prize (2005)
  German Society for Experimental and Clinical Pharmacology and Toxicology
- Chica & Heinz Schaller Prize (2006)
- Research Award (2006)
  Rotary Club, Heidelberg
- First Prize for Basic Research on Pain (2007)
  German Pain Society (DGSS)
- Ingrid zu Solms Wissenschaftspreis (2008)

Siegfried Mense
- Muscle Pain Award (2004)
  Wiss. Arbeitskreis Muskel und Schmerz
- Honorary Pain Award (2006)
  Deutsche Gesellschaft für Schmerztherapie

Andreas Meyer-Lindenberg
- Bench-to-Bedside Award (2004-2006)
  NIMH/ORD/NIAAA
- Roche/Nature Medicine Award for Translational Neuroscience (2006)
- Joel Elkes International Award for Clinical Research (2006)
  American College of Neuropsychopharmacology
- E. Bennett Research Award (2007)
  Society of Biological Psychiatry
Hannah Monyer

Gottfried Wilhelm Leibniz Prize (2004)
  German Research Council
Member of the German Academy of Sciences Leopoldina (2006)
Philip Morris Foundation Research Award (2006)
Member of the Heidelberg Academy of Sciences and Humanities (2008)

Ulrike Müller

Alzheimer Forschungspreis (2008)
  Hans und Ilse Breuer Stiftung

Christof Niehrs

Gottfried Wilhelm Leibniz Prize (2003)
  German Research Council
Member of the Heidelberg Academy of Sciences and Humanities (2007)

Gudrun Rappold

European Society of Human Genetics Award (2003)
  (S. Schiller)
Young Scientist Award (2004)
  European Society of Human Genetics (N. Sabherwal)

Martin Schmelz

Sertürner Award (2003)
Award of the German Society for Anesthesiology (2003)
Collaborative Research Award (2003)
  International Association for the Study of Pain

Gerhard Schratt

Career development Award (CDA) (2006)
  Human Frontier Science Program
Analytica Forschungpreis (2008)
  (jointly with Albert Sickmann)

Christoph Schuster

Neurosciences Excellence Award (2004)
  Hertie-Foundation

Peter Seeburg

InBev-Baillet Latour Health Prize (2007)

Rainer Spanagel

Sir Hans Krebs Award (2003)
Albrecht-Ludwig-Berblinger Award (2005)
James B. Isaacson Award (2008)

Hartwig Spors

  Max-Planck Society

Klaus Unsicker

Honorary Member of the Romanian Society for Cell Biology (2007)

Wolfgang Wick

Novartis-Award for Clinical Research (2003)
Sibylle-Assmus Award for Neurooncology (2005)
Pette Award (2006)
  German Society of Neurology
Young Investigator Award (2008)
  American Society of Clinical Oncology (M. Weiler)

Gabriel Wittum

doIT Software Award (2005)
IZN Funding and grant giving bodies

IZN Funding and grant giving bodies

Basic funding

Basic funding for IZN research groups is provided by their home institutions:

- University of Heidelberg
- University Clinics Heidelberg
- University Clinics Mannheim
- Central Institute for Mental Health, Mannheim (ZI)
- German Cancer Research Center (DKFZ)
- Max-Planck Institute for Medical Research (MPIMF)
- European Molecular Biology Laboratory (EMBL)

Grant giving Organizations

Additional funding (‘Drittmittel’) is provided by the following grant giving organizations:

- Abbott GmbH
- Alexander von Humboldt-Stiftung
- ALS Association, USA
- Alzheimer Forschung Initiative e.V.
- American Tinnitus Association, USA
- Association for International Cancer Research (AICR), UK
- BASF-Foundation
- Becton Dickinson GmbH
- Boehringer Ingelheim Fonds
- BPDRF, USA
- Bundesministerium für Bildung und Forschung (BMBF)
- Cluster of Excellence, Cellular Networks, University of Heidelberg
- Deutsche Forschungsgemeinschaft (DFG)
- Deutsche José Carreras Leukämie-Stiftung e.V.
- Deutsche Krebshilfe e.V.
- Deutscher Akademischer Austauschdienst (DAAD)
- Dietmar-Hopp-Stiftung
- Eli Lilly Foundation, USA
- European Molecular Biology Organisation (EMBO)
- European Society for Pediatric Endocrinology (ESPE)
- European Union (EU)
- Forschungsschwerpunktprogramm des Landes Baden-Württemberg
- Fritz Thyssen Stiftung
- Génoscope, France
- German-Israeli Foundation (GIF)
- Hans und Ilse Breuer Stiftung
- Heidelberg Academy of Sciences
- Hertie Stiftung
- Human Frontier Science Program (HFSP)
- Klaus Tschira Stiftung
- Landesgraduiertenförderung Baden-Württemberg
- Landesstiftung Baden Württemberg
- Manfred Lautenschläger Stiftung
- Merz AG
- Michael J. Fox Foundation, USA
- Ministerium für Wissenschaft, Forschung und Kunst Baden-Württemberg
- National Institute of Drug Abuse (NIDA), USA
- National Institutes of Health (NIH), USA
- National Parkinson Foundation, USA
- Netzwerk Alternsforschung (NAR)
- Pfizer Pharma GmbH
- PROSKELIA S.A.S., France
- Schering GmbH
- Schilling Stiftung
- Storz, Switzerland
- Tinnitus Research Initiative
- Volkswagenstiftung
- Wilhelm Sander Stiftung
Guest scientists

Many colleagues from abroad have taken advantage to work at the laboratories of various IZN groups for a certain period of time, to discuss ideas and exchange methods, and to make use of the common infrastructure provided by the IZN.

**Bading**

- **Peter Vanhoutte** (2003), MRC Lab. of Molecular Biology, Cambridge, UK
- **Marvin Steijaert** (2004), Technische Universiteit, Eindhoven, The Netherlands
- **Dmitri Tkachev** (2004), Babraham Institute, Cambridge, UK
- **Xiaoxuan Qi** (2007), University of Saint Andrews, UK

**Draguhn**

- **Rafael Gutierrez** (2003), Fisiologia, Biofisca y Neuro-sciencias, Centro de Investigacion y Estudios Avanzados del I.P.N., Mexico

**Frings**

- **Joseph Lynch** (2003), University of Queensland, Australia

**Gilmour**

- **Michael Granato** (2006-2007), University of Pennsylvania, USA

**Holstein**

- **Mihaela Žigman** (2006-2007), Institute of Molecular Biotechnology of the Austrian Academy of Science, Vienna
- **Toshika Fujisawa** (2007-2008), National Institute of Genetics, Mishima, Japan
- **David Vactor** (2008), Harvard Medical School, Boston, USA
- **Shan Wang** (2008), National Institute of Genetics, Mishima, Japan

**Kirsch**

- **Dean Smith** (2008), Texas Tech University, Lubbock, USA

**Mense**

- **D.B. Simons** (2001-2003), Emory University, Atlanta, USA
- **Heinz Steffens** (2003-2004), Physiology, Universität Göttingen, Germany
- **Siavash Gholami** (2004-2005), Shiraz University, Iran
- **Marucia Chacur** (2007), Sao Paulo University, Brazil

**Monyer**

- **Smaragda Lambrianou** (2003), Pasteur Institute, Paris, France
- **Roberto Bruzzone** (2002-2004), Pasteur Institute, Paris, France
- **Mark Cunningham** (2004-2006) University of Leeds, UK
- **Ruth Benavides** (2004), Instiuto Cajal, Madrid, Spain
- **Pablo Pelegrin** (2006), University of Sheffield, UK
- **Jason McLean** (2006), Columbia University, New York, USA
- **Brendan Watson** (2006), Columbia University, New York, USA
- **Matthew McGinley** (2007), Portland, Oregon, USA
- **Roger Traub** (2007-2008), SUNY Downstate Medical Center, Brooklyn, N.Y., USA
- **Pierre Pratley** (2008), University of Groningen, The Netherlands

**Niehrs**

- **Wei Wu** (2008), Tshingua University, China

**Pauen**

- **Laraine McDonough**, Brooklyn College, New York, USA

**Pollerberg**

- **Galina Schevzov** (2006), University of Sidney, Australia
- **Susanne Theiss** (2006), University of Vancouver, Canada
Guest scientists

**Francisco Ropero-Padilla** (2007), University of Madrid, Spain
**Shinji Fushiki** (2008), University of Kyoto, Japan

**Rappold**

**Zilin Zhong** (2007-2008), Anhui Medical University, Hefei, Anhui, PR China

**Schmelz**

**Martin Angst** (2003), Stanford University, USA

**Schratt**

**Mette Christensen** (2007), University of Kopenhagen, Denmark

**Schuster**

**Hiroshi Kuromi** (2005), Gunma University, Maebashi, Japan
**Yoshiaki Kidokoro** (2006-2007), University of California at Los Angeles, USA

**Schütz**

**Ute Moll** (2006-2007), Stonybrook University, New York, USA

**Simon**

**Richard Dyck** (2004-2005), University of Calgary, Canada

**Spanagel**

**Dai Stephens**, University of Sussex, UK
**Theodora Duka**, University of Sussex, UK

**Tucker**

**Almut M. Ellwanger** (2005-2006), Mt. Holyoke College, USA
**Fabiola Zelada Gonzalez** (2005), Zoology, Universität Heidelberg, Germany

**Unsicker**

**Noga Ratner** (2003), Katzir Highschool, Rehovot, Israel
**Tuna Cakar** (2003), Biological and Bioengeneering Program, Sabanci University, Turkey

**Dorota Dudys** (2004), Dept. Of Pharmacology, Institute of Phamacology, Krakau, Poland
**Schu-Fee Yang** (2004), MCB Program, DKFZ, University of Heidelberg, DKFZ, Heidelberg, Germany
**Nato Kotaria** (2004-2005), Group of Chemical Neuro-anatomy, Institute of Physiology, Tbilisi, Georgia
**Maxim Sheroziya** (2004-2005, 2007), Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Science, Moscow, Russia
**Shlomi Krispin** (2007), Hebrew University, Jerusalem, Israel

**Von Deimling**

**Prabal Deb** (2007), All India Institute of Medical Sciences, New Delhi, India

**Wittbrodt**

**Pilar Esteve** (2004), Instituto Cajal, Madrid, Spain
**Juan-Ramon Martinez-Morales** (2008), University of Sevilla, Spain

**Wittum**

**Randolph E. Bank**, UCSD, La Jolla, USA
**J. Xu**, PennState, College Park, USA
**Roger Traub**, SUNY, New York, USA
**Mary Wheeler**, ICES, UTexas, Austin, USA
Collaborations

IZN Investigators have build up and continuously expand a widespread network of collaborations, both internal and external, in which they intensely interact with groups from all fields of neurosciences.

Arendt

François Nedelec/ Ernst Stelzer, EMBL, Germany
Mathematical modelling of Platynereis swimming

Harald zur Hausen, Freie Universität Berlin, Germany
Electron optic characterisation of Platynereis photoreceptor cells

Günter Purschke, Universität Osnabrück, Germany
Electron optic characterisation of Platynereis photoreceptor cells

Nicole Rebscher, Universität Marburg, Germany
Platynereis germ cells

Maria Ina Arnone, Stazione Zoologica, Naples, Italy
Photoreceptor cell evolution

Michael Akam, Cambridge University, UK
Patterning of the bilaterian body plan

Gregor Bucher, Universität Bayreuth, Germany
Patterning of the bilaterian body plan

Rolf Urbach, Universität Mainz, Germany
Patterning of the bilaterian body plan

Bading

Christof Niehrs, Heidelberg, Germany
Functional characterization of a novel Wnt regulator in the central nervous system

Klaus Unsicker, Institut für Neuroanatomie und Zellbiologie, Universität Heidelberg, Germany
Development of neuroendocrine derivatives of the neural crest (NC)

Günther Schütz, DKFZ, Heidelberg, Germany
The role of the nuclear receptor ‘tailless’ in development and adult neural stem cells

Christoph Schuster, Institut für Neurobiologie, Universität Heidelberg, Germany
Learning in Flies

Rainer Spanagel, ZI Mannheim, Germany
Addiction

Andre Fiala, Universität Würzburg, Germany
Learning in Flies

Mathias Bähr, Institut für Neurobiologie, Universität Göttingen, Germany
Neuronal Survival

Amin Rustom, AG Spatz, MPI für Metallforschung Stuttgart, Universität Heidelberg, Germany
Role of TNTs in Ca-Signalling

William Wisden, University of Aberdeen, Institute of Medical Sciences, UK
De novo methyltransferase

Patrick Descombes, Genomics Platform at the University of Geneva, Switzerland
Mechanisms of neuroprotection

Malte Wittmann, Karolinska Institute, Stockholm, Sweden
Dynamics of nuclear geometry

Lars Christian Ronn, NeuroSearch, Ballerup, Denmark
Gene regulation in ischemia

Armando Genazzani, Dept. of Chemical, Food, Pharmaceutical and Pharmacological Sciences (DISCAFF) at the Università del Piemonte Orientale A. Avogadro, Novara, Italy
Neuroprotective mechanisms in the cerebellum

Bartsch

Eric Kandel, Columbia University, USA
Minibrain

Jörg Striessnig, Universität Innsbruck, Österreich
Cav1.3

Michael Kiebler, Universität Wien, Österreich
Neuronal differentiation

Cornelius Gross, EMBL, Monterotondo, Italy
Stress and serotonin
### Collaborations

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<th>Marlies Knipper, Universität Tübingen, Germany</th>
<th>Magnus Institute of Neuroscience, University Medical Center, Utrecht, The Netherlands</th>
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<td>Cav1.3 and hearing</td>
<td>Pain perception in Posttraumatic Stress Disorders</td>
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<td>Matteo E. Mangoni, University of Montpellier, France</td>
<td>Andrea Lüthi/ I. Mansui, ETH Zürich, Friedrich Miescher Institut, Basel, Schweiz</td>
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<td>Cav1.3 in heart</td>
<td>Entwicklung von Tiermodellen zur Stressregulation bei Borderline-Störungen (BPDRF)</td>
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<td>Sussumu Tonegawa, Massachusetts Institute of Technology, Boston, USA</td>
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<td>Conditional mutations in rat</td>
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<td>Roland Buelow, Open Monoclonal Technology (OMT) Inc., USA</td>
<td>Bohus</td>
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<td>Zn finger nucleases</td>
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<td><strong>Ciccolini</strong></td>
<td><strong>Bohus</strong></td>
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<tr>
<td>Klaus Unsicker, Institut für Neuroanatomie und Zellbiologie, Universität Heidelberg, Germany</td>
<td>Marsha M. Linehan, University of Washington, USA</td>
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<tr>
<td>Role of GDF 15 in neural stem cells</td>
<td>Treatment development</td>
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<tr>
<td>Günther Schütz, DKFZ, Heidelberg, Germany</td>
<td>Thomas Lynch, Duke University, Durham, USA</td>
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<td>Role of CREB and CREM in neural stem cells</td>
<td>Conditioning in addictive behaviour</td>
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<tr>
<td>Kerry Tucker, Institut für Neuroanatomie und Zellbiologie, Universität Heidelberg, Germany</td>
<td>Larry Siever, Mount Sinai School of Medicine, Dept. of Psychiatry, Bronx VA Medical Centre, USA</td>
</tr>
<tr>
<td>FACS sorting of neurons and stem cells from the embryonic mouse brain</td>
<td>Genetic Consortium in BPD</td>
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<td>Anthony D. Ho, Innere Klinik V, Universität Heidelberg, Germany</td>
<td>Mary C. Zanarini, McLean Hospital, Harvard Medical School, USA</td>
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<td>FACS sorting of neural precursors</td>
<td>Genetics in borderline personality disorder</td>
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<td>A. Paula Monaghan, School of Medicine, University of Pittsburgh, USA</td>
<td>Shelly McMain, Dept. of Psychiatry, University of Toronto, Canada</td>
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<tr>
<td>Role of Tlx in neural stem cell maintenance</td>
<td>Genetic Consortium in BPD</td>
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<td>Ruth Lanius, University of Western Ontario, Canada</td>
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<td></td>
<td>fMRL of dissociative states</td>
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<td></td>
<td>Klaus Heinemann, Charité, Berlin, Germany</td>
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<td>Dragnuhs</td>
<td>Modulation of hippocampal networks</td>
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<td>Uwe Heinemann, Charité, Berlin, Germany</td>
<td>Klaus Willecke, Universität Bonn, Germany</td>
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<tr>
<td>Gap junctions and neuronal synchrony</td>
<td>James D. Bremner, Dept. of Psychiatry, University of Atlanta, Georgia, USA</td>
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<td>William Wisden, University of Aberdeen, Scotland, UK</td>
<td>Neuroimaging studies of dysfunctional stress regulation in patients with traumatic experiences</td>
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<tr>
<td>Roger D. Traub, SUNY Health Center, New York, USA</td>
<td>Bernet Elzinga, University of Amsterdam, The Netherlands</td>
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<tr>
<td>Modelling of network oscillations</td>
<td>Pain perception in stress related disorders</td>
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<td></td>
<td>John Livesley, Dept. of Psychiatry, Faculty of Medicine, University of British Columbia, Vancouver, Canada</td>
</tr>
<tr>
<td>Genetics of categorical and dimensional factors of personality disorders</td>
<td>Genetics in borderline personality disorder</td>
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<td></td>
<td>Herman G.M. Westenberg, Dept. of Psychiatry, Rudolf Magnus Institute of Neuroscience, University Medical Center, Utrecht, The Netherlands</td>
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<tr>
<td></td>
<td>Neuron subclass specification</td>
</tr>
</tbody>
</table>
Katrin Huber, Institut für Neuroanatomie und Zellbiologie, Universität Heidelberg, Germany
Transcription factors in neuronal differentiation

Klaus Unsicker, Institut für Neuroanatomie und Zellbiologie, Universität Heidelberg, Germany
Adrenal chromaffin cell differentiation

Hidemi Misawa, Tokyo Metropolitan Institute for Neuroscience, Tokyo, Japan
Regulation of cholinergic gene expression

Euler

Peter B. Detwiler, University of Washington, USA
Diverse projects concerning retinal information processing

Silke Haverkamp, Institut für Neuroanatomie, MPI für Hirnforschung, Frankfurt/M., Germany
Color processing in the non-primate retina

Brendan J. O’Brian, University of Auckland, New Zealand
Sodium channels in starburst amacrine cells

Rowland W. Taylor, Oregon Health & Science University, Portland, WA, USA
Direction-selective ganglion cells

Shigang He, Chinese Academy of Sciences, Beijing, China
Receptive field properties of starburst amacrine cells in the rabbit retina

Jost B. Jonas/ Frank Schlichtenbrede, Universitäts-Augenklinik, Mannheim, Germany
Toxicity Assessment of intravitreal Triamcinolone and Bevacizumab in an ex-vivo mouse model

Thomas Kuner, Institut für Anatomie und Zellbiologie, Universität Heidelberg, Germany
Chloride gradients in retinal neurons

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Klaus van Ackern, Institut für Anästhesiologie, Universität Heidelberg, Germany
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Hubert J. Bardenheuer, Institut für Anästhesiologie, Universität Heidelberg, Germany
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Andreas Heinz, Charité – Universitätsmedizin Berlin, Germany
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Collaborations

Angela Friederici, MPI für Kognition- und Neurowissenschaften, Leipzig, Germany
Neural mechanisms of language processing - conceptual combination in sentence processing and working memory

Martin Reuter, Psychologisches Institut, Universität Bonn, Germany
Cognitive effects of neurotransmitter gene polymorphisms

Edward Smith, Dept. of Psychology, Columbia University New York, USA
Conceptual combination in sentence processing and working memory

Hauke Heekeren, MPI für Bildungsforschung, Berlin, Germany
An fMRI study of cost-benefit analysis in the brain

Fiebach

Mark D’Esposito, Helen Wills Neuroscience Institute and Dept. of Psychology, University of California, Berkeley, USA
Neurocognitive bases of verbal working memory

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Collaborations

Christian Buechel, Universitätsklinikum Hamburg-Eppendorf, Germany
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Gunther Schumann, Institute of Psychiatry, King’s College, London, UK
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Trevor W. Robbins, University of Cambridge, UK
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David N. Stephens, University of Sussex, UK
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Tomas Paus, University of Nottingham, UK
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John Rogers, Delosis Ltd.(SME), UK
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Romain Valabrègue, SCITO S.A. (SME), France
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Jean Baptiste Poline, Commissariat à l’Energie, Atomique, France
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Mark Lathrop, Consortium National de Recherche en Genomique, France
IMAGEN

Patrick Konstant, PERTIMM PERTINENT ET IMMEDIAT (SME), France
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Tormod Thomsen, NordicNeuroLab (SME), Norway
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Laura Petrini, Dept. of Health Science and Technology, University of Aalborg, Denmark
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Beatriz García, UNED Research Institute (CEEN), Dept. of Basic Psychology II, Universidad Nacional de Educación a Distancia (UNED), Spain
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Frings

Thomas Kuner/ Hartwig Spors/ Hannah Monyer,
Institut für Anatomie und Zellbiologie, Universität Heidelberg/ MPI für Medizinische Forschung, Heidelberg/ Institut für Neurobiologie, Universität Heidelberg, Germany
DFG Research group “Information processing in the olfactory system”

Martina Schnölzer, DKFZ, Heidelberg, Germany
Proteomic analysis of olfactory neurons

Joseph Lynch, University of Queensland, Australia
Chloride imaging methods
**Jon Bradley**, Université Paris 5, France  
Chloride channel cloning

**Johannes Reisert**, Monell Taste and Smell Center, USA  
Chloride channel biophysics

**Thomas Gensch**, Jülich Research Center, Germany  
Chloride homeostasis in sensory neurons

**Gass**

**Marco Riva**, Dept. of Pharmacology Science, University of Milano, Italy  
Neuronal signalling and Depression

**Rainer Hellweg**, Psychiatrische Klinik, Charité, Berlin, Germany  
Neurotrophins and Depression

**Susana Aznar**, Dept. of Neurobiology, University of Copenhagen, Denmark  
Serotonin and Depression

**Gilmour**

**Jochen Wittbrodt**, EMBL, Heidelberg, Germany  
Three-Dimensional imaging/tracking of Cell Movements in embryos using DSLM

**Holstein**

**Brad Amos**, Cancer research UK, imaging and microscopy laboratory, University of Cambridge, UK  
EURESCO Multi-harmonic Generation imaging using a confocal microscope

**Hans C. Gerritsen**, Dept. of Molecular Biophysics, Dept. of Physics & Astronomy, Science Faculty, Universiteit van Utrecht, The Netherlands

**Maarten Balzar**, Nikon Instruments Europe B.V., Product Support Group, The Netherlands

**Hans Bode**, Dept. of Developmental Biology, University of Irvine, USA  
Hydra Genome Project

**Dan Rokhsar**, Dept. of Molecular and Cell Biology, University of Berkeley, USA  
Hydra Genome Project

**Kins**

**Joachim Kirsch**, Institut für Anatomie und Zellbiologie, Universität Heidelberg, Germany  
Subcellular localization of APP/APLPs

**Kirsch**

**Ulrike Müller**, Institut für Pharmazie und Molekulare Biotechnologie, Universität Heidelberg, Germany  
Genetic manipulation of mice

**Jochen Herms**, Ludwig-Maximilians-Universität, München, Germany  
APP mediated synaptogenesis

**Marino Zerial**, MPI für Molekulare Zellbiologie und Genetik, Dresden, Germany  
Rab5 dependent Endocytosis

**Ruppert Egensperger**, Ludwig-Maximilians-Universität, München, Germany  
Electronmicroscopic anlyses of APP transport vesicles

**Scott Brady/ Gerardo Morfini**, University of Illinois, Chicago, USA  
Molecular interaction of APP and Kinesin

**Sangram Sisodia**, University of Chicago, Chicago, USA  
Molecular interaction of APP and Kinesin

**Ole Kjaerulff**, Copenhagen University, Copenhagen, Denmark  
Electrophysiological studies of APP transgenic *Drosophila* larvae

**Gunther Merdes**, Institute for System Biology, Basel, Switzerland  
Generation of transgenic flies

**Takuya Sasaki**, University of Tokushima, Tokushima, Japan  
Genetic manipulation of Rab3GAP

**Eckart Friauf**, Universität Kaiserslautern, Germany  
Organotypic cultures of the brain stem

**Heinrich Betz**, MPI für Hirnforschung, Frankfurt, Germany  
Cellular analysis of collybistin knock-out mice

**Collaborations**

**Joachim Kirsch**, Institut für Anatomie und Zellbiologie, Universität Heidelberg, Germany  
Subcellular localization of APP/APLPs

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**Ulrike Müller**, Institut für Pharmazie und Molekulare Biotechnologie, Universität Heidelberg, Germany  
Genetic manipulation of mice

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Organotypic cultures of the brain stem

**Heinrich Betz**, MPI für Hirnforschung, Frankfurt, Germany  
Cellular analysis of collybistin knock-out mice
Collaborations

Dean Smith, Dept. of Physiology, Texas Tech University, USA
Electrical properties of newborn and immature neurons

Peter Lauf, Cell Biophysics Group, Dept. of Pathology, Wright State University, Dayton, USA
Regulation KCC2 in newborn and immature neurons

Köhr

Egidio D’Angelo, Dept. of Cellular-Molecular Physiology and Pharmacology, University of Pavia, Italy
Cerebellar plasticity

Chris I. De Zeeuw, Dept. of Neuroscience, University of Rotterdam, The Netherlands
Eyeblink conditioning

Anita Lüthi, University of Lausanne, Switzerland
Long-term depression

Øivind Hvalby/ Vidar Jensen, Dept. of Neurophysiology, University of Oslo, Norway
Dopamine-NMDA-Interactions

Kuner R

Bernhard Bettler/ E. Casanova, Dept. of Biomedicine, Institute of Physiology, University of Basel, Switzerland
Endogenous control of pain by GABA-B1

Silvia Arber, Biozentrum, University of Basel, Switzerland
Genetic labelling of sensory neurons

Mike Costigan/ Clifford Woolf/ Irmgard Tegeder, Dept. of Anesthesia and Critical Care, Massachusetts General Hospital and Harvard Medical School, USA
(Costigan/ Woolf)/ Goethe- Universität, Frankfurt, Germany
Neuropathic pain in transgenic mice

Sugiura Takeshi/ Gerald Gebhart, Dept. of Anesthesiology, Pittsburgh Center for Pain Research, University of Pittsburgh, USA
Visceral pain in transgenic mice

Shanelle W. Ko/ Min Zhuo, Dept. of Physiology, Faculty of Medicine, University of Toronto, Canada
Forebrain plasticity in pain

Anthony Dickenson, Dept. of Neuropharmacology, University College, London, UK
Tumor-induced pain

Seifollah Ahmadi/ Hanns U. Zeilhofer, Institut für Pharmakologie und Toxikologie, Universitätsklinikum Erlangen, Germany
Synaptic plasticity in pain

Gary Lewin, Molecular Physiology of Somatic Sensation, Max-Delbrück-Zentrum für Molekulare Medizin, Berlin, Germany
Inflammation and pain

Giovanni Marsciano/ Beat Lutz, Institut für Physiologische Chemie, Johannes Gutenberg-Universität, Mainz, Germany
Cannabinoid receptors and pain

Robert Feil, Interfakultäres Institut für Biochemie, Universitätsklinikum Tübingen, Tübingen, Germany
cGK1-mechanisms in pain

Kuner T

George Augustine, Duke University Medical Center, USA
Chloride signalling

Daniel Gitler, Ben Gurion University, Israel
Synaptic vesicle cycle

Eckart Gundelfinger, Institut für Neurobiologie, Universität Leibzig, Germany
CAZ proteins bassoon and piccolo in calyx

Benedikt Grothe, Ludwig-Maximilians-Universität, München, Germany
Auditory system

Rohini Kuner, Institut für Pharmakologie, Universität Heidelberg, Germany
Virus-mediated perturbations

Peter Seeburg, MPI für Medizinische Forschung, Heidelberg, Germany
Glutamate receptor mouse models
Mense

Thomas Unger, Center for Cardiovascular Research/Institut für Pharmakologie and Toxikologie, Charité, Berlin, Germany
Neuroinflammation and chronic muscle pain: role of glial cells in central sensitisation

Lars Arendt-Nielsen, Center for Sensory-Motor Interaction, Aalborg, Denmark
NGF-induced hyperalgesia in muscle

Kazue Kumazawa, Dept. of Neuroscience II, Division of Stress Recognition and Response Research Institute of Environmental Medicine, Nagoya University, Japan
Glia cells and muscle pain

Karl Messlinger, Institut für Physiologie und Pathophysiologie, Universität Erlangen-Nürnberg, Germany
Environmental influences on muscle pain

Bob Gerwin, Pain & Rehabilitation Medicine, Bethesda, USA
Myofascial trigger points

Monyer

Roger Traub, SUNY Health Center, New York, USA
The role of AMPA receptors in GABAergic interneurons for network synchronicity

Gary Westbrook, Vollum Institute, Portland, USA
Study of defined cell types in the olfactory bulb; exchange of Postdocs

Gyorgy Buzsaki, Rutgers University, Newark, USA
Analysis of data obtained from in vivo recordings

Miles Whittington, University of Newcastle, UK
The role of AMPA receptors in GABAergic interneurons for network synchronicity

Nick Rawlins, Dept. Exp. Psychology, University of Oxford, UK
Behavioral studies of genetically altered mice

Bill Wisden, Institute of Medical Sciences, University of Aberdeen, UK
Mice with altered GABA receptors in parvalbumin-positive cells, AMPA receptor KO in cerebellar granule cells

Hans van Hoof, Institute of Neurobiology, University of Amsterdam, The Netherlands
Analysis of 5HT3 EGFP transgenic mice

Roberto Bruzzone, Pasteur Institute, Paris, France
Functional characterization of recombinant pannexins

Reto Weiler, Institut für Biologie und Umweltwissenschaften, Universität Oldenburg, Germany
Analysis of connexin and pannexin expression in identified neurons in the retina

Peter Seeburg, MPI für Medizinische Forschung, Heidelberg, Germany
Conditional NR2B knockout mice. Generation of transgenic mice with altered C-termini

Andrei Rozov, MPI für Medizinische Forschung, Heidelberg, Germany
Functional characterization of calretinin-positive interneurons. Analysis of GluRD knockout mice

Markus Schwaninger, Institut für Pharmakologie, Universität Heidelberg, Germany
Stroke model in genetically altered mice

Müller

Heinrich Betz, MPI für Hirnforschung, Frankfurt, Germany
Glycine receptors

Konrad Beyreuther, Zentrum für Molekulare Biologie Heidelberg, Universität Heidelberg, Germany
APP transport

Sangram Sisodia, University of Chicago, USA
APP transgenic mice

Martin Korte, Technische Universität Braunschweig, Germany
APP and synaptic function
Collaborations

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<td><strong>Ulrich Zeilhofer</strong>, University of Zürich, Switzerland</td>
<td>Pharmacology of pain</td>
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<tr>
<td><strong>David Wolfer</strong>, University of Zürich, Switzerland</td>
<td>Mouse behavioural phenotyping</td>
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<tr>
<td><strong>Jochen Herms</strong>, Institut für Neuropathologie, Ludwig-Maximilians-Universität, München, Germany</td>
<td>Neuropathology of transgenic mice</td>
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CAM signalling and trafficking

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Screening of mutant mice for deficiencies in the visual system

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Long-term time lapse imaging of axons in histotypic context

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Microneurography in volunteers and pain patients

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Histopathological analysis of nuclear receptor mouse mutants

Peter Krammer, DKFZ, Heidelberg, Germany
Histopathological analysis of nuclear receptor mouse mutants

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   Affymetrix-based analysis of gene expression

Stefan Offermanns, Institut für Pharmakologie, Universität Heidelberg, Germany
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Alfred Nordheim, Institut für Zellbiologie, Universität Tübingen, Germany
   Neuronal migration in the murine rostral migratory stream requires SRF

Hans-Peter Lipp, Institute of Anatomy, University of Zürich, Switzerland
   Loss of the limbic mineralocorticoid receptor impairs behavioral plasticity

Leszek Kaczmarek, Nencki Institute of Experimental Biology, Warsaw, Poland
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   β1 integrins regulate mammary gland proliferation and maintain the integrity of mammary luminal alveoli.

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MuSK-induced CMS

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AChR subunit trafficking
Research Profiles
The evolution of the animal central nervous system

Research Summary

We are intrigued by one of the remaining great mysteries in animal evolution: how did our central nervous system come into existence? What did it look like at first and how did it function? We are especially interested in the CNS of an extinct animal known as Urbilateria, the last common ancestor of humans, flies and most other ‘higher’ animals that live today.

Curriculum Vitae

Degrees: 1995 M.Sc.  
1998 Ph.D.  
1998-2002: Postdoctoral fellow at the EMBL, Heidelberg  
2002-2006: Team Leader Developmental Biology Unit EMBL, Heidelberg  
2006-2007: Group Leader Developmental Biology Unit EMBL, Heidelberg  
since 2007: Group Leader and Senior Scientist Developmental Biology Unit EMBL, Heidelberg

Current Research

The molecular comparison of neuron types

We combine morphological and molecular approaches in a novel evo-devo approach, the molecular comparison of neuron types. Animal central nervous systems are made up of different types of sensory neurons, interneurons, motor and neurosecretory cells as well as support and glial cells. Each type displays a characteristic “molecular fingerprint”, which is the unique combination of specifying transcription factors and downstream effector genes such as receptors, transmitters or neuropeptides that are expressed in these cells. The molecular fingerprint is a conservative trait that can be retained over more than 600 millions of years and allows the tracing of cell types through animal evolution (Arendt, 2004; Arendt et al., 2004; Arendt, 2005; Denes and Jekely et al., 2007; Tessmar-Raible et al., 2007). Fig. 1 depicts our current working hypothesis on homologouc cell types shared between the polychaete and vertebrate forebrain, as a summary of the past years’ work. Molecular fingerprinting with cellular resolution is greatly facilitated by the novel Wholemount reflection CLSM (see above). Our molecular dissection of Platynereis development has been complemented by ultrastructural studies on cellular morphologies carried out in collaboration with G. Purschke (Osnabrück) and H. Hausen (Berlin).

Molecular dissection of Platynereis eye and photoreceptor development

Three pairs of eyes and three pairs of chemo-/mechanosensory organs connect to the Platynereis brain (e.g., Arendt et al., 2002). Ongoing and future projects aim at the further molecular and functional characterisation of the Platynereis head sensory cell types, in order to trace their evolution throughout Bilateria. We have shown that the Platynereis brain harbours ciliary photoreceptor cells that share a common “molecular fingerprint” with the rods and
cones of the vertebrate retina (Arendt et al., 2004). For example, we discovered a vertebrate-type *Platynereis* Opsin expressed in these cells (violet in Fig. 1). This is strong indication that rods and cones have evolved from a precursor population of deep brain ciliary photoreceptors that existed already in the last common ancestors of the bilaterians, the Urbilateria.

We are also investigating the larval eyes of the *Platynereis* trochophora larva. These are of special importance for phylogenetic comparisons because very similar larval eyes also exist in basal Deuterostomia such as enteropneusts. We propose that such larval eyes existed already in Urbilateria.

*Platynereis* larval eyes are eyespots composed of two cells only: a photoreceptor and a shading pigment cell. They thus resemble Darwin’s ‘proto-eyes’, considered to be the first eyes to appear in animal evolution. These eyespots cannot form images but enable the animal to sense the direction of light. They are characteristic for the zooplankton larvae of marine invertebrates and are thought to mediate larval swimming towards the light. Phototaxis of invertebrate larvae contributes to the vertical migration of marine plankton, which is thought to represent the biggest biomass transport on Earth. We have recently shown how simple eyespots in marine zooplankton mediate phototactic swimming, using the marine annelid *Platynereis dumerilii* as a model.

Fig. 1: Homologous cell types in the *Platynereis* larval episphere and in the vertebrate prosencephalon. Violet: ciliary photoreceptor cells; yellow: rhabdomeric photoreceptor cells/retinal ganglion cells; green: molecular clock cells. Red: Vasotocin-secreting extraocular photoreceptors. Blue: serotonergic cells. Brown: FMRFamidergic chemosensory cells. ae: adult eye, cPRC: ciliary photoreceptor cell, le: larval eye, nsc: nucleus suprachiasmaticus, pin: pineal, ret: retina, RGC: retinal ganglion cells, rPRC: rhabdomeric photoreceptor cells

**Sensory-neuroendocrine cell types in the *Platynereis* brain**

To elucidate the evolution of neurosecretory centres in bilaterian brains, we molecularly characterise and compare early differentiating neuron types in the nk2.1-positive medial forebrain region in *Platynereis* and in the zebrafish (Tessmar-Raible et al., 2007) At the current state of analysis, we identified two conserved cell types by molecular fingerprint comparison.

First, we characterized a population of cells in *Platynereis* that co-express the transcription factors nk2.1, otp and rx, a vasotocin (vasopressin/oxytocin) - neurophysin prohormone, and ciliary opsins, and discovered cells of identical “molecular fingerprint” in fish. This indicates the presence of vasotocinergic deep brain photoreceptor cells in both species. Second, we identified a population of flask-shaped, sensory-neurosecretory cells in the *Platynereis* brain that co-express the transcription factor otp and resemble a subset of vertebrate central-spinal-fluid-contacting neu-
rons by cytoarchitecture, and by RFamide neuropeptide content. Corroborating homology of the vasotocinergic and FMRFamidergic cell types across Bilateria we find that in both Platynereis and fish they form part of a small population of cells in the developing brain that is demarcated early on by the specific expression of the conserved microRNA miR-7.

Motor-, inter, and sensory neurons of the ventral nerve cord

The larval polychaete trunk comprises four larval segments. Each segment harbours motor-, inter-, and sensory neurons that control larval swimming. We have started to determine the molecular fingerprint and the mediolateral distribution of these neurons types at larval stages, assigning them to the different mediolateral progenitor domains as outlined above (Denes et al., 2007). For example, we found that hb+ cholinergic somatic motor neurons emerge from the Px6+, nk6+ progenitor domain in Platynereis as they do in vertebrates. We validated by cholinesterase staining that these neurons directly innervate the somatic musculature also in Platynereis and that contractions are abolished by acetyl choline receptor antagonists.

We further determined that serotonergic neurons emerge from the medial nk2.2 column and sensory neurons from the lateral msx+ domains in polychaete and vertebrate. Altogether, these findings are consistent with an overall conserved mediolateral architecture of the polychaete and vertebrate trunk CNS, and thus with a common evolutionary origin of nervous system centralisation. This would imply modification of the mediolateral architecture in the fly and in the nematode.

Top publications

Current Research

Changes in the concentration of intracellular calcium as a result of synaptic activity control virtually all adaptive responses in the adult nervous system. Calcium activates mechanisms that affect synaptic connectivity, regulate learning and memory, promote survival, modulate pain, or cause cell death. Most activity-induced adaptations are initiated by synaptic NMDA receptors and require for their maintenance signal-induced changes in gene expression. For synapse-to-nucleus communication neurons exploit the spatial and temporal diversity of calcium transients associated with electrical activation. Transcriptional responses depend on how calcium enters the neurons, the amplitude of the signal, how long it lasts and what subcellular compartment it invades. One means of conveying a signal to the nucleus involves ERK-MAP kinases that translocate to the nucleus and stimulate transcription factors upon being activated by a calcium micro-domain in the immediate vicinity of the site of calcium entry. However, the principal mediator in the dialogue between the synapse and the nucleus is calcium itself. Synaptic activity and NMDA receptor stimulation can initiate calcium transients that propagate towards the cell soma and enter the cell nucleus.

Nuclear calcium: universal signal in neuronal survival and long-term memory

Nuclear calcium signaling controls the expression of a wide variety of target genes, primarily by stimulating CREB/CBP-mediated transcription. Our hypothesis is that nuclear calcium acts as a universal signal for persistent adaptations in the nervous system. To test this hypothesis, we have focused on two adaptive processes: activity-dependent neuronal survival (i.e. acquired neuroprotection) and memory formation. Using tools to interfere selectively with calcium signaling in the nucleus of hippocampal neurons, we
have been able to demonstrate that the neuroprotection afforded by action potential bursting and synaptic NMDA receptor activation is indeed dependent upon nuclear calcium signaling. Whole genome transcriptional profiling in hippocampal neurons revealed a nuclear calcium-regulated genomic survival program consisting of about a dozen genes. The neuroprotective activity of some of these genes has been demonstrated in vitro as well as in in vivo models of neurodegeneration. The role of nuclear calcium in learning and memory is being analyzed in the fruit fly *Drosophila melanogaster*. The results obtained so far indicate that the formation of long-term memory following associative olfactory learning is impaired in transgenic flies expressing an inhibitor of nuclear calcium signaling.

**Nuclear calcium imaging in vivo**

A major challenge for the future is to develop tools and technologies to detect nuclear calcium signals in vivo. Given the central role of nuclear calcium in synaptic plasticity-related gene expression, we are particularly interested in studying nuclear calcium transients during learning. We are using stereotaxic delivery of recombinant adeno-associated viruses to express recombinant calcium indicators targeted to the cell nucleus in the rodent brain. Techniques of imaging calcium signals in vivo are being developed. We have also generated transgenic *Drosophila melanogaster* expressing a recombinant nuclear calcium indicator in the
nervous system. These flies are being used to monitor nuclear calcium signals during associative olfactory learning.

**Extrasynaptic NMDA receptor signaling: CREB shut-off and cell death pathways**

The transcription-promoting activities of synaptic NMDA receptor-induced nuclear calcium signals are antagonized by a calcium signaling pathway that is initiated by calcium flux through NMDA receptors located outside synaptic contacts. Extrasynaptic NMDA receptors couple to a CREB shut-off pathway and cause cell death. Thus, the decision whether a neuron survives (and perhaps undergoes plasticity) or dies after glutamate exposure is dependent on the location of the NMDA receptor activated. This concept of differential signaling by synaptic and extrasynaptic NMDA receptors has wide-ranging implications, especially for the understanding and treatment of neuro-pathological conditions such as stroke in which brain damage may be caused by the stimulation of extrasynaptic NMDA receptors.

**Top publications**


**Fig. 4:** 3D image reconstruction of nuclei from hippocampal neurons. Picture by Gillian Queisser and Malte Wittmann.

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**Technicians:** Iris Bünzli-Ehret, Andrea Hellwig, Ruth Jelinek, Ursula Weiss
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Molecular and cellular basis of normal and pathologic cognition, learning and memory, and mental retardation

Research Summary
We study normal and pathological learning and memory in molecular terms. Although the role of genes in basic synaptic functions can be studied in cultured neurons, the role of genes in cognition can be studied only in the functional brain. Therefore, we create targeted and regulated genetic modifications of candidate genes specifically in the areas of the rodent brain involved in learning and memory. The genetically modified mice and rats are then studied using current methods of molecular biology, electrophysiology, behavior and pharmacology.

Curriculum Vitae
Degrees: 1984 Ph.D. in Biology, Charles University, Praha, Czech Republic
1979-1983: B.S., Molecular Biology and Virology, Charles University, Praha
1983-1984: PhD, Biology, Charles University, Praha
1984-1987: Staff scientist, Dept. of Exp. Virology, Institute for Sera and Vaccines, Praha
1987-1988: Guest scientist, German Cancer Research Center (DKFZ), Heidelberg, Germany
1988-1992: Postdoctoral fellow, DKFZ
1992-1993: Postdoctoral research fellow, HHMI and Center for Neurobiology & Behavior, Columbia University, New York, USA
1993-2000: Research associate scientist, Columbia University, New York
since 2000 Professor of Molecular Biology at University of Heidelberg and Central Institute of Mental Health, Mannheim, Germany

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Current Research
Role of voltage gated calcium channels in learning and memory
Our focus is the role of LVGCCs in learning and memory, memory extinction and age dependent memory loss. Since no subunit-specific antagonists or agonists of LVGCCs are available, genetic tools are necessary to dissect the specific role of Cav1.2 and Cav1.3 in normal and pathologic brain functions. We have generated mice with conditional Cav1.3 alleles. By breeding them with mice with tissue-specific expression of tamoxifen-inducible Cre recombinase, we are able to study the roles of Cav1.3 in defined tissues at specific time-points, thus allowing to differentiate the role of Cav1.3 in developing, adult and aging organs. We have generated and tested forebrain and hippocampus-specific promoters driving the Cre recombinase, enabling us to study the role of Cav1.3 in hippocampus-dependent learning and memory. Recently, we were able to target sub-hippocampal regions. Such genetic modifications allow us to study the role of Cav1.3 in brain and other selected tissues and generate mouse models for specific role of LVGCCs in diverse physiological functions.

Role of MEGAP in mental retardation
Mental retardation is a common condition affecting between 0.3-3% of the population, depending on severity. We have generated mice with mutations mimicking a recently identified mutation in a novel RhoGAP protein family (MEGAP) found in a patient with severe mental retardation (Endris et al.; 2002). We generated mice with stop codon in exon 3 of Megap gene, resulting in premature termination of MEGAP protein translation. Megap -/- mice develop hydrocephalus and show defects in neuronal morphology. On the behavioral level, Megap -/- mice demonstrate increase in anxiety. Molecular studies with Megap -/- mice indicate that the ERK1 signaling pathway is significantly affected in Megap knockout mice.
Modeling serotonergic defects in depression using conditional regulation of serotonin concentration in transgenic mice

The serotonergic system is an important modulator of many developmental, behavioral and physiological processes, and its perturbation is a major etiological component of depression. The serotonin transporter (SERT) plays a key role in the regulation of central serotonergic neurotransmission by removing serotonin from the synaptic cleft. Stressful life events in humans are known to be followed by depressive episodes in susceptible individuals. Vulnerability seems to be genetically anchored in the serotonergic system. Tph2 is a key enzyme in serotonin synthesis. We have generated congenic B6.D2-Tph2 C1473G mice carrying the tryptophan hydroxylase 2 allele (Tph2) of the DBA2 mouse strain with the C1473G polymorphism in the defined C57BL/6J genetic background. The C1473G mutation results in reduced activity of Tph2 enzyme. By combining B6 and B6.D2-Tph2 C1473G mice with conditional alleles of Tph2 and Sert generated in our laboratory, we are able to manipulate the serotonin concentration in the mouse brain either during development or in adult animals. B6.D2-Tph2C1473G mice show increased anxiety. Currently, we test the interaction of C1473G polymorphism with chronic mild stress. This model provides an opportunity to study regulatory pathways specifically affected in vulnerable animals under stressful conditions.

Inducible and regulated gene expression in the rat brain

The recent progress in molecular neuroscience allows first insights in mechanisms of neuronal function on molecular and cellular level. On the behavioral level, this has been to some degree complemented by studies in genetically modified mice. Largely due to the lack of germline forming embryonic stem cells (ES) in rats, major effort to re-establish many of well studied behavioral, pharmacological and electrophysiological rat models in mice was undertaken; so far with only partial success. Many of the complex behaviors exhibited by rats are not matched by similar mouse behaviors. We therefore developed molecular tools that allow us to study the role of genes in complex behaviors in rats. We explore inducible transgene expression using the tetracycline inducible tTA system and CreERT2 mediated recombination and the miRNA technology for generating inducible gene knockdowns in the rat brain. By combining the above methods, we hope to manipulate bi-directionally (overexpression and knockdown) gene expression of rat genes and make rat models accessible to reverse genetics.

Age dependent memory loss

Aging is associated with a decline in memory. This impairment is progressive and widespread, affecting about 40% of people over the age of 65. Animal models have been developed to study both the genetic and environmental components of age-dependent memory decline. Interestingly, even in inbred strains of rats or mice, only a part of the genetically homogenous population develops memory deficits with aging, indicating that epigenetic changes, involving changes in gene expression, are the molecular keys to the memory decline. We have generated genetic tools which allow us to manipulate concentrations of both NMDA receptor and LVGCCs selectively in the hippocampus of transgenic rats during their lifespan. We have generated transgenic rats with the NMDA receptor (NR1) and LVGCC (Cav1.3) expression controlled reversibly by a tetracycline regulated promoter (NMDAtet-O and LVGCCtet-O). To target the expression...
Fig. 2: Inducible expression of eGFP in the forebrain of transgenic rats. Rats with the tetracycline activator driven by CamKII promoter CamKII-tTA) were bred to rats with ptet promoter driven eGFP. Double transgenic rats (CamKII-tTA x ptet-eGFP) show high expression of eGFP as detected by anti-GFP antibody. The expression of the reporter is detectable in the forebrain and can be regulated by doxycycline in drinking water. Here, we used an insulator LC1 BAC to obtain reproducible and highly inducible expression of the tetO driven transgene.

of both receptors to the hippocampus, we breed the NMDAtet-O and LVGCCtet-O mice with tTACaMKII rats expressing the tTA activator under control of the CaMKII promoter.

To inducibly and reversibly decrease the NMDAR and LVGCC concentration in the neurons, we have developed a tTA based expression system for overexpression of miRNAs targeting both receptors. These genetic tools allow us to perform long-term manipulations of NMDAR and LVGCC concentration in the rat hippocampus. We can thus perform longitudinal studies with the same rats over their lifetime and combine behavioral analysis with neuroimaging.

**Top publications**


**Structure of the Group**

**Group Leader:** Dusan Bartsch  
**Postdoctoral fellows:** Stefan Berger, Kai Schönig, Robert Weltert, Tillmann Weber  
**PhD students:** Vera Beier, Katrin Bartels, Sergej Kutscherjav, Siri Malmgren  
**Technicians:** Ariana Frömmig, Katja Lankisch, Sabine Nescholta, Brigitte Pesold
Current Research

Pain perception assessed by Laser-Evoked Potentials and functional MRI in patients with Borderline Personality Disorder

Background: Borderline Personality Disorder (BPD) is a frequent psychiatric disorder, and pain perception was shown to be attenuated in BPD. Our findings from a study using laser-evoked pain potentials suggest that sensory-discriminative pain components seem to be unaffected in this patient population and affective-motivational pain components may be altered in BPD. Studies in healthy subjects have revealed a pain circuit consisting of thalamus, somatosensory cortex, insula, and anterior cingulate cortex (ACC). We used functional MRI and heat pain stimuli to localize alterations in pain processing in BPD.

Method: Patients with Borderline Personality Disorder according to DSM-IV and healthy controls are investigated using brief radiant heat pulses and 7 channel EEG recordings. In addition participants underwent functional MRI during heat pain stimulation. Two stimulus conditions were applied in a randomized fashion: First, a fixed temperature was used. Second, a temperature that was perceived equally painful by all participants was applied.

First results: BPD patients tended to have higher pain thresholds and pain ratings were reduced to 25% of controls. In contrast, mean amplitudes of LEPs in the BPD group were not reduced compared to those of controls. The ability to spatially discriminate painful stimuli did not differ between both groups. In fMRI, all classical pain regions were activated by stimulation with heat pain in BPD patients as well as controls. Group comparison revealed less activation in Somatosensory Association Cortex (Area 7) in BPD compared to controls under fixed stimulus intensity. During stimulation with equal subjective pain intensities we found more deactivation in ACC (perigenual cingulate) in BPD compared to controls.
Conclusions: Results of our study are consistent with the idea that the anterior cingulate cortex plays a role in altered pain perception in patients with BPD.

**Neuroendocrinological dysregulations in female patients with Borderline Personality Disorder**

**Background:** Borderline personality disorder (BPD) is characterized by a long lasting, often chronic pattern of dysfunctions in emotional regulation, interpersonal relationships, self-image, and impulse control. The cardinal symptom is a state of aversive tension. Experiencing these symptoms several times a day might lead to a state of chronic stress. Several studies have investigated the physiological consequences of BPD symptoms on neuroendocrine systems. Dysregulations of the hypothalamic-pituitary-adrenal (HPA) axis, however inconclusive, have been found.

**Methods:** In this study, we set out to examine BPD patients in a standardized psychosocial stress paradigm, which is known to lead to substantial increases in HPA axis parameters. Cortisol and catecholamines were measured. A total of 21 female BPD patients and 21 control subjects currently follows the study protocol. All subjects are medication free, have a regular menstrual cycle and are taking part in the study during their luteal phase. Comorbidity with psychiatric disorders like schizophrenia, current depression, current drug abuse, and current severe eating disorders is excluded.

**Results:** Preliminary results show that patients with a BPD diagnosis showed similar baseline levels in cortisol and catecholamines as in control subjects. However, in the patients group a substantial hyporeactivity in HPA axis function has been found in comparison to the controls as a reaction to the stressor. Furthermore, sympathetic activity as measured by the catecholamines was higher in patients prior to the stressor, but no differences have been observed after the stressor.

**Conclusions:** The results will be discussed with regard to the effects that borderline-typical psychopathology might have exerted on neuroendocrine function.

Fig. 1: Group comparison of responses to a temperature individually adjusted to produce equally perceived pain intensity. Brain activity during individually adjusted painful heat stimulation differed between patients with borderline personality disorder (BPD) and controls during the early-stimulation phase in the left dorsolateral prefrontal cortex and the right posterior parietal cortex. In the late phase of individually adjusted heat pain, intergroup differences in the brain activity were seen in the perigenual part of the anterior cingulated cortex and in the right amygdala.

**Impact of Hydrocortisone and Psychotherapy on Traumatic Memory Processing in Patients with complex PTSD**

Overall aim of this project: to investigate the role of glucocorticoids (GC) in traumatic memory retrieval. Animal and human researches indicate that elevation of central glucocorticoid levels facilitates memory consolidation while impairing delayed memory retrieval. Thus, we postulate that patients suffering from severe PTSD should benefit from hydrocortisone application during exposure based psychotherapy.

The project is composed of the following parts:

1. A clinical trial investigates both the efficacy of oral hy-
drcortisone and dialectical cognitive therapy (DCT) and the combination of both in the retrieval of traumatic memories and overall symptomatology in patients suffering from severe chronic PTSD.

2. In order to define neurobiological predictors for (early) treatment response, HPA-axis function will be assessed in all patients prior to treatment.

3. To study the central mechanisms of glucocorticoid-mediated traumatic memory processing, individualized trauma related scripts will be presented during fMRI and modified by either oral hydrocortisone or the glucocorticoid-antagonist mifepristone (misoprostol).

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**Top publications**


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**Structure of the Group**

Group Leader: Martin Bohus  
Senior Scientist: Christian Schmahl  
Postdoctoral fellows: Uli Ebner-Priemer, Nicolaus Kleindienst, Petra Ludäscher, Jana Mauchnik  
Scientists: Sonia Kiko, Iris Klossika, Petra Ludaescher, Anna Mall, Jana Mauchnik, Matthias Limberger, Joachim Wiskemann  
Technicians: Ingar Niedfeldt
Francesca Ciccolini

Proliferation and differentiation of neural stem cells

Research Summary
Multipotent and self-renewing neural stem cells (NSCs) in the adult mammalian brain continue to generate new neurons throughout the life span of the animal. Proliferation of NSCs in the telencephalon is regulated by temporal and regional clues, which reflect modulatory signalling interaction between the NSCs and their niche. To directly study this regulation we have developed a strategy to isolate neural stem cells from different regions of the embryonic and the adult brain. The ultimate goal of our work is to device a strategy to identify neural stem cell behaviour in vivo.

Curriculum Vitae
Degrees: 1994 Ph.D.
1991-1994: University of Rome la Sapienza, Rome, Italy, and Imperial Cancer Research Fund (ICRF) Tumour Virus Group (TVG, Department of Pathology, University of Cambridge, UK
1994-1996: ICFRF, TVG, Department of Pathology, University of Cambridge, UK
1997-2002: MRC Cambridge Centre for Brain Repair, and Laboratory of Molecular Signalling, Babraham Institute, Cambridge, UK
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Current Research
NSC proliferation and maintenance
During aging the number of neural stem cells and their ability to proliferate progressively decrease. The mechanisms underlying these changes are not clear. While proliferating stem cells can generate two different daughter cells by undergoing asymmetric cell division or identical progeny by dividing symmetrically. In addition, stem cells are capable of self-renewing as well as differentiating cell divisions. Symmetric self-renewing, asymmetric self-renewing and symmetric differentiating cell divisions will lead respectively to expansion, maintenance and depletion of the stem cell pool. In adult tissues a further layer of control of the stem cell pool homeostasis is represented by the ability of stem cells to undergo transitions between active and quiescent states of proliferation. Therefore, to fully understand how any factor may affect stem cell proliferation it is not enough to determine its mitogenic activity but also to consider how it may affect stem cells self-renewal and whether it acts at the levels of actively proliferating or quiescent stem cells.

A major obstacle to such studies is represented by the fact that due to the absence of specific markers stem cell identification is mostly based on retrospective attribution of stem cell properties. Defining characteristics of NSCs are their ability to maintain long-term self-renewal and multipotency and they are tested in vivo by means of clonal assays. Reports from several laboratories, including ours, have shown that Epidermal Growth Factor not only is the main mitogen inducing clone formation from perinatal and postnatal adult NSCs but also that levels of EGF (EGFR) receptor expression specifically increase during development in NSCs and that FGF-2 increases expression EGFR in NSCs. In addition, using a fluorescently tagged EGF and flow cytomentry (Fig. 1), we have isolated cell
populations expressing high levels of EGFR (EGFR\textsuperscript{high}) from different regions of the embryonic and adult telencephalon and have shown that they are highly enriched for NSCs. We are using this direct mean of NSC identification to investigate regional and temporal specification of NSCs and the mechanisms underlying the effect of growth factors on NSC proliferation and maintenance.

**Effect of neural activity on NSC proliferation and differentiation**

It is well known that the behaviour of NSC is not only modulated by growth factors and cell interactions but also by neural activity. Changes in neural activity affect not only the proliferation and differentiation of NSC derived progenitors but they may also regulate the proliferation of the primitive NSCs. A growing body of evidence indicates that non-synaptic release of neurotransmitters such as GABA and glutamate affects the proliferation of NSC, probably by modulation of intracellular calcium homeostasis. However, due to the problems associated with NSC identification it is not known whether these effects are direct or indirect. It is also not clear how neural activity interacts with other identified signalling components of the stem cell niche. We are using calcium imaging and electrophysiology to functionally characterize the membrane properties of isolated NSCs (Fig. 2). This functional characterisation is combined with the analysis of gene expression in NSCs of relevant neurotransmitters and the effect of their activation on NSC function.

Fig. 1: Detection of cells expressing high levels of EGFR in freshly dissociated telencephalic cells. Example of sorting plot obtained after staining with EGF coupled to alexa 488 (E-A488) and Propidium Iodide (PI).

Fig. 2: Photograph of representative EGFR\textsuperscript{high} cells taken before whole-cell patch clamp recording at 40x magnification observed with DIC.
Francesca Ciccolini

Top publications


Structure of the Group

Group Leader: Francesca Ciccolini
Postdoctoral fellows: Tiziana Cesetti, Nidhi Gakhar
PhD-Students: Kirsten Obernier, Yongjoon Suh
Undergraduate: Phillip Hundeshagen
Technicians: Gabriele Hölz-Wenig, Claudia Mandl
Current Research

Identification of epigenetically silenced tumor suppressor gene candidates in glioblastomas. (Dr. W. Mueller)

Epigenetic silencing of genes by promoter hypermethylation constitutes an alternative way of gene inactivation. In an effort to identify novel tumor suppressor gene candidates (TSG), we took advantage of the reversibility of epigenetic silencing by pharmacological manipulation of cultured gliomas with the substance 5′-aza 2′-deoxicitidine (5′-aza-dC). Combined with a genome wide, microarray-based gene expression profiling it was possible to identify novel TSG candidates, that were inactivated primarily by promoter hypermethylation. The expression profile of cells that were not treated with 5′-aza-dC where compared to the expression profile of the same cells following demethylation treatment. Genes that reveal significant up-regulation of their expression after 5′-aza-dC manipulation are candidates to be tested in ongoing studies. Methylation patterns in promoters of RUNX3 and TES have already been determined (see Fig. 1). Candidates with differential methylation in glioblastomas may prove to be relevant prognostic or predictive markers such as MGMT or future targets for tailored therapy.

Molecular diagnostics in phase I, phase II and phase III trials. (PD Dr. C. Hartmann)

We provide molecular diagnostics for the following studies:

RTC 22033-26033 (Evaluating primary chemotherapy with temozolomide vs. radiotherapy in patients with low grade gliomas with stratification for genetic 1p/19q loss: a phase III study) is coordinated by the European Organization for Research and Treatment of Cancer (EORTC). The objectives are to compare the progression-free survival of patients with low-grade gliomas treated with radiotherapy versus
temozolomide, and to compare overall survival, the incidence of late toxicity, toxic effects and the quality of life of patients treated with these regimens. Patients are stratified according to participating centre, chromosome 1p status, contrast enhancement on MRI, age, and WHO performance status. Patients are randomized to 1 of 2 treatment arms.

Lilly LY317615 (Enzastaurin (LY317615) with concomitant radiation therapy, followed by enzastaurin maintenance therapy in subjects with newly diagnosed glioblastoma - a multicenter, open-label, uncontrolled Phase II study) is coordinated by the Klinische Kooperationseinheit Neuroonkologie (DKFZ). The objectives are evaluation of progression-free survival in patients with newly diagnosed glioblastoma without promoter methylation of the MGMT gene treated with enzastaurin, and to investigate safety and tolerability. NOA-04 (Randomized phase III trial of sequential radiochemotherapy for anaplastic oligodendroglial and astrocytic gliomas WHO grade III using PCV or temozolomide) is coordinated by the department for neurology at the university Tübingen. The objectives are to determine time to second progression or time to death before second progression in patients treated either by Temozolomide or PCV chemotherapy before radiation therapy or Temozolomide or PCV chemotherapy after radiation therapy, and to validate differences in outcome of patients with anaplastic oligodendroglial and astrocytic gliomas in respect to 1p/19q status and MGMT methylation status.

UKT-05 (Radiotherapy and concomitant low-dose Indometacin and temozolomide therapy and adjuvant temozolomide therapy (one week on/one week off) in newly diagnosed glioblastoma: a phase II study) is coordinated by the department for neurology at the university Tübingen. The objective is to test if patients treated by intensified temozolomide chemotherapy in conjunction with the COX inhibitor indometacan during radiation therapy followed by weekly alternating temozolomide chemotherapy perform better than those patients in the chemotherapeutical arm of the EORTC 26981 study.

GGN-II/CP1 (German Glioma Network/Central Project 1) is coordinated by the Klinische Kooperationseinheit Neuropathology (DKFZ). Microarray-based profiling will

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**Fig. 1:** Bisulfite sequencing and MSP (methylation sensitive PCR) of RUNX3 and TES in primary cultures of glioma, U87 and controls. Presence or absence of methylated CpGs matches the results of MSP.
Black dot - methylated CpG; white dot - unmethylated CpG; M - methylated in MSP assay; U - unmethylated in MSP assay
be performed at the genomic and transcriptional level to systematically characterize molecular aberrations in glioblastomas.

**Neurofibromatosis type I (D. Reuss)**

Plexiform neurofibromas in NF1 patients are at risk for transformation to malignant peripheral nerve sheath tumors (MPNST). It is widely agreed on that the occurrence of an additional somatic mutation within the second copy of the NF1 gene in a Schwann cell population is an essential early step in the pathogenesis of both neurofibroma and MPNST. The only well-characterized function of the NF1 gene product neurofibromin is its RasGAP activity, contained in the central GAP related domain. Neurofibromin function also seems to be involved in the cAMP protein kinase A (PKA-) pathway. We aim at identification and characterisation of new Ras-dependent and Ras-independent functions of neurofibromin. Furthermore we focus on the identification of potential new therapeutic targets to target Schwann cells harbouring a somatic NF1 mutation thus allowing a therapy that does not exhibit substantial toxic side effects on other cell types. As new tumors arise throughout the life of patients with NF1, we are also interested in evaluating mechanisms of tumor immune escape in peripheral nerve sheath tumors and their implications for pathogenesis and therapeutic approaches.

**Apoptosis in malignant gliomas (Dr. M. Siegelin)**

Despite aggressive multimodal treatment, malignant gliomas are almost fatal. The resistance to apoptosis contributes to low radiation and drug sensitivity of glioma cells. The presence of high levels of anti-apoptotic factors, such as the inhibitor of apoptosis proteins (IAP) confers resistance to cancer cells. One of our interests focuses on IAP-Proteins and their antagonists. For this purpose, we analyze protein interactions between hypoxia-induced proteins and IAP proteins. Special attention is given to migration, proliferation and apoptosis of hypoxic glioma cells in respect to modifications in IAPs.

**Top publications**


**Structure of the Group**

**Group Leader:** Andreas von Deimling

**Scientists:** Christian Hartmann, Wolf Müller, David Reuss, Jörg Balß, David Capper, Andrey Korshunov

**Technicians:** Antje Habel, Ulrike Lass, Jochen Meier, Franziska Mößler, Jana Mucha, Kerstin Weber
Winfried Denk
Structure of and activity in neuronal networks

Curriculum Vitae

Degrees: 1984 Diploma in Physics 1990 Ph.D. in Physics
1981-1984: Studies in Physics, Eidgenössische Technische Hochschule (ETH), Zurich, Switzerland
1984-1989: Graduate Studies, Cornell University, Ithaca, NY, USA
1989-1991: Postdoctoral Research fellow, IBM Research Lab in Rueschlikon, Switzerland
Member of the Technical Staff, Biological Computation Research Department
since 1999: Director of the department for Biomedical Optics at the Max Planck Institute for Medical Research, Heidelberg, Germany
since 2002: Adjunct Professor, Faculty of Physics, University of Heidelberg

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Top publications

Andreas Draguhn

Functional analysis of cortical neuronal networks

Research Summary

Our group is interested in neuronal communication and the resulting functional organization of neuronal networks. We focus on memory-related systems, especially the mammalian hippocampus and neighbouring structures. Using mostly electrophysiological methods, we analyse the function and plasticity of inhibitory synapses and fast network oscillations, trying to elucidate conditions and mechanisms of information processing.

Curriculum Vitae

Degrees: 1991 MD University of Heidelberg
1999 Habilitation Humboldt University Berlin
1980-1987: Studies in medicine, physics and philosophy at Bonn University
1987-1990: Thesis work (MPI for Biophysical Chemistry, Göttingen, MPI for Medical Research, Heidelberg)
1991: Residency (PJ) in Remscheid, Germany
1992-1994: Research assistant, Dept. of Physiology, University of Cologne, Germany
1994-1997: Research assistant, Dept. of Physiology, Humboldt University Berlin (Charité)
1997: Senior research fellow, University of Birmingham Medical School, Birmingham, UK
1998-2002: Senior research assistant, Dept of Physiology, Humboldt University Berlin (Charité)
since 2002: Professor of Physiology and Chair, Institute of Physiology and Pathophysiology, University of Heidelberg, Germany

Current Research

Function and plasticity of GABAergic synapses

The complex organisation of central synapses offers multiple mechanisms for regulation and modulation of synaptic strength. We focus on inhibitory synapses in the mammalian CNS which use GABA (gamma-aminobutyric acid) as transmitter. In previous work, we and others have provided evidence that changes in presynaptic GABA content do change the efficacy of inhibitory transmission. The availability of GABA is regulated by its uptake, synthesis and degradation. The relative contribution of these functions can change in situations of enhanced or reduced activity. Increased uptake of GABA, for example, may occur under conditions of high activity when exocytosis of GABA from synaptic terminals is enhanced. This will, in turn, increase recycling of the inhibitory transmitter and thus stabilize inhibitory transmission. Prolonged periods of enhanced activity result in increased expression of the GABA-synthetizing enzyme GAD while a chronic decrease of neuronal activity leads to a down-regulation of GAD. Thus, multiple mechanisms seem to act together to adapt the efficacy of GABAergic transmission to the degree of activity in the local network. These feedback loops constitute a mechanism of homeostatic network plasticity. We are presently testing this hypothesis using various electrophysiological, histological and biochemical techniques. We also have established a model system for epileptiform discharges in mouse brain slices in vitro. We use these pathophysiological patterns of network activity for the analysis of different pharmacological approaches which aim at increasing presynaptic levels of GABA. In a third line of research, we study GABAergic signalling in the developing nervous system, focussing on inhibitory interneurons in the early postnatal dentate gyrus. This work is integrated into the joined research cluster SFB488.

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Leading questions:

• How does the presynaptic concentration of GABA affect inhibitory synaptic transmission?
• Which transport systems are involved in regulating presynaptic GABA?
• How is GABA release modulated by presynaptic ionotropic GABA receptors?
• How are tonic and phasic activation of GABA receptors regulated during ontogenesis?
• Can we identify pharmacological means to enhance presynaptic GABA content in epilepsy?

High-frequency network oscillations in the mouse hippocampus

Rhythmic activity is a key functional feature of the brain, as evident from the EEG. Meanwhile, many neuroscientists agree that such network oscillations are “meaningful” and provide an important background for temporal coding of information. The basic concept is that synchronized oscillations bind neurons into transient assemblies where co-active neurons constitute transient representations (e.g., spatial memories). In our group we focus on one type of network oscillations in the rodent hippocampus, namely “ripples” at ~200 Hz as originally described by John O’Keefe, G. Buszáki and others. We are studying high-frequency oscillations in rodent hippocampal slices in vitro. In previous work we have described the crucial role of gap junctions for neuronal synchronization at this fast scale. Presently, we are trying to elucidate the functional properties of those cells which participate in ripples. We are also addressing pathophysiological questions regarding impaired memory in depressive patients. Here, we focus on alterations of high-frequency network oscillations by corticosteroids. This work is done in cooperation with several groups joined in the research cluster SFB636.

Leading questions:

• Do members of transient neuronal assemblies have distinct electrophysiological properties?
• How does the information encoded by transient assemblies propagate through the hippocampal loop?
• How many functional assemblies do coexist in the hippocampus? How stable or plastic are they?
• Are fast hippocampal network oscillations influenced by changing levels of glucocorticoids?

Further projects:

• Role of glutamate-uptake in epileptic seizures (cooperation with Department of Pediatric Neurology);
• Function of native and mutated inwardly rectifying potassium channels (cooperation with Clinics of Cardiology);
• Pathogenetic mechanisms of Alzheimer’s disease (cooperation with Abbott GmbH, Ludwigshafen).

Fig. 1: Plasticity of GABAergic synapses
Top: GABA is synthesized from glutamate and packed into synaptic vesicles. Sources of GABA are GABA-uptake by GAT-1 and glutamate-uptake by EAAC1. These membrane-bound transporters compete with uptake of transmitters into adjacent glia cells.
Bottom: Increased strength of GABAergic transmission following high-frequency stimulation of stratum radiatum in CA1. The right panel shows enlarged miniature inhibitory postsynaptic currents following stimulation. This increase is due to the release of both, GABA and glutamate, which are subsequently taken up into the terminal and increase vesicular GABA content. Thereby, activity within the network is linked to the strength of inhibition.
Fig. 2: Analysis of fast network oscillations
Top: Schematic drawing of a neuronal assembly in CA1. The highlighted neurons are selectively activated during a network event (e.g., a high-frequency ripple oscillation) and elicit action potentials in a fixed temporal sequence. All other cells are suppressed by synaptic inhibition.
Bottom: Field potential recordings of sharp wave-ripple complexes from a mouse hippocampal slice. Right panel shows extended view of one spontaneous network event. Bottom traces show isolated unit discharges, filtered field potential with oscillation at ripple frequency and original recording.
Right: Cross-correlogram between units and field ripples showing the tight synchronization of single action potentials by the underlying network oscillation.

Top publications

Structure of the Group
Group Leader: Andreas Draguhn
Postdoctoral fellows: Martin Both, Jurij Brackack, Claus Bruehl, Valeri Lopantsev, Astrid Bertsche (guest)
PhD-Students: Florian Bähner, Gunnar Birke, Nana Duhme, Martin Oehmen, Susanne Reichinnek, Jan Schönberger, Elisa Weiss, Maura Zylla
Undergraduates: Nils Kasties, Beate Hienz
Technicians: Andrea Lewen, Nadine Zuber
Secretaries: Elke Jochum, Ute Schmitt
Development of nerve cells and generation of neuronal diversity

Research Summary
To understand how population-specific and general neuronal properties are acquired during neuronal development, we analyze the expression of genes coding for neurotransmitter-synthesizing enzymes and synaptic proteins. In sympathetic ganglia growth factors from the BMP family induce early widespread expression of both classes of genes. GDNF family ligands are later involved in the differentiation of neuronal subtypes.

Curriculum Vitae
Degrees:
1985 M.Sc.
1988 Ph.D.
2000 Habilitation
1985-1988: Thesis work (MPI for Psychiatry, Martinsried
Christian-Albrechts-Universität, Kiel)
1988-1991: Postdoctoral fellow,
Department for Biology,
University of California, San Diego, USA
1992-1998: Postdoctoral fellow in the Department for
Neurochemistry, MPI for Brain Research, Frankfurt
1999-2004: Postdoctoral fellow in
the Department for Anatomy and Cell Biology III,
University of Heidelberg
since 2000: Group Leader, Neuroanatomy, University of Heidelberg

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Current Research
In recent years, significant progress has been made to understand the generation of neuronal diversity. One of the key models used for the study of this question is the peripheral sympathetic nervous system of mammals and birds. Sympathetic ganglia contain two neuron populations which develop from the same precursor pool but differ in their transmitter, noradrenaline or acetylcholine, respectively. Analyzing the expression of genes coding for the transmitter-synthesizing enzymes, our interest is to identify growth factors and transcription factors which are crucially involved in the segregation of neuronal fates. In addition, we analyze signals regulating the expression of general neuronal genes such as those coding for synaptic proteins to understand how general neuronal differentiation and population-specific development are coordinated.

Noradrenergic induction - specifying neurons by coordinate gene expression
Noradrenergic properties are induced early during sympathetic neurogenesis by BMP growth factors and Phox2 transcription factors in birds and mammals. Comparing the expression of tyrosine hydroxylase and dopamine β-hydroxylase, we could show that these two enzymes of the noradrenaline biosynthesis cascade are expressed at the same time during sympathetic neuron differentiation. The induction by the same growth and transcription factors suggests regulation of these enzymes as a synexpression group that is conserved in evolution from birds to mammals.

Genes coding for synaptic proteins - induction of general as compared to population-specific properties
Synaptic proteins are more generally expressed in different classes of neurons than individual transmitter-synthesizing
enzymes which are restricted to certain neuron populations. They function in different aspects of transmitter release and synapse organization. Overexpression studies show that synaptotagmin I and neurexin I can be induced by BMP growth factors and Phox2 transcription factors in sympathetic precursors. Thus, it appears that induction of general and population-specific neuronal characters involves common mechanisms. In the closely related adrenal chromaffin cells, different regulation of these genes provides evidence for early segregation of neuronal and endocrine lineages.

**Generation of neuronal diversity in sympathetic ganglia**

Choline acetyltransferase (ChAT) and the vesicular acetylcholine transporter (VACHT) are two main features of cholinergic neurons which are coordinately transcribed from the cholinergic gene locus. The loss of ChAT and VACHT expression in sympathetic ganglia of c-ret mutant mice demonstrates that signaling via receptors for growth factors of the GDNF family is necessary for the development of cholinergic sympathetic neurons. Expression of c-ret in cholinergic sympathetic neurons of the chick embryo suggests that its role may be evolutionary conserved. Whereas c-ret acts late during maturation in sympathetic ganglia, factors involved in the early induction of cholinergic properties remain to be determined.
Future Research and Goals

Our interest is to understand how signalling by growth factors and regulation by transcription factors coordinates the acquisition of general neuronal features and the diversification of neuronal lineages. Analyzing developmental expression patterns of genes coding for different synaptic proteins which are expressed across many neuron populations, we ask whether different neuron classes share common differentiation pathways. We then search for the transcriptional regulators involved to understand whether general neuronal features are induced by population-specific or rather by widely expressed transcription factors. In comparison, we investigate the expression of genes coding for enzymes of neurotransmitter biosynthesis and transport which are specific for defined neuron populations. Understanding the factors involved in their expression, we hope to comprehend how general and population-specific aspects of neuronal differentiation are coordinated.

Top publications

Current Research

Visual information processing begins in the retina. Stimulus features, such as spatial extent, intensity, color, edges, motion, direction etc., are extracted for each retinal location, involving circuits built from various types (~70) of neurons. This information is coded for transmission via the optic nerve to higher visual centers. The retina is a part of the brain that can be easily isolated and stays fully functional for hours. The tissue is highly transparent and, thus, ideal for optical recordings using multi-photon microscopy (Denk & Detwiler, 1999, PNAS 96:7035-40). Furthermore, the retina is amenable to genetic manipulations, for example by viral gene transfer via intraocular injection, which, unlike for other part or the brain, does not require surgery and stereotactical targeting.

Computation of image motion direction in the retina

One type of interneuron we study (in close collaboration with P. Detwiler, University of Washington, Seattle, and W. Denk) is the so-called ‘starburst’ amacrine cell (SAC, Fig. 1). SACs are presynaptic to direction-selective (DS) ganglion cells, which fire strongly when a visual stimulus moves in a certain direction but remain silent when the stimulus moves into the opposite direction (Barlow et al., 1964, J Physiol 173:377-407). Earlier studies have shown that DS ganglion cells receive directionally tuned synaptic input (reviewed in Demb, 2007, Neuron 55:179-186). With multi-photon Ca^{2+} imaging of SAC dendrites we have shown that light stimuli moving from the soma to the dendritic tips (centrifugal, CF) elicit larger Ca^{2+} signals than motion in the opposite direction (centripetal, CP). Thus, SAC dendrites provide a directionally tuned output signal. The SAC’s dendritic sectors operate largely independently and can be viewed as processing units that signal CF motion. We studied the mechanisms underlying the computation of DS signals in SAC dendrites by measuring the electrical

Thomas Euler

Signal processing in the retina

Research Summary

Our group studies the processing of visual information in the retina using electro- and multi-photon optophysiological techniques. We focus on the question how dendrites process information. This is of particular interest in the retina, where the largest class of interneurons, the amacrine cells, typically lack axons and use their dendrites both for receiving input and making output synapses.

Curriculum Vitae


Contact

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responses to CF and CP moving stimuli using whole-cell patch-clamp recordings. Spectral analysis revealed larger non-linearities in the electrical response to CF motion than to CP motion. Dendritic DS persists in the absence of inhibitory transmission, which indicates that inhibitory network interactions are not essential for DS in SACs. The relationship between non-linearity and holding potential indicates motion direction-dependent activation of voltage-gated channels, pointing at a dendritic DS mechanism that relies on intrinsic properties. Calcium changes in SAC dendrites evoked by voltage steps and monitored by multi-photon imaging (Fig. 1) indicate that Ca$^{2+}$ channels are active at rest. The data suggests that, in part due to glutamatergic input, the distal dendrite is tonically depolarized relative to the soma. The resulting somato-dendritic voltage gradient is likely a key element in “dendrite-autonomous” DS computation, because it allows distal Ca$^{2+}$ channels to operate at a point in their activation range where the gain is maximal and small voltage deflections result in large currents.

In related experiments we map light-stimulus evoked Ca$^{2+}$ signals along SAC dendrites and apply pharmacology. Here we aim to determine the contribution of different types of Ca$^{2+}$ channels to the SAC response. Further we want to find out if intracellular Ca$^{2+}$ signaling, which is known to play a role in transmitter release from amacrine cells, contributes to the SAC’s output signals.

**Bipolar cells are parallel information channels in the retina**

Another focus of the group is on signal processing in retinal bipolar cells. For example, we studied the role of intracellular [Cl$^{-}$] gradients and their dynamics in neuronal processing (in collaboration with T. Kuner). ON bipolar cells, which are depolarized by light, have long been proposed to sustain an axo-dendritic [Cl$^{-}$] gradient that allows these cells to process GABAergic input differentially at their two ends, the dendrites and the axon terminal. To test this hypothesis we used ratiometric multi-photon microscopy and mapped the local [Cl$^{-}$] in bipolar cells expressing the genetically-encoded Cl$^{-}$ indicator Clomeleon (Kuner & Augustine, 2000, Neuron 27, 447-459). We found that ON bipolar cells generate [Cl$^{-}$] gradients with high [Cl$^{-}$] in their dendrites (Fig. 2), allowing these cells to receive via the same neurotransmitter, GABA, excitation at their dendrites and inhibition at their axon terminal. Dendritic [Cl$^{-}$] is particularly high in so-called blue-cone bipolar cells, which receive input exclusively from short-wavelength (‘blue’) sensitive cones. To find
out if high dendritic [Cl⁻] in these bipolar cells is playing a particular role in chromatic processing, we now study the blue-cone circuit in mouse retina with both anatomical (in collaboration with Silke Haverkamp, MPIH, Frankfurt) and physiological techniques.

Fig. 2: Clomeleon-expressing bipolar cells (A) injected with fluorescent dye (red) and imaged with multi-photon microscopy (fixed section; Clomeleon labeling in green). Several retinal layers can be distinguished: OPL: outer plexiform layer; INL: inner nuclear layer; IPL: inner plexiform layer; double-labeled bipolar cell in yellow. Fixed flat-mounted retina (B) co-labeled with antibodies against GluR5 (red) revealing cone pedicles. A subset of Clomeleon bipolar cells (*) contacts only few pedicles (examples encircled), which belong to blue-sensitive cones [5]. Blue cone-selective bipolar cells (C) marked by asterisks. Left: YFP fluorescence; right: map of intracellular Cl⁻ concentration ([Cl⁻]). [Cl⁻] is high in the varicosities (arrowheads), where cone pedicles are contacted. Traces showing dendritic (red) and somatic (blue) [Cl⁻] (D) in a blue cone-selective bipolar cell during GABA application and during co-application of GABA antagonists. The transient decrease in dendritic [Cl⁻] suggests that GABA mediates depolarization in blue cone-selective bipolar cells. (Scale bars: 20µ; a-c: collapsed image stacks; d: traces are averages of 3 trials)

**Structure of the Group**

**Group Leader:** Thomas Euler

**Postdoctoral fellows:** Xavier Castell, Julia Mack-Bucher

**PhD-Students:** Tobias Breuninger, Minggang Chen, Sun Le

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**Top publications**

- Huang, L., et al. (2003). The novel G protein subunit Ggamma(13) is co-expressed with Galpha(o), Gbeta(3) and Gbeta(4) in retinal ON bipolar cells. J. Comp. Neurol. 455, 1-10.
Christian Fiebach

Cognitive Neuroscience: Neural mechanisms of higher cognitive functions

Research Summary
We use modern, non-invasive neuroimaging techniques such as functional magnetic resonance imaging and electro- and magnetoencephalography to explore the neural mechanisms underlying higher cognitive functions in humans. Our main areas of research involve cognitive functions such as language, working memory, decision making, and goal directed behavior. In addition, we are particularly interested in specifying the neural mechanisms underlying individual differences in these cognitive functions.

Curriculum Vitae
Degrees: 1998 Diploma (M. Sc.)
2001 Ph.D. (Dr. rer. nat. Psychology)
2001-2003: Postdoctoral fellow, MPI for Human Cognitive and Brain Sciences, Leipzig
2003-2006: Postdoctoral fellow, Department of Psychology & Helen Wills Neuroscience Institute, University of California, Berkeley, USA
since 2006: Group Leader, Emmy-Noether Research group: “Neurocognition of individual differences”, Departments of Psychology, Neuroradiology and Neurology, University of Heidelberg

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Current Research
Our research aims at understanding the neural mechanisms that underlie higher cognitive functions in humans, such as language, working memory, or goal-directed behavior in general. To this end, we employ functional magnetic resonance imaging to identify brain regions that are specifically activated under certain, highly controlled cognitive demands. In addition, we also explore how different brain regions are functionally coupled during specific task demands, using statistical methods that exploit the functional connectivities between brain regions.

Neural bases of individual differences
Neural mechanisms underlying inter-individual differences in working memory capacity and higher cognitive abilities (intelligence, complex problem solving) are poorly understood. Three potential sources of variability may contribute to these higher cognitive abilities: variability in component processes of cognition, personality differences, and variability of dopamine neurotransmitter activity. This research project integrates these at present mostly unconnected research strands, and explores their relations and their contribution to higher cognition at a neurocognitive level.

Cortical representations of behavioral goals
The ability to plan and solve complex problems is crucial for intelligent human behavior in a multitude of domains such as school, work, and everyday life. Planning and problem solving are driven by goals: We have problems to solve when our goals are not immediately achievable. Such complex behaviors therefore require the ability to maintain goals and subgoals over time, to resolve goal conflicts, and to adapt behavioral goals to environmental changes. Human functional neuroimaging studies
show that frontopolar cortex is strongly activated when planning demands are high. This may be a result of the need to perform one or more subgoal tasks in the service of a primary task goal: Subgoal processing, or ‘cognitive branching’ selectively activates the frontopolar cortex. It is unlikely that frontopolar cortex processes goals and subgoals in isolation; rather, it is assumed that frontopolar cortex functionally interacts with prefrontal and other task-relevant brain regions. In this project, we use functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) to investigate the neurocognitive organization of various aspects of goal management and goal maintenance.

**Neurocognition of verbal working memory**

Verbal working memory is often characterized in the context of the multicomponent model of Baddeley and collaborators. In this model, maintenance of linguistic information in verbal working is strictly based on phonological codes. This postulate of a special purpose mechanism for verbal working memory is inconsistent with working memory models based on neurophysiological data, such as Fuster’s active memory model. In work started at the D’Esposito Neuroimaging Laboratory at UC Berkeley, we use fMRI to investigate the contribution of different language systems (i.e., visual-orthographical, lexical, semantic, phonological) to verbal working memory maintenance (e.g., Fiebach et al., 2006; cf. Figure 1). The aim of this work is to model the neurocognitive bases of verbal working memory using domain-general, neurophysiologically plausible organizational principles.

**Brain mechanisms of emotion x cognition interaction**

Traditionally, cognitive psychologists and cognitive neuroscientists investigate mental processes in isolation. However, from our everyday experience, we know that emotional states and arousal can greatly influence our actual performance. For example, in a recent experiment, we demonstrate that performance in a working memory task is modulated by the incidental presence of positive and negative emotion in the stimulus materials (Fig. 2). We assume that the influence of emotion on cognition is mediated by functional interactions of neuroanatomical systems involved in these processing domains. We use fMRI and multivariate analyses of functional connectivities to explore how cognition and emotion interact in working memory and decision making.

Fig. 1: (left panel) Word-sensitive region in left inferotemporal cortex. (right panel) Working memory modulation of brain activation of the inferotemporal region displayed in (left panel), dependent on stimulus type (words vs. pseudowords) and working memory load (green: 2 items; orange: 5 items)

Fig. 2: Emotion by cognition interaction in a verbal working memory task. Percentage of correct responses dependent on working memory load (2 words vs. 5 words) and valence (red: negative; grey: neutral; green: positive). A valence-by-cognition interaction shows that under low cognitive demands (i.e., low working memory load), subjects perform better for positive and negative relative to neutral items. Under high cognitive demand, however, only negative emotion has a beneficial influence on performance. This suggests the existence of mechanisms that prioritize potentially threatening information, even under high cognitive resource usage.
Functional neuroanatomy of the language system

The ability to produce and understand language is one of the greatest cultural achievements of mankind. Using techniques such as functional magnetic resonance imaging, electroencephalography and magnetoencephalography, we study neural mechanisms underlying the recognition of written and spoken words, as well as the mechanisms underlying the comprehension of complex syntactic structures (i.e., complex sentences). In Figure 3, data is presented that demonstrates the involvement of prefrontal cortex in interference resolution during word recognition, in cases where the orthographic neighborhood of a letter string stimulus conflicts with its lexical status (Fiebach et al., 2007).

Top publications


Fig. 3: Left dorsolateral prefrontal cortex area modulated by lexicality (words vs. nonwords) and orthographic neighborhood size (N; small vs. large). Behaviorally, it has been shown that a large orthographic neighborhood, i.e., the presence of many words that are similar to the target nonword, renders lexical decisions difficult. In the present fMRI study, we demonstrate that the left dorsolateral prefrontal cortex is particularly strongly activated for nonwords with a large neighborhood, presumably in an effort to resolve the conflict between target nonword and global lexical activation induced by the target’s orthographical neighbors.
Current Research

Learning, neuronal plasticity and psychopathology

Research on this topic targets the development and maintenance of emotional memories and their neuronal correlates in the context of psychopathology. Herta Flor is the spokesperson of DFG collaborative research grant 636 on „Learning, memory and neuronal plasticity: Implications for psychopathology“. Rather than taking a nosological approach to mental disorder, which leads to the problem of overlapping psychopathological characteristics, similarities and differences of the underlying mechanisms of learning and neural plasticity across a variety of disorders are examined. The Flor group pursues the role of basic associative and non-associative learning mechanisms and their neuronal correlates, which are fundamental for the understanding of disorders characterized by hyperexcitable neuronal fear circuits (e.g., post-traumatic stress disorder, social phobia), disorders characterized by a deficit in associative learning of aversive consequences (e.g. psychopathy) as well as disorders characterized by altered appetitive and aversive motivational processes (e.g. depression, bipolar disorder, addiction). One major theme is the relative contribution of learning processes and genetic variables in the development of these disorders. Behavioral and combined pharmacological-behavioral interventions, that address learning related maladaptive plasticity are developed and their influence on cortical and subcortical plasticity are studied.

The group is also involved in a collaborative EU grant that studies reinforcement-related learning processes, their neuronal correlates and genetic determinants with respect to the development of mental disorders in adolescents. Finally, aging-related alterations in memory and learning and associated neuronal plasticity are also investigated.

Herta Flor

Learning and neuronal plasticity

Research Summary

Our research focuses on the interaction of brain and behavior, in particular the question how behavior and experience influence neural processes and how neural processes alter behavior and experience. A special focus is on the role of implicit learning and memory processes in the development and maintenance of mental and psychophysiological disorders. This includes research on memory processes in chronic pain, tinnitus, anxiety disorders, addiction and depression. The methods that are employed range from experimental psychology to noninvasive brain imaging and peripheral psychophysiology.

Curriculum Vitae


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Learning and neuronal plasticity in chronic pain and abnormal body sensation

The Flor group was the first to describe the role of cortical reorganization for the development and maintenance of phantom limb pain as well as other pain syndromes such as chronic back pain and fibromyalgia. Within the framework of the DFG Clinical Research Group “Learning, Plasticity and Pain” (CRG 107) and within two BMBF-funded collaborative grants “Pain Perception” and “Neuropathic Pain” cortical and subcortical alterations related to chronic pain are examined and novel treatment options that target the extinction of central pain memories by behavioral and pharmacological interventions are developed and tested. Another focus is the development of indicators for differential assignments of treatments to psychologically and neurobiologically characterized subgroups of pain patients. In this context we are also studying how early pain experience may affect the processing of nociceptive input in children and how this may induce neuronal plasticity of the somatosensory system. A related EU grant focuses upon the development of innovative procedures to assess phantom phenomena and the exploration of the bases of phantom perception and phantom pain. The differential contribution of frontal and parietal brain areas to painful versus nonpainful phantoms and related body illusions is examined.

Novel brain-based interventions that use brain-computer interfaces, transcranial magnetic stimulation, mirror treatment or virtual reality are examined in their capability to alter central processes involved in pain and abnormal somatosensory phenomena.

Neuronal plasticity in the auditory system

One important line of research concerns the contribution of neuronal plasticity in the auditory system to the development and maintenance of Tinnitus symptoms. After having demonstrated that Tinnitus phenomena are associated with a reorganization of the tonotopic map in primary auditory cortex and general cortical hyperexcitability, we have developed several new
approaches to the treatment of Tinnitus. These include behavioral auditory discrimination and extinction trainings with or without additional pharmacological interventions designed to enhance extinction processes. Our most recent research focuses on the interaction of limbic and auditory areas in the processing of emotional stimuli in Tinnitus patients and factors that contribute to the long-term-development of Tinnitus. This research is currently being extended to focus on affective-sensory interaction and the brain processes involved in these interactions in general.

Method development

In all research areas methods of experimental psychology are combined with noninvasive brain imaging, brain stimulation and peripheral psychophysiological methods as well as genetic testing and behavioral and pharmacological interventions to comprehensively study brain-behavior interactions in healthy humans and patients. A special focus is on the development of multimodal imaging methods that integrate structural and functional aspects and trace also dynamic alterations of cortical and subcortical changes related to the perceptual phenomena studied by the group. This also includes the analyses of the interaction between peripheral and central physiological changes. These methodological developments are made in close interaction with the members of the South German Brain Imaging Center that includes researchers from the Universities of Mannheim and Heidelberg as well as the Central Institute of Mental Health.

**Top publications**


**Structure of the Group**

| Group Leader: | Herta Flor |
| Postdoctoral fellows: | Beate Herbert, Christiane Hermann, Eugen Diesch, Carsten Diener, Martin Diers, Alexander Kroll, Anita Kult, Simone Lang, Christoph Oberthuer, Kati Thieme, Michèle Wessa |
| PhD-Students: | Isabelle Bomba, Wenke Brusniak, Jens Foell, Johanna Hohmeister, Sandra Kamping, Claudia Liebscher, Slawomira Lipinski, Maurice Moayer, Julia Ofer, Stephanie Ridder, Iris Wollgarten, Pinar Yilmaz, Katrin Zohsel |
| Technicians: | Annette Hornbach, Michael Rehm, Birgül Sarun, Claudia Stief, Heike Schmidt, Artemis Tsoupas, Angelika Wieters |
Signal transduction in sensory neurons

Research Summary
We examine the molecular pathways of signal transduction in primary afferent neurons of the mammalian olfactory and nociceptive systems. We concentrate on the regulation of transduction channels and the generation of excitatory receptor potentials. Of particular interest for us is the question how these neurons adjust their sensitivity and bring about adaptation or sensitization.

Curriculum Vitae
Degrees: 1985 Diploma in Biology  
1989 Ph.D.  
1997 Habilitation in Zoology, University of Cologne  
1980-1985: Studies of Biology at the University of Konstanz  
1985-1989: PhD Student at the University of Otago Medical School, Dunedin, New Zealand  
1989-1992: Postdoctoral fellow at the Department of Physiology, University of Saarland, Homburg/Saar  
1992-2002: Postdoctoral fellow at the Institute of Biological Information Processing, Jülich Research Center  
since 2002: Professor for Molecular Physiology at Heidelberg University

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Current Research
Regulation of cAMP-gated transduction channels in olfactory sensory neurons
Upon detection of odorants in the inhaled air, a transduction cascade is initiated in the sensory cilia of olfactory sensory neurons. cAMP is synthesized and opens calcium-permeable transduction channels. These channels are gated by direct binding of cAMP, and they are regulated by calcium/calmodulin. Activation and inhibition are mediated by modulatory channel subunits which determine cAMP-sensitivity and calmodulin binding. We explore the allosteric regulatory mechanisms that operate in this channel. We perform structure-function studies on heterologously expressed channels carrying mutations in key domains of the heteromeric channel protein.
We are particularly interested in the formation of a regulatory complex that consists of two cytoplasmic channel domains and calmodulin. We explore the stoichiometry of this complex in vitro by studying the assembly of calmodulin with peptides representing the relevant channel domains. Our goal is to understand the regulation of the cAMP-gated channels by calcium.

Chloride-mediated signal amplification in olfactory sensory neurons
Most of the odor-induced receptor current in olfactory sensory neurons is carried by chloride ions. We characterize the properties of calcium-activated chloride channels using a combination of electrophysiology and single-cell fluorescence recording (Fig. 1). We examine the role of these channels in stimulus-induced excitation and the molecular mechanisms of chloride accumulation which form the ionic basis of the excitatory chloride currents.
**Chloride-dependent sensitization of nociceptors by inflammatory mediators**

Just like olfactory neurons, nociceptive neurons of the pain system can use chloride-dependent signal amplification (Fig. 2). But in contrast to olfactory neurons, nociceptors seem to adjust the efficiency of amplification through inflammatory mediators. We investigate this dynamic regulation of sensitivity as a novel concept for the generation of inflammatory hyperalgesia.

We use an *in vitro* inflammation model to study the effects of inflammatory mediators on chloride homeostasis in dorsal root ganglion neurons. Applying the inflammatory agents increases net chloride uptake, raises the intracellular chloride concentration, and increases the driving force for depolarizing chloride currents through calcium-activated chloride channels. Our goal is to quantify the contribution of these chloride currents to the generation of the peripheral nociceptive signal.

**Fig. 1: Recording calcium-dependent chloride currents**
To activate calcium-activated chloride channels, a cell is filled with a compound that releases calcium upon illumination (caged calcium) and a fluorescent calcium indicator (fluo-5F). A series of UV flashes causes a step-wise increase of the intracellular calcium concentration which, in turn, increases the fluorescence signal (F). Triggered by the increasing calcium level, chloride channels open and conduct a chloride current (I) out of the cell. In olfactory sensory neurons, this depolarizing chloride current leads to electrical excitation.

**Fig. 2: Chloride imaging in somatosensory neurons**
Using the chloride-sensitive fluorescent dye MQAE, the intracellular chloride concentration was monitored by two-photon fluorescence lifetime imaging microscopy (2P-FLIM) in an intact dorsal root ganglion. The chloride concentration within the cytosol (corresponding to the area between the two circles) differs between individual neurons. Some neurons have low (~20 mM, blue), some medium (~50 mM, green), some high (~75 mM, red) chloride levels. 2P-FLIM measurements in the presence of inflammatory mediators (PGE2, ATP, NGF, bradykinin) reveal a widespread increase of chloride levels among somatosensory neurons.

Our work, so far, shows that the two types of primary afferent neurons - olfactory sensory neurons and nociceptors - share an unusual mechanism for signal amplification. These neurons are able to actively accumulate chloride, and to employ an outward-directed chloride gradient to generate a depolarizing chloride efflux. This chloride current boosts the receptor potential and promotes electrical excitation. We study proteins which mediate chloride homeostasis in the sensory neurons. In particular, we examine the regulation of electroneutral chloride transporters
Stephan Frings

(NKCC1 and KCC2) which provide the driving force for the depolarizing chloride currents. Our data indicate that the sensory cilia of olfactory receptor neurons accumulate chloride through the activity of NKCC1 as well as through chloride-bicarbonate exchange. This electroneutral chloride uptake loads the cilia with chloride, and the electrogenic chloride efflux amplifies the receptor potential 10-fold during odor detection. A central problem for research of anion-based signal amplification has yet to be solved: The gene that encodes the key protein - the calcium-activated chloride channel - is not identified. In the absence of any structural information it is difficult to explore the amplification mechanism in detail. In collaboration with the DKFZ, we work on the molecular identification of this channel in olfactory receptor neurons. Using a proteomic approach, we have isolated the sensory cilia from olfactory receptor neurons and characterized the membrane proteins in the ciliary membrane by mass spectrometry. We are currently searching for the calcium-activated chloride channel in this ciliary proteome. Once the chloride channel is identified, it will be possible to explore anion-based signal amplification on the level of channel regulation and protein-protein interaction. This will open new possibilities to study sensory transduction in the olfactory and nociceptive systems. Thus, our group works on sensory transduction on the levels of protein structure, ion transport, and cellular physiology. Methods range from protein biochemistry to electrophysiology and fluorescence microanalysis.

Top publications


Structure of the Group

Group Leader: Stephan Frings
Postdoctoral fellows: Frank Möhrlen
PhD-Students: Philipp Daiber, Katharina Funk, Thomas Hengl, Semir Jeridi, Nicole Ungerer, Kerstin Vocke, Clemens Waldeck
Technicians: Gabriele Günther
Animal models of psychiatric disorders

Research Summary
Using a translational approach we have established mouse models for affective disorders by two strategies:
i) behavioral studies of transgenic mouse strains with mutations of genes that have been implicated in the pathogenesis of depression, e.g. glucocorticoid receptors;
ii) acute or chronic stress procedures. Our goal is to induce defined alterations of the animals’ emotional behaviors in a panel of specific behavioral tests that could serve to model essential features of complex psychiatric diseases, such as major depression.

Curriculum Vitae

Degrees: 1988 MD (Neuropathology)
1996 Habilitation in Neuropathology, University of Heidelberg
1983-1990: Medical School, University of Heidelberg, University of Illinois and Cornell University (Ithaca, N.Y., USA)
1990-1995: Residency in Neuropathology, University of Heidelberg
1996-1998: Research fellow, Dept. of Molecular Biology of the Cell (Prof. G. Schütz), DKFZ Heidelberg
1999-2005: Residency in Psychiatry, CIMH
2004: Extraordinary Professor of Psychiatry, Clinical Faculty Mannheim, University of Heidelberg
since 2004: Oberarzt (Consultant) at the the Central Institute of Mental Health Mannheim
since 2004: Head of RG Behavioral Biology of Affective Disorders at the CIMH

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Current Research

The role of glucocorticoid receptors in specific neuronal systems for emotional behavior: a combined transgenic and environmental approach (within SFB 636)

Glucocorticoid receptors (GRs) have been postulated to play an important role in affective disorders such as depression. However, it is not known where in the brain increased corticosteroid levels or altered GR functioning may have deleterious effects. These questions can be studied using conditional transgenic techniques in combination with specific mouse models for affective disorders. During the first grant period we have characterized behaviorally and neuroendocrinologically two strains of mice underexpressing (GR+/-) and overexpressing (YGR) glucocorticoid receptors throughout the nervous system. We could show that GR+/- mice have a predisposition to develop typical stress-induced depression-like changes (Fig. 1), while YGR mice turned out to be stress-resistant. Searching for potential molecular correlates (apart from GR) for this altered behavior we found a downregulation of BDNF in “depressive” GR+/- mice (Fig. 1) and an upregulation in YGR animals, which is in agreement with the so-called neurotrophin hypothesis of depression.

Since the GR gene is dysregulated during the whole ontogenesis in these strains, it is not clear, when and where (in the brain) a dysbalance of GR is important for affective disorders. Furthermore it is not known which pathophysiological and pathobiochemical alterations occur in these brain regions. These questions should be investigated during the next grant period using conditional mouse strains with specific alterations of GR expression, i.e. in the forebrain, the serotonergic system and the noradrenergic system. To identify/rule out a developmental role of GR expression, we will study strains with a constitutive knockout in these brain regions as well as an inducible knockout. Furthermore we will investigate
the effect of early and late environmental manipulations (i.e. maternal care and enriched environment) in GR compromised mice to identify potential gene-environment-interactions inducing alterations of emotional behaviors. As a first line of evidence we will study the behavior of these mice in specific depression models (e.g. learned helplessness, chronic stress) and tests for emotional behaviors. In a second step we will analyze changes in neural plasticity that could correlate with the behavioral alterations by biochemical (monoaminergic systems), pathophysiological (electrophysiology) and neuroanatomical (spine morphology) methods. In an alternative approach we plan to study in which brain areas the GR is activated following environmental and pharmacological manipulations. For this purpose we will generate a “GR-reporter mouse”, using a construct in which a GR response element (GRE) drives the expression of a reporter enzyme whose activity can be measured in vitro and in situ.

The Role of Glutamate und Glutamate Receptors in Mouse Models for Emotional Behaviors and Mood Disorders (DFG GA427/8-1, in cooperation with R. Sprengel, MPI Heidelberg)

Recent studies have indicated that the neurotransmitter glutamate is involved in the pathophysiology and treatment of mood disorders (Fig. 2). The goal of this proposal is to better understand the role of glutamate in mouse models for affective disorders. We would like to find out to which extent just levels of glutamate (impaired reuptake) are important and how specific alterations of glutamate induced signalling underlie stress-related “disease states” or stress-resistance, respectively. We subject different genetically modified mice with impaired glutamate homeostasis and glutamate signalling to behavioral, neuroendocrinological, molecular and pharmacological studies. A variety of mutant mice with specific deficits in glutamate uptake (EAAT-1 and EAAT-2 transporters) or glutamatergic neurotransmission, e.g. of ionotropic (AMPA- and NMDA-type) glutamate receptors (GluR-A, GluR-C, NR-1, NR-2A) will be analysed. All mice will be subjected to stress-induced depression models (learned helplessness, chronic stress) and a testing battery for emotional behaviors. We will use a step by step approach to test the “glutamate hypothesis” of mood disorders, starting with conventional mutant strains demonstrating the maximum effect of gene deletions (glutamate receptors/transporters genes) on emotional behavior. This will identify those genes that contribute to a behavioral phenotype. We will then identify the brain regions (e.g. hippocampus, forebrain) where the genes of interest are relevant by restricting the gene deletions to specific brain areas. As a proof of concept we will try to rescue specific behavioral phenotypes by a transgenic or alternatively a virus-mediated gene transfer. We will investigate whether glutamatergic drugs that shape emotional behavior in murine depression models have altered effects in mice with genetically depleted glutamate receptors. We will try to identify alterations in molecular/biochemical/cellular signalling pathways that have been postulated for the pathogenesis or pathophysiology of depression. Altogether, these experiments will improve our knowledge of the neurobiological processes underlying the pathophysiology of mood disorders, and may indicate novel targets for antidepressant therapy.
**Top publications**

- Chourbaji, S., et al. (2008). AMPA receptor subunit 1 (GluR-A) knockout mice model the glutamate hypothesis of depression. Faseb J. 22, 3129-3134.

**Structure of the Group**

**Group Leader:** Peter Gass  
**Postdoctoral fellows:** Sabine Chourbaji, Dragos Inta, Nada Ben Abdallah  
**PhD-Students:** Miriam Vogt  
**Technicians:** Christiane Brandwein, Christof Dormann

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Fig. 2: Hypothetical scheme of abnormal glutamatergic neurotransmission in mood disorders  
Glu=glutamate; Gln=glutamine; mGluR=metabotropic glutamate receptor; EAAT=excitatory amino acid transporter; CREB=cyclic adenosine monophosphate response binding element protein; BDNF=brain derived neurotrophic factor.
Darren Gilmour

The role of chemokine-mediated tissue migration in generating mechanosensory organs in the zebrafish lateral line

Research Summary

The coordinated migration of groups of cells is a hallmark of morphogenesis. We have developed the zebrafish lateral line primordium as a model system for the study of this poorly understood process. By combining in vivo imaging with functional approaches, such as genetic mosaics, laser nanosurgery and small molecule inhibitors, we have begun to address the chemical and mechanical cues that coordinate cell movement in the PNS.

Curriculum Vitae

Degrees: 1991 B.Sc. 1996 Ph.D.
1991-1996: Thesis work, Gurdon Institute, Cambridge University, UK
1996-2004: Postdoctoral fellow, MPI for Developmental Biology, Tübingen
since 2004: Group Leader at EMBL Heidelberg

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Current Research

Mechanical regulation of sensory organ morphogenesis in the zebrafish lateral line (Virginie Lecaudey)

We have addressed the relationship between the formation of rosette-like neuromast organs and the formation of sensory hair cells at their centre. Both of the processes are initiated while the primordium is still migrating. Surprisingly, we have found that the assembly of cells into organ precursors precedes the focussing of proneural genes to their centre. Furthermore, direct mechanical perturbation of tissue migration leads to predictable changes in the size and pattern of the neuromast organs deposited.

Internal FGF-signaling coordinates cell movements within moving tissues (Gulcin Cakan)

Our previous work has shown that a small number of Cxcr4-expressing “leader” cells are able to guide the migration of Cxcr4-deficient “followers”. In a search for potential “internal” guidance molecules, we have identified a pair of FGF-family ligands (FGF3 and FGF10) that are essential for the coordinated movement of cells within this tissue.

Deconstructing a migrating tissue by laser nanosurgery (Petra Haas)

The vast majority of migrating cell move in cohesive groups and the lateral line primordium is no exception. It moves as a migrating epithelium, with cells connected via adherens and tight junctions. In order to address the role of cell-cell contacts in allowing coordinated cell movement within tissues, we have performed a comprehensive series of laser dissection experiments using a computer controlled, pulsed “laser-knife” developed by the Stelzer group at EMBL. This has revealed a suprising role for dynamic cell-cell interactions in determining directionality in this context.
SDF1a coordinates tissue migration through the spatially restricted activation of chemokine receptors Cxcr7 and Cxcr4b (Guillaume Valentin, Ana Fernandez-Minan)

We have previously shown that the lateral line primordium requires spatially-restricted receptors to mediate the response to an external path of the chemokine SDF-1. Cxcr4 is required in leading regions to stretch and guide the tissue along the SDF-1 source whereas Cxcr7 is expressed at the trailing edge from where neuromasts are deposited.

Current work is focused on how the combined expression of these SDF1 receptors allows these different behaviours. One approach we are currently taking is to generate transgenic reporters that allow Cxcr4 and Cxcr7 signaling to be observed in vivo.

Fig 1: Time-lapse showing rescue of lateral line primordium migration by a small number of transplanted Cxcr4b expressing “leaders” cells (red).

Fig 2: Triple-staining showing the lateral line primordium (green), Cxcr4b mRNA (blue) and Cxcr7 (red). These chemokine receptors are expressed overlapping spatial domains that correlate with different cell behaviours within the migrating tissue.

Top publications


Structure of the Group

Group Leader: Darren Gilmour
Postdoctoral fellows: Ana Fernandez-Minan, Andreea Gruia, Petra Haas, Virginie Lecaudey
PhD-Students: Gulcin Cakan-Akdogan, Guillaume Valentin
Technician: Andreas Kunze
Research Summary
Research in our group is concerned with two major areas in biology: Developmental neurobiology and the evolution of body plans. Using molecular approaches we study these questions in basal metazoans (cnidarians) on the comparative and functional level. Our principal goal is to understand the basic genetic mechanisms by which the nervous system evolved, and how these developmental processes are related to the organisation of the Bilateria. Of further interest are nematocytes, a highly sophisticated neuronal cell type found exclusively in cnidarians.

Current Research
Cnidarians an the origine of lower Metazoans
The origin of the nervous system and the evolution of multi-cellular animals (Metazoa) from single cell organisms is largely unclear at present. The first animals that developed a nervous system are the cnidarians (coralls, sea anemones and jelly fish). These ancient animals (>500 million years ago) have a simple nerve net and they are important to understand the origin of a central nervous system (CNS). To trace back the evolution of the nervous system, we are analysing developmental processes and neurogenesis in the freshwater polyp Hydra and the sea anemone Nematostella. Genome projects in Hydra and Nematostella have now revealed the existence of an extensive set of conserved gene families and developmental pathways regulating embryogenesis throughout higher metazoans like worms, flies and vertebrates.

Wnt and BMP signalling
The molecular nature of signalling centers (organizers) plays a pivotal role in the origin and evolution of metazoan body axes. Our lab has cloned wnt/wg genes from Hydra and Nematostella (Fig.1). The families of Wnt/Wingless secreted proteins act as short-range inducers and long-range organizers in axis formation, organogenesis and tumour formation in vertebrates. In cnidarians, the canonical Wnt signalling pathway is expressed in the polyp’s oral signalling center (organizer), which corresponds to the blastopore of metazoan embryos. In Nematostella different wnt genes form staggered expression domains along the oral-aboral axis (“wnt-code”), governing axial differentiation, and neuronal differentiation of early multi-cellular animals. Notably, an orthologue to vertebrate dickkopf-1, -2, and -4 genes is expressed in the body column, complementary to the expression domain of the wnt/β-catenin/tcf/brachyury genes. Dickkopf proteins, which are major Wnt antagonist
in vertebrates, also act in cnidarians and we propose that they also promote neuronal differentiation. We are currently testing these hypotheses by using transgenic lines and promoter constructs for \textit{wnt}, \textit{dkk}, and \textit{bmp} genes as well as by testing corresponding recombinant \textit{Hydra} and \textit{Nematostella} proteins.

\textbf{Wnt signalling and cell adhesion}

To analyse the potential link between cell signalling and cell adhesion during organizer formation we have identified a \textit{Hydra} Cadherin (HyCad) by its physical interaction with \textit{Hydra} \(\beta\)-Catenin in a yeast two-hybrid screen. We propose that a basic function of the Cadherin-Catenin complex was to stabilize an autocatalytic feedback loop leading to the definition of signalling centers. We test this hypothesis by ectopic expression and promoter analysis of both genes.

\textbf{The evolutionary origin of the central nervous system}

The cnidarian nerve net is diffuse and no brain-like structures have been reported. The goal of our work is to uncover the molecular mechanism of neurogenesis in cnidarians and to understand how it is related to the origin, evolution and patterning of neurogenesis among the metazoans (Fig. 2).

\textbf{Comparisons between vertebrates and insects have revealed a great deal of conservation also in the genetic control of neurogenesis.} This suggests that the common ancestor of Bilateria used the same set of genes to regulate neurogenesis. Yet, not all genes seem to be conserved between insects and vertebrates. Dkk proteins for example, which are important antagonists in the Wnt pathway and play a role in suppressing the anti-neuronal function of \textit{wnt} genes, were not identified in insects and nematodes. Furthermore, \textit{zic} genes, which have a conserved role in neurogenesis in all vertebrates downstream of Chordin and upstream of bHLH transcription factors, have not been reported to act in neurogenesis of insects. We are therefore interested to learn how these regulatory genes are activated by the cnidarian patterning system.

\textbf{Imaging the dynamics of cnidarian neuronal differentiation}

We use stable transgenes of \textit{Hydra} interstitial cells to analy-
ze neuronal differentiation in embryos, intact polyps, and aggregates. Neuronal cells arise from pluripotent interstitial stem cells that differentiate into several populations of neuronal cells (ganglion cells, sensory neurons and nematocytes). Commitment of these cells occurs in the body column and precursor cells can migrate to the sites of final differentiation. This stem cell system is highly reminiscent to the neural crest system in vertebrates. We analyze the behaviour of proneuronal cells along the oral aboral axis in vivo and under various conditions by using confocal laser scanning microscopy (CLSM), spinning disc confocal microscopy, and 2-photon microscopy. We also analyze the mechanisms of recruitment of proneuronal cells in Nematostella. This is particularly exciting since previous work has shown that neuronal cells arise in more basal cnidarians directly from precursor cells located in the ectodermal epithelium. Important questions answered by this set of experiments are, whether precursor cells arise by asymmetric cell division, whether they undergo additional proliferation steps, and how the pattern of neuronal and nematocyte recruitment is related to the axial patterning of the polyp.

Proteom of nematocytes

The most conspicuous character of Cnidarians is the presence of nematocysts, which are complex exocytotic organelles formed inside a specialized neuronal cell type, the nematocyte (stinging cell). Nematocysts are used for catching prey, and their discharge is one of the fastest events in biology (we showed that the initial phase of discharge is 700 nanoseconds short generating an acceleration of 6,000,000 g). The forces sustained during explosive discharge require extraordinary mechanical strength and elastic modulus in the capsular wall material. Although we made substantial progress in unravelling the molecular structure of nematocysts, the molecular assembly is only partially understood. Based on our cloning of minicollagens and NOWA we now analyze the assembly process in a proteom project (2D-gel electrophoresis, peptide mass fingerprinting, and tandem-MS). In parallel we generate antibodies and GFP-fusion constructs to analyze the assembly process.

Top publications


Structure of the Group

Group Leader: Thomas Holstein
Senior scientists: Toshitaka Fujisawa, Suat Özbek, Gabriele Petersen
Postdoctoral fellows: Barbara Kostron, Ulrike Engel, Anne Kuhn, Yukio Nakamura, Hiroshi Watanabe
PhD-Students: Patrizia Adamcyk, Prakasch Balasubramanian, Bianca Bertulat, Tobias Lengfeld, Robert Mättner, Martin Rittaler
Technicians: Aurelia Procol, Dagmar Sealey,
Current Research

Alzheimer’s disease (AD) is characterized by a gradual neuronal degeneration and loss of synapses. The microtubule associated protein Tau and the Amyloid Precursor Protein (APP) were identified as key players in the pathology of AD, but the reasons for the loss of synaptic connections and the sequential steps of neurodegeneration in the course of AD are not understood yet. The APP gene family consists in mammals of APP, APLP1 and APLP2, and we could show that it functions in diverse biological processes, such as cell adhesion, regulation of synaptic function and axonal transport. We assume that deregulation of the normal APP physiological function causes neurodegeneration and loss of synapses that might be causative for AD and possibly explain the high risk of aging in AD.

Fig.1: Modell of APP function at the synapse
The members of the APP gene family, APP, APLP1 and APLP2, form homo- and heterotypic transdimers at the synapse. Further sAPP, promoting neuronal outgrowth, is secreted in the synaptic cleft. Both features argue for an important role of APP/APLPs in synaptogenesis and/or synaptic plasticity.

Stefan Kins

Alzheimer’s Disease, APP function and transport

Research Summary

Our research focuses on the neuronal function of the Amyloid Precursor Protein (APP) gene family and the molecular mechanisms underlying its intracellular transport in neurons. Thereby we focus on alterations of APP transport and function while aging and its consequences for AD.

Curriculum Vitae

Degrees: 1996 M.Sc. (Diploma) 1999 Ph.D.
1996-1999: Thesis work at the MPI for brain research, Frankfurt
1999-2003: Postdoctoral fellow at the Department of Psychiatric research at the University of Zurich and the ZMBH
2003-2006: Project Leader at the ZMBH
2007-2008: Group Leader at the ZMBH
Since 2008: Professor for Human Biology and Human Genetics at the TU Kaiserslautern

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Specifically our research is addressing the following aims:

1. **Determination of the molecular mechanisms underlying APP anterograde transport**

APP is anterogradely transported by very high velocity (≤10 µm/sec) and is possibly cleaved while transport along the axon to the presynaptic terminal. It has been reported that APP couples the motor machinery by direct binding to kinesin-1. However, recent work from our and several other research groups suggests that the hypothesis that APP serves as a kinesin-1 receptor and that the proteolytic processing machinery responsible for generating Aβ is transported in the same vesicular compartment in axons of peripheral nerves requires revision (Back et al., 2007; Lazarov et al., 2005; Rusu et al., 2007). In a proteomic approach we now identified components of the active zone complex as a kinesin cargo receptor of APP transport vesicles, co-transporting α-secretase. As α-secretase activity abolish generation of the neurotoxic Aβ peptide that accumulates in plaques of AD patients, we assume that changes in the velocity of APP anterograde transport, as described for aged neurons, play a pivotal role in the etiology of AD. We will determine the molecular composition of the content of the APP transport vesicle type, the precise mode of interaction of the motor machinery and the physiological consequences of alterations in transport velocity on APP pathogenic and physiological function.

![Fig. 3: Neuronal sorting of APP to dendrites and axons.](image)

Fluorescence microscopy image of a primary mouse neuron (DIV8) overexpressing mutant APP co-stained with anti-myc (green) and anti-MAP2 (red) antibodies. Arrowheads mark dendrites, arrows mark axons. Rectangular fields represent areas of quantification. For details see Back et al., 2007.

2. **Characterization of the cell adhesion features of APP/APLPs**

We found that APP/APLPs can trigger cell-cell contacts via homo- and heterotypic transdimerization of the ectodomains (Soba et al., 2005). Interestingly, the heterocomplex of APP and APLP1 can be co-immunoprecipitated from synaptic membrane fractions, suggesting a putative function of APP/APLPs transdimerization at synaptic sites. To extend these studies we started now detailed immunohistological analysis with newly generated anti-
APP/APLPs antibodies on the ultra structural level of neuronal tissues and investigate in cell culture models its impact on synaptogenesis and synaptic plasticity. Further we initiated studies addressing the consequences of APP/APLPs dimerization on processing and cell migration. These analyses will give new insights in the physiological function of APP/APLPs and its relevance for neurodegeneration in AD.

### 3. Investigations of the amyloidogenic pathway of APP processing in recycling vesicles

For the understanding of intracellular transport it is of high impact to determine crucial sorting motifs and the underlying molecular machinery, including scaffolding, regulatory and motor proteins. We found that PAT1a binds to the basolateral sorting signal of APP/APLPs and affects their subcellular localization and cleavage by α- and β-secretase (Back et al., 2007; Kuan et al., 2006). We want to determine the molecular mechanisms underlying the effect of PAT1a on APP/APLPs transport and processing. For this purpose we perform structural analysis and investigate the influence of PAT1a on the sorting of APP/APLPs in the endocytotic pathway in neuronal cells. Using the yeast two-hybrid system, we identified a novel Rab5GEF that regulates Rab5-dependent endocytosis as a novel interaction partner of PAT1a. Currently, we determine the molecular interplay of Rab5, the novel identified Rab5GEF, PAT1a and APP/APLPs in the endocytotic pathway of APP/APLPs.

### 4. In vivo analyses of APP/APLPs neuronal function using viral miRNA

Investigations of the loss of function of APP/APLPs in adult mice were prohibited by early postnatal death of the double- and triple knock-out mice. We have generated lentiviral constructs driving miRNA and EGFP mRNA expression under a Type II polymerase promoter. After unilateral stereotactic injection of the recombinant virus in different regions of the adult brain, we will analyse those neurons with reduced protein levels of APP, APLP1 or APLP2. The knock-down cells will be analyzed by immunohistological, electronmicroscopic and electrophysiological methods.

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### Top publications

- Soba, P., et al. (2005). Cell interactions are promoted by trans-dimerization of APP family members, arranged as homo- or hetero-complexes in synaptic membranes. EMBO J. 24, 3624-3636.

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### Structure of the Group

- **Group Leader:** Stefan Kins
- **Postdoctoral fellows:** Anita Szodorai
- **PhD-Students:** Simone Back, Silke Hunzelmann, Nadine Lauther, Katja Wagner
- **Undergraduates:** Benjamin Gimbler
- **Technicians:** Sylvia Kreger
**Research Summary**

Fast neurotransmission is mediated by highly organized pre- and postsynaptic protein complexes. The molecular mechanisms which establish, maintain, and alter these synaptic nanomachines are poorly understood. Our work focuses on the molecular mechanisms that regulate pre- and postsynaptic protein complexes.

**Current Research**

Ontogeny and regulation of glycinergic synapses in spinal cord and hippocampus

Components of the translational machinery are associated with juvenile glycine receptors and are redistributed to the cytoskeleton upon aging and synaptic activity. Whereas adult-type glycine receptors (GlyR) are hetero-oligomeric ligand-gated ion channels composed of α1 and β subunits, juvenile/early postnatal GlyR are homo-oligomeric channels composed of α2 subunits. The physiological role of juvenile/early postnatal GlyR expression for the functional differentiation of glycinergic synapses in the developing rat brain is not well understood. It is believed that the activation of the neonatal GlyR by taurine is depolarizing and accompanied by an increase in intracellular Ca$^{2+}$ concentrations. Moreover the failure of neonatal GlyR activation as a consequence of taurine deprivation can severely influence the migration of cortical neurons and thus the development of the cortical architecture. In the developing rodent brain glycinergic and GABAergic neurotransmission was shown to be depolarizing leading to Ca$^{2+}$-influx through L-type channels or NMDA receptors. We could show that activation of juvenile/early postnatal GlyR is crucial for the formation...
of postsynaptic gephyrin scaffolds, which subsequently trap adult-type glycine receptors via binding of the GlyR β subunit cytoplasmic pole. Moreover, the formation of gephyrin scaffolds in cultured embryonic rat spinal cord neurons requires Ca$$^{2+}$$ influx through L-type channels. Recently, we could demonstrate, that the GlyR α2 subunit is associated with translation eukaryotic elongation factor 1α (eEF1A) in pulldown experiments with rat brain extracts. Moreover, additional proteins involved in translation like ribosomal S6 protein and p70 ribosomal S6 kinase as well as ERK1/2 and calcineurin were identified in the same pulldown approaches. Moreover, GlyR activation in young spinal cord neurons resulted in an increased phosphorylation of ribosomal S6 protein. Immunocytochemistry showed that eEF1A and ribosomal S6 protein are localized in the soma, dendrites. Their immunoreactivities were partially overlapping with that of the GlyR at synapses of cultured hippocampal and spinal cord neurons. Surprisingly, eEF1A immunoreactivity was redistributed to the cytoskeleton in about 45% of neurons after 5 weeks in culture. Notably, the degree of redistribution could be increased at earlier stages of in vitro differentiation by inhibition of either the ERK1/2 pathway or GlyRs and simultaneous N-methyl-D-aspartate receptor activation. Our findings suggest a functional coupling of eEF1A with both inhibitory and excitatory receptors, possibly involving the ERK-signaling pathway. As the monomeric GTPase eEF1A is not only involved in protein synthesis but also thought to participate in other cellular functions such as actin bundling, cell cycle regulation, and apoptosis, we investigate its cellular functions in neurons with respect to dendrite morphology and synapse formation and maintenance.

Identification of novel cytomatrix proteins

In analyzing the candidates identified in the screen we focused on a cDNA encoding as an yet uncharacterized protein, which we termed mover. Analysis of the deduced primary structure revealed that mover is a vertebrate-specific non-transmembrane protein. Biochemical data suggest that it can associate with synaptic vesicles. Upon overexpression in cultured neurons it is targeted to presynaptic terminals. Confocal immunomicroscopy revealed a differential localization of mover at distinct subsets of CNS synapses. Whereas mover immunoreactivity colocalizes with presynaptic markers in the calyx of Held and localizes to mossy fibre terminals in the hippocampus,
it is absent from inhibitory nerve terminals in hippocampus but present at inhibitory terminals throughout the cerebellar cortex. Our results suggest that mover may act in concert with generally expressed scaffolding proteins in distinct sets of presynaptic terminals. Future work aims at the identification of mover interaction partners and at investigating the role of mover at distinct subsets of synapses. Moreover, we want to elucidate by RNAi experiments, which step of synaptic vesicle transport, fusion or recycling can be influenced by mover.

Proteomics studies on brain peroxisomes

Peroxisomes are single membrane enclosed organelles that catalyze a broad variety of catabolic as well as anabolic reactions. Peroxisomal genetic diseases, like X-linked adrenoleukodystrophy (X-ALD) or the Zellweger syndrome are characterized by severe malformations of the CNS, indicating an important role of these organelles in brain development. Whereas hepatic peroxisomes were functionally characterized in detail in the past, there is still lack of information on the protein pattern of peroxisomes in neuronal tissue. Since peroxisomes of high purity are a prerequisite of accurate protein identification, protocols for peroxisome isolation from brain tissue are currently under development using a combination of centrifugation techniques and free flow electrophoresis. Quantitative mass spectrometry will be used to unravel detailed changes in the protein pattern of ALDp-knock out and wild type mice, to obtain further insights in the process disturbed in the most prevalent peroxisomal disorder X-ALD.

Fig. 4: FLASH during Telophase.

Top publications

- Bluem, R., et al. (2007). Components of the translational machinery are associated with juvenile glycine receptors and are redistributed to the cytoskeleton upon aging and synaptic activity. J. Biol. Chem. 282, 37783-37793.

Structure of the Group

| Group Leader: | Joachim Kirsch |
| Senior scientist: | Jochen Kuhse |
| Postdoctoral fellows: | Thomas Dresbach, Markus Islinger, Thomas Kremer, Ralph Nawrotzki |
| PhD-Students: | Raphael Blüm, Daniel Quinones, Stefanie Schumacher |
| Technicians: | Andrea Schlicksupp, Ingeborg Vogel |
Current Research

Cross talk between excitatory and inhibitory synapses

GABA release from cerebellar molecular layer interneurons can be modulated by presynaptic glutamate and/or presynaptic GABAB receptors when perfusing the respective agonists. However, it is unclear how release and potential spillover of endogenous transmitter lead to activation of presynaptic receptors. High frequency firing of granule cells, as observed in vivo upon sensory stimulation, could lead to glutamate and/or GABA spillover. Using paired recordings from connected stellate cells and imaging techniques (Fig. 1), we study how sustained glutamatergic activity in the granule cell layer modulates GABA release in the molecular layer.

Hippocampal synaptic plasticity

Long-term potentiation (LTP) or long-term depression (LTD) of synaptic transmission are widely acknowledged as the primary candidate manifestation of the cellular basis of learning and memory. Most forms of LTP and LTD follow a Hebbian rule, requiring coincident presynaptic and postsynaptic activity during their induction. The presynaptic signal is thought to be glutamate release, whereas the postsynaptic signal is depolarization, allowing influx of calcium through NMDA receptors and/or voltage-gated calcium channels, and further supported by release of calcium from intracellular stores. For the expression of synaptic plasticity, presynaptic and/or postsynaptic mechanisms can be involved.

Within the hippocampus, mossy fiber synapses onto CA3 pyramidal neurons have unique features distinct from other excitatory synapses. Regarding synaptic plasticity, the most striking difference is that NMDA receptor-independent LTP can be induced upon high frequency presynaptic stimulation. Given that mossy fibers activate substantial NMDA receptor-mediated currents in CA3

Georg Köhr

Cross talk between excitatory and inhibitory synapses and ion channel & signaling function of NMDA receptors

Research Summary

Sensory experience affects neuronal activity, which modifies the strength or efficacy of synaptic transmission at excitatory and/or inhibitory synapses. Synaptic transmission can be enhanced or depressed lasting from milliseconds to hours or days. Our group studies short-term synaptic plasticity between GABAergic interneurons in the cerebellum involving spillover of transmitter, and long-term synaptic plasticity at two hippocampal synapses involving NMDA receptors. In addition, we are investigating ion channel function and signaling pathways of distinct NMDA receptor subtypes.

Curriculum Vitae

Degrees: 1989 Ph.D. in Neurophysiology
1996 Habilitation in Pharmacology and Toxicology
1985-1989: Thesis work, Department of Neurophysiology, MPI for Psychiatry, Martinsried and Institute of Physiology, Univ. of Cologne
1990-1991: Postdoctoral fellow, Department of Neurology, Stanford University, USA
1992-1996: Postdoctoral fellow, Center for Molecular Biology, University of Heidelberg
1996-2000: Lecturer for Pharmacology and Toxicology, University of Heidelberg
1997-2006: Project and Group Leader, MPI for Medical Research
since 2001: Lecturer for Physiology, Univ. of Heidelberg
since 2007: Research Group Leader, MPI for Medical Research

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neurons, the role of the NMDA receptors at this synapse is unclear. We investigate whether patterns of activity different from high frequency stimulation can recruit NMDA receptors to induce synaptic plasticity at mossy fiber-to-CA3 synapses in acute slices of P21 rodents. Fig. 2 illustrates one example of spike timing-dependent plasticity (STDP; +10 ms), which induces LTP. At CA3-to-CA1 synapses, the involvement of NMDA receptors during induction of synaptic plasticity is well established. Using genetic and pharmacological tools, our current goal is to determine whether particular NMDAR subtypes (see below) are recruited by different plasticity inducing protocols.

**NMDA receptor subtypes: functional properties and localization**

NMDA receptors are heterotetrameric complexes composed of two NR1 and two NR2 subunits (NR2A-D) subunits. Increasing expression of NR2A in hippocampal neurons after birth leads to the formation of diheteromeric NR1/NR2A and NR1/NR2B as well as triheteromeric NR1/NR2A/NR2B receptors (Fig. 3A). Despite compelling evidence for triheteromeric NMDA receptors, the functional

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Fig. 1: (A) Scheme of a cerebellar section including electrodes for paired recordings (ML, molecular layer; GL, granule cell layer). (B) Test and conditioned IPSCs in the postsynaptic cell (-35 mV; upper row) were evoked by paired depolarization pulses elicited in the presynaptic cell (-60 mV; lower row). Conditioned eIPSCs were preceded by train stimulation (30 stimuli at 50 Hz). (C) A stellate cell was filled with 100 µM Oregon Green BAPTA-1, and granule cells were electroporated (500 µM Alexa Fluor 594) during train stimulation. Axonal Ca^{2+} transients were evoked by paired-pulse spiking (20 ms) and were acquired by two-photon microscopy. Scale bar = 20 µm. Conditioned eIPSCs were preceded by train stimulation (30 stimuli at 50 Hz). (C) A stellate cell was filled with 100 µM Oregon Green BAPTA-1, and granule cells were electroporated (500 µM Alexa Fluor 594) during train stimulation. Axonal Ca^{2+} transients were evoked by paired-pulse spiking (20 ms) and were acquired by two-photon microscopy. Scale bar = 20 µm.

Fig. 2: Excitatory postsynaptic potentials (EPSPs) were evoked by mossy fiber stimulation (see scheme) in CA3 neurons of P21 rats in 10 µM bicuculline and 10 µM glycine. LTP was induced by 60 EPSP-action potential (AP) pairs. The three APs were evoked at 50 Hz and delayed by 10 ms after the evoked EPSP. The APs of the voltage traces are clipped. Note that the paired-pulse facilitation did not change after spike timing.
role of these receptors in synapses is still unknown. We are currently investigating deactivation (Fig. 3B) and peak open probability of synaptic NMDA receptor subtypes in acute hippocampal slices of wild-type and NR2A knockout mice as these functional properties are very different between recombinant NR1/NR2A and NR1/NR2B receptors.

Fig. 3: (A) Expression of two different NR2 subunits within a neuron can lead to the formation of three distinct NMDAR subtypes. (B) NMDA receptor-mediated EPSCs were evoked in CA1 neurons of P28 wild-type (WT) and NR2A knockout (NR2Ako) mice in 10 µM bicuculline, 5 µM NBQX and 10 µM glycine at -40 mV. (C) Schematic drawing of an excitatory synapse containing a presynaptic terminal (triangle) and a postsynaptic spine carrying synaptic NMDA receptors (black paired structures). Two astrocytes ensheath the synapse and express glutamate transporters (T) whose activity influences the activation of perisynaptic NMDARs (dark gray). An extrasynaptic NMDAR is present in the dendritic shaft (light gray).

Besides subunit composition, distinct NMDA receptor functions likely also depend on the spatial distribution of NMDA receptor subtypes within a neuron. Certain interactions of NMDA receptor subunits with other transmembrane receptors (e.g., Dopamine) and/or intracellular signaling molecules (e.g., kinases or phosphatases) may occur at synaptic but not at peri- or extrasynaptic sites (Fig. 3C). Importantly, these interactions change during postnatal development when scaffolding and signaling complexes reorganize in the postsynaptic densities coinciding with increasing expression of a second NR2 subunit. We investigate distinct signaling pathways in apical and basal dendrites of CA1 neurons by means of protein overexpression or protein knockdown using short interfering RNAs (siRNAs).

Top publications

- Pawlak, V., et al. (2005). Frequency dependent impairment of hippocampal LTP from NMDA receptors with reduced calcium permeability. EJN. 22, 476-484.

Structure of the Group

Group Leader: Georg Köhr
Postdoctoral fellows: Simone Astori, Marie Pollard, Sven Berberich
PhD-Students: Claudia Rauner
MD-Students: Marina Fendel
Rohini Kuner

Molecular mechanisms underlying chronic pain

Research Summary

We aim at understanding molecular mechanisms underlying chronic pain resulting from long-lasting inflammation or cancer. A major focus is laid on addressing signalling mechanisms which underlie activity-dependent changes in primary sensory neurons transmitting pain (nociceptors) and their synapses in the spinal dorsal horn. Our current work spans molecular, genetic, behavioural, electrophysiological and imaging approaches in vitro as well as in vivo in rodent models of pathological pain.

Curriculum Vitae

Degrees: 1994 Ph.D. 2005 Habilitation
1994: PhD in Pharmacology und Toxicology, Dept. of Pharmacology, College of Medicine, University of Iowa, Iowa City, USA
1995-1998: Postdoctoral fellow, ZMBH, University of Heidelberg; Department of Molecular Neurobiology, MPI for Medical Research
2000-2001: Scientist, Pharmacology Institute, Univ. Heidelberg
Since 2002: Group Leader of an independent, DFG-financed Emmy Noether-Program group, Pharmacology Institute, Univ. Heidelberg
2005: Habilitation, Medical Faculty of the University of Heidelberg
2006: Professor for Pharmacology, University of Heidelberg

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Current Research

Mechanisms of plasticity at synapses between nociceptors and spinal neurons in states of peripheral inflammation

Several current projects are directed at elucidating novel mediators of synaptic plasticity at synapses between primary afferents and spinal neurons. In addition to transgenic approaches, the RNAi methodology and Adeno-associated viruses (AAV) are our key tools for inducing molecular perturbations in the spinal cord. We use several models of inflammatory pain, including arthritis, to study alterations in pain behaviour in vivo. Furthermore, patch-clamp recordings and calcium imaging on spinal cord slices are employed for addressing potentiation of synaptic transmission.

Conditional deletion of gene encoding pain-relevant proteins, including receptors, kinases, G-proteins and ion-channels, specifically in peripheral nociceptive neurons

We utilise mouse models to test the contribution of important neuromediators towards learning and memory in pain pathways and the generation of post-inflammatory pain. We work with transgenic mice which lack receptors of important neuromediators (e.g. Cannabinoid receptors, GABA-B receptors, Glutamate receptors, Endothelin receptors, TRP channels) or their key signaling effectors (e.g. G-proteins, Protein kinases) in a temporally and spatially-controlled manner using the Cre-loxP approach. We also work on the identification and development of novel therapeutic approaches for chronic pain disorders, with the help of viral gene delivery vectors and in vivo RNAi in mice.
Molecular mediators of pain caused by bone cancer and tumor-nerve interactions

Pain is a frequent and devastating symptom of various forms of cancer. Various types of carcinomas and sarcomas originating from the breast, lung and prostrate metastasize to bones and elicit pain. These tumour cells induce bone remodelling as well as ongoing and movement-evoked pain behaviours similar to those found in patients with bone cancer pain. In addition, there is a significant reorganization of the spinal cord that received sensory input from the cancerous bone and this reorganization generated a neurochemical signature of bone cancer pain that is both dramatic and significantly different from that observed in mouse and rat models of chronic neuropathic or inflammatory pain. Pancreatic carcinoma is also associated with excruciating pain. Cancer pain is believed to be a unique form of pain. A distinguishing feature of cancer pain involves tumor-associated mediators which are released by tumor cells and act on sensory nerves to induce changes that elicit chronic pain. A major goal of our laboratory is to identify such tumor-associated mediators, to clarify their role in cancer pain and to develop novel therapeutic approaches to interfere with their function.

Structural plasticity of nociceptive nerves in disease states

Structural plasticity of nerves in disease states is theme central to several of our projects. For example, in states of bone cancer, nociceptive terminals sprout in the epidermis of the skin adjoining the tumor. Similarly, in chronic pancreatitis as well as pancreas carcinoma, nerves innervating the pancreas demonstrate marked hypertrophy and sprouting. Because these structural changes are usually studied in post-mortem tissues, it is difficult to judge whether they are responsible for a range of sensory abnormalities or whether they are mere adaptive changes occurring in response to the pathology and pain. In order to study the functional aspect of such structural changes, it is necessary to use imaging methods in living tissue. Towards this end, we have established a mouse line, called SNS-EGFP, expressing the live fluorescent label, EGFP solely in nociceptive fibers. Furthermore, in SST2-EGFP mice, an additional mouse line which we have generated, EGFP
is expressed selectively in non-peptidergic nociceptors. Using such tools, we would like to address molecular mechanisms underlying dynamic changes in nociceptive terminals in disease states.

Fig. 3: Pain-sensing neurons in the dorsal root ganglia display unique properties and form specific synaptic connections with neurons in the spinal cord. Activity-dependent plasticity at this first synapse in the somatosensory pain pathway is believed to be an important component of mechanisms leading to chronic pain.

**Plexin-semaphorin interactions in neural development**

*(joint project with the group of Prof. Stefan Offermanns, Pharmacology Institute, Univ. Heidelberg)*

Semaphorins and their receptors, plexins, are key regulators of neuronal migration and axonal pathfinding. In contrast to the well-characterized plexin-A family, very little is known about the expression and functions of plexin-B family proteins in the developing nervous system. In the past, we have addressed the role of the plexin-B signaling complex in growth cone behaviour and nerve outgrowth in collaboration with the research group of Stefan Offermanns. Furthermore, our expression analysis revealed that plexin-B1 and plexin-B2 and their ligand semaphorin 4D (Sema4D) are expressed at key regions at critical time points during the development of the peripheral and central nervous system. We have also addressed the role of plexin B-Sema4D interactions in epithelial-mesenchymal interactions during kidney development. Our current projects are focussed on characterizing mouse mutants lacking plexin-B1 or plexin-B2 for defects in the development of the peripheral and central nervous system.

**Top publications**


**Structure of the Group**

**Group Leader:** Rohini Kuner  
**Postdoctoral fellows:** Martina Kurejova, Ceng Luo, Anke Tappe-Theodor, Eszter Paldy, Manuela Simonetti, Nitin Agarwal, Daniel Vardeh  
**PhD-Students:** Vijayan Gangadharan, Alexandra Kulkova, Kiran Kumar Bali, Lucas Vicuna, Christian Njoo, Deepitha Selvaraj, Jianning Lue  
**Technicians:** Dunja Baumgartl-Ahlert, Tamara Djuric, Hans-Joseph Wrede, Eva Reiss
Current Research
Molecular structure and function of central nerve terminals

Synaptic communication between neurons relies on the transfer of all-or-none signals: presynaptic action potentials are translated into graded synaptic currents on the postsynaptic side. Mainly two scaling factors define the efficacy of this translation: the magnitude of the response generated by a single action potential and the frequency-dependent modulation of this translation process. Most synapses

Thomas Kuner
Structure and function of synapses

Research Summary
Our work is aimed at understanding the molecular mechanisms of synaptic transmission, mainly focusing on presynaptic nerve terminals. We employ a multidisciplinary approach ranging from molecules to behavior: molecular perturbation, viral gene transfer, genetically encoded indicators, high-resolution fluorescence microscopy, electron microscopy, 3D analyses, quantitative fluorescence imaging, electrophysiology and behavior.

Curriculum Vitae
Degrees: 1998 MD
1992-1997: Thesis work with Peter Seeburg at the ZMBH, University of Heidelberg
1998-2000: Postdoctoral fellow training with George Augustine at Duke University, Durham, USA
2000-2006: Group Leader at the department of Bert Sakmann, MPI for medical research, Heidelberg
since 2006: Professor at the University of Heidelberg, Institute for Anatomy and Cell

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Fig. 1: Calyx of Held presynaptic nerve terminal visualized by viral expression of GFP. Width of image ~40 µm.
respond to repeated action potentials by a transient and short-lasting reduction of synaptic scaling, known as short-term depression (STD). This synaptic filtering has a fundamental impact on neuronal computation. Current evidence suggests that the depletion of synaptic vesicles (SV) and the rate of recruitment of recycled or new SVs to the active zone (AZ) determines the extent of STD at an individual synapse. Therefore, the dynamics of membrane trafficking events control an important parameter of synaptic transmission and neuronal communication.

We study synaptic transmission in a giant nerve terminal of the rat auditory brain stem known as the calyx of Held. The synapse formed by the calyx with its postsynaptic neuron, the principal cell of the medial nucleus of the trapezoid body (MNTB), is the only central synapse of vertebrates from which simultaneous pre- and postsynaptic electrophysiological recordings can be routinely achieved. We combine molecular biology & genetics, electrophysiology, fluorescence imaging, immunohistochemistry, three-dimensional reconstructions and high-pressure quick-freeze electron microscopy to study these questions in an integrated multi-dimensional approach.

**Neuronal chloride signaling imaged with a genetically encoded indicator**

The polarity of GABAergic or glycinergic synaptic transmission is controlled by the transmembrane gradient of Cl⁻ and the resting membrane potential. At a typical membrane potential of -70 mV, GABA and glycine yield hyperpolarizing responses at low intracellular concentrations of Cl⁻, but depolarizing responses at high concentrations of Cl⁻. Hence, the control of intracellular Cl⁻ can have a fundamental influence on GABAergic and glycinergic neurotransmission by defining the polarity of the postsynaptic response. Using Clomeleon, a genetically encoded indicator for Cl⁻, we study the spatial and temporal distribution of Cl⁻ in hippocampal neurons and the impact of Cl⁻ gradients and local accumulation on GABAergic synaptic transmission. Clomeleon is expressed in selected neuronal subtypes by transgenic or viral techniques. We use quantitative ratiometric confocal and two-photon imaging combined with electrophysiology to study intracellular Cl⁻ dynamics in neurons.

**From molecules to behavior: neuronal mechanisms of odor discrimination**

Lateral inhibition is a prominent mechanism generating contrast enhancement in sensory systems. In the olfactory system, lateral inhibition is thought to be mediated by a
synaptic interaction between mitral cells (MC) and granule cells (GC) of the olfactory bulb. Dendrites of MCs and GCs are connected by the reciprocal synapse, a specialized bidirectional contact capable to act as a receiver and sender of synaptic signals. Thus, glutamate release from MC dendrites can translate into a graded response involving either GABA release from the same terminal (reciprocal inhibition), from nearby ones (local lateral inhibition), or even from all terminals of a GC (global lateral inhibition). The contribution of these mechanisms to odor discrimination in the mouse is only poorly understood. We study the effect of specific molecular manipulations at the reciprocal synapse of GCs on odor discrimination in mice. Acute targeted genetic perturbations (ATGp) will be used to specifically interfere with molecular targets in granule cells of the olfactory bulb. The behavioral consequences of perturbations will be assessed with an odor discrimination test (Abraham et al., 2004). After behavioral testing identified relevant perturbations, the physiological consequences will be examined with electrophysiological and imaging techniques on the level of individual GCs.

**Top publications**


**Structure of the Group**

- **Group Leader:** Thomas Kuner
- **Postdoctoral fellows:** Nixon Abraham, Robert Renden, Anna Dondzillo
- **PhD-Students:** Christian Kempf, Christoph Körber, Daniel Nunes, Darius Schwenger, Bhavana Shrivastava, Francisco Urra, Maryia Vasileva
- **Technicians:** Heinz Horstmann, Michaela Kaiser, Claudia Kocksch

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Fig. 3: Expression of Clomeleon in hippocampal CA1 neurons of a Clomeleon indicator mouse line.
Siegfried Mense

Neurobiological mechanisms of chronic muscle pain

Research Summary
Animal experiments in vivo address the role of neuroactive mediators in peripheral and spinal muscle nociception, as well as the potential involvement of spinal glial cells in the development of chronic muscle pain. Further, the studies aim at comparing neurobiological mechanisms of chronic pain in a locomotor muscle with those in low back muscles.

Curriculum Vitae
Degrees: 1973 MD
1979 Habilitation
1966-1971: Thesis work at the Dept. of Nuclear Medicine, University of Bonn
1971-1978: Postdoctoral fellow in Electrophysiology at the Dept of Physiology, University of Kiel
1978-1979: Assistant professor at the Dept. of Physiology of the University of North Carolina at Chapel Hill
1979-1985: Group Leader at the Department of Physiology, University of Kiel
1985-2008: Professor at the University of Heidelberg, Institute for Anatomy and Cell Biology

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Current Research
Sensitisation of dorsal horn neurones by subthreshold potentials
Electrophysiological experiments in the rat have shown that under normal circumstances many dorsal horn neurones react to input from muscle nociceptors with subthreshold membrane potential changes, only. Intramuscular injections of the neurotrophin nerve growth factor, for example, activate many nociceptive muscle afferents but at the level of spinal dorsal horn neurones, this activation elicits mainly subthreshold potentials. These potentials do not evoke subjective pain sensations but nevertheless sensitise central nociceptive neurones. The intracellular recordings in vivo give a more complete picture of the spinal wiring of muscle nociceptors compared to the conventional extracellular microelectrode techniques. These data are the

Fig.1: Stimulating effects of nerve growth factor (NGF) on dorsal horn neurones.
A) Original registrations of a dorsal horn neurone responding with subthreshold excitatory postsynaptic potentials (EPSP) but no action potentials (APs) to an intramuscular NGF injection. Likewise, noxious pressure (Nox. p.) stimulation of the muscle evoked EPSPs only (upper panel).
B) Number of neurones responding to intramuscular NGF injection. Only a few dorsal horn neurones responded with occasional APs (and EPSPs) to the NGF injection, a greater number showed EPSPs only. The mean AP frequency after NGF was extremely low (2.6 APs per min).
basis of a more detailed understanding of spinal processes induced by tonic, subthreshold membrane potential changes in nociceptive dorsal horn neurones. The understanding of central sensitisation evoked by tonic subthreshold input provides new insight in neurobiological mechanisms that underlie chronic muscle pain syndromes that often develop without a perceived tissue lesion.

**Role of spinal microglia in central sensitisation**

Previous studies of our group had shown that muscle inflammation does not only lead to marked changes in the responsiveness of dorsal horn neurones but also induces morphological and functional alterations in spinal astrocytes. One aim of the current research is to employ immunohistochemical, behavioural, and electrophysiological methods to investigate the contribution of spinal microglial cells to the development of chronic muscle pain. Microglia is assumed to play an important role in chronic pain states. In a rat model of chronic muscle inflammation, morphological alterations of spinal microglial cells can be evaluated by quantitative OX-42 immunohistochemistry. OX-42 is a specific marker of spinal microglia. In behavioural experiments, the effects of intrathecally applied minocycline - a specific blocker of microglia activation - on pain-related behaviour caused by muscle inflammation are studied. Simultaneously, processes at the neuronal level are investigated with intracellular recordings of nociceptive dorsal horn neurones. In these experiments, the influence of neuroactive substances released by microglial cells- or of blockers of these substances - is examined.

![Fig. 2: Quantitative evaluation of microglial OX-42 immunoreactivity (IR) in intact rats and in rats with a chronic muscle inflammation.](image)

A) As areas of interest, six fields (179 µm x 133 µm each) were defined, 3 in the superficial dorsal horn and 3 in the deep dorsal horn. Within the rectangles, the OX-42 immunoreactive (ir) areas and their boundary lengths were measured.

B) OX-42 IR in the deep dorsal horn visualised by the green fluorescent marker Cy2 (lamina V, GS muscle inflamed).

C) 8-bit grey image of OX-42 IR (same figure as shown in B).

D) Quantitative evaluation of immunostaining. The threshold level for immunostaining against background was defined as the mean background grey value in unstained areas between the fluorescent microglia (white rectangle in C) plus three standard deviations.

E) In animals with an inflamed muscle (inflamed), the mean boundary length of the immunoreactive (ir) areas were significantly shorter in the deep dorsal horn (Eb; ***, P < 0.001), whereas in these region the ir area was not reduced (Ea). The decrease in boundary length is probably due to a retraction of the cell processes during inflammation-induced activation of the microglial cells.

**Neurobiological mechanisms of chronic low back pain**

Although the prevalence of chronic pain in low back muscles is very high, there are practically no basic science data on possible mechanisms of this type of pain. Most of the current knowledge of mechanisms of muscle pain was obtained in studies on locomotor muscles of the extremities. We are now performing systematic animal experiments to investigate the neurobiological mechanisms of low back pain and compare the data with those obtained in
experiments on locomotor muscles. The central nervous connections of low back muscles are examined by injecting retrograde tracers into supraspinal centres and visualising nociceptive dorsal horn neurones with input from the low back using the cFos reaction. We just completed the first systematic study of the responsiveness of dorsal horn neurones to noxious stimulation of low back muscles. In these experiments, single neurones were recorded from with extracellular recording techniques.

Fig. 4: Lumbar dorsal horn neurone retrogradely labelled from the peri-aqueductal gray matter (PAG) with Fluorogold (Aa). The same neurone also exhibited cFos-immunoreactivity after noxious stimulation of low back muscles (Ab). B) Responses of a nociceptive dorsal horn neurone to noxious stimulation of deep tissues in the low back. The neurone also responded to noxious pressure applied to the paw. Each vertical line in the original recordings is an action potential. The data show that neurones with input from the low back project to the PAG and exhibit a marked input convergence from various tissue types.

Top publications


Structure of the Group

Group Leader: Siegfried Mense
Postdoctoral fellows: Ulrich Hoheisel, Toru Taguchi
PhD-Students: Natalia Bode, Viola John, Jonas Tesarz
Scientists: Daniela Lambertz
Technician: Beate Quenzer, Marion Schmitt, Marina Szymbara, Claudia Tolliver
Andreas Meyer-Lindenberg

Translational neurogenetics of psychiatric disorders

Research Summary

Many severe psychiatric disorders and complex behaviours are highly heritable. We investigate genetic variation associated with risk for disorders such as schizophrenia, depression and autism and behavioural phenomena such as attachment or impulsive violence in a translational approach, with an emphasis on multimodal neuroimaging to identify neural systems mediating genetic risk. The ultimate goal is the construction of a neural risk architecture of the studied target behaviour as guide for the discovery and evaluation of novel treatment strategies.

Current Research

Neurogenetic risk mechanisms of schizophrenia

We study the impact on genetic risk variants (COMT, PP1R1B, DISC1, RGS4, etc.) on neural function and cognition using multimodal neuroimaging. A recent focus of that work is the investigation of epistatic interactions (COMT x GRM3, COMT x RGS4), relating multiple genetic variants to neural phenotypes, and the study of neural mechanisms predictive of therapeutic response and course in a longitudinal perspective (Meyer-Lindenberg et al., 2005b; Meyer-Lindenberg et al., 2005c; Meyer-Lindenberg et al., 2006b; Goldman et al., 2007; Tan et al., 2007)

Neurogenetic risk mechanisms of depression and anxiety

Here, we focus on mechanisms of gene x environment interactions and the neural circuits mediating association of genetic variation with trait anxiety. Genetic variants studied here include 5-HTTLPR, MAO vntr, and BDNF. (Pezawas et al., 2005).

Neural mechanisms of complex social behaviours under genetic control

Many aspects of social behaviour are highly heritable, are key components of severe psychiatric disorders that are themselves heritable, and are essential for reproductive fitness. Consequently, we have launched a program to investigate genetic contributions to the human social brain. We have identified neurogenetic mechanisms contributing to violence, impulsivity, attachment and personality traits. In parallel, we are interested in studying social phenomena that show a high degree of conservation across species, such as social hierarchies.(Meyer-Lindenberg et al., 2005a)

Curriculum Vitae

Degrees: 1991 MD (Neurochemistry)
1999 Habilitation University of Giessen
1984-1991: University of Bonn (Medical School)
1989: Research fellow, Cornell University, New York
1997-2001: Visiting Associate Research fellow, National Institute of Mental Health, Clinical Brain Disorders Branch, Bethesda, USA
2001-2005: Staff scientist, NIMH, Clinical Brain Disorders Branch, Co-director of the Imaging Core Facility since 2007: Professor and Chairman of Psychiatry and Psychotherapy, University of Heidelberg, Clinical Director of the Department of Psychiatry and Psychotherapy and Director of the Central Institute of Mental Health

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plasticity in the prefrontal cortex (PFC) *in vivo* is quantified using a combination of repetitive transcranial magnetic stimulation (rTMS) and functional neuroimaging to derive detailed measurements of cortical physiology at an intermediate phenotype level. We expect that systems-level correlates of plasticity will be impaired in carriers of a functional val66met variant in the BDNF gene and modulated by variants in the genes COMT, NRG1, and GRM3. (Pezawas et al., 2004).

**Top publications**

Hannah Monyer

Neuronal synchrony and plasticity

Research Summary

The studies of this lab are directed at the identification of genes critically involved in the generation of synchronous oscillation in neuronal networks, at the functional analysis of different interneuronal populations and at the characterization of the role of AMPA and NMDA glutamate receptor subtypes in different forms of plasticity.

Curriculum Vitae

Degrees: 1983 MD  1994 Habilitation
1976-1982: Medical School, Thesis work, University of Heidelberg
1983-1984: Resident at the University Hospital for Psychiatry, Department of Child Psychiatry, Mannheim
1984-1986: Resident at the University Hospital for Pediatrics, Department of Pediatric Neurology, Lübeck
1986-1987: Postdoctoral research fellow, Stanford University Medical Center, Department of Neurology, EEG Laboratory, Stanford, USA
1987-1989: Postdoctoral research fellow, Stanford University Medical Center, Department of Neurology, Neurology Research Laboratory, Stanford, USA
1989-1994: Postdoctoral research fellow, Center for Molecular Biology, University of Heidelberg
1994-1999: Hermann-and-Lilly-Schilling-Foundation Professor at the Center for Molecular Biology, University of Heidelberg
since 1999: Head of the Department of Clinical Neurobiology, IZN and Neurological University, University Hospital Heidelberg
since 2002: Speaker of the Graduate College Programme GK 791

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Current Research

Molecular mechanisms underlying synchronous activity in the central nervous system

A number of compelling studies and computational simulations data provide evidence that networks of inhibitory neurones play a pivotal role in the generation of certain forms of oscillations that arise as a network property. Oscillatory activity in different frequency ranges has been proposed to be critical for a number of cognitive tasks, including object representation, learning and memory.

The goal of our studies is to identify ‘key’ molecules in GABAergic interneurones that underlie oscillatory activity and that are involved in controlling synchronous firing of ensembles. Our studies entail analysis from the single cell level to the network activity in vitro (acute slice preparation) and in vivo. Genetically modified mice with altered expression of critical genes (e.g. AMPA receptors, NMDA receptors, connexins) in GABAergic interneurones are a critical tool for subsequent electrophysiological studies to investigate synchronous network activity in cortex and hippocampus in the freely moving mice. These investigations are further complemented by behavioural studies.

Characterization of different interneuronal populations

Given the large diversity of GABAergic interneurones (based on the presence of certain parameters, for instance chemical markers, morphological criteria, connectivity), present projects aim at the identification of GABAergic subpopulations of neurones (e.g. parvalbumin-, somatostatin-, calretinin-positive cells). To this end transgenic mice are produced in which these neuronal subpopulations are labelled using the in vivo marker green fluorescent protein. The subsequent electrophysiological studies on fluorescent neurones in these mice should aid...
in identifying the GABAergic cell types involved in different forms of network oscillations. In transgenic mice that express EGFP in a particular subset of GABAergic interneurones, we have found that unlike the vast majority of GABAergic interneurones that are generated embryonically, certain GABAergic interneurones continue to be generated after birth. Postnatal neurogenesis of GABAergic interneurones that migrate into the cortex and hippocampus is a novel form of plasticity. The analysis is based on anatomical and electrophysiological techniques as well as imaging studies of migrating neurones. Furthermore, these mice are used for gene expression analysis in EGFP-labelled neuronal populations by means of laser dissection microscopy.

**AMPAR receptor interacting proteins and synaptic plasticity**

AMPAR receptors, another subtype of the glutamate receptor family, mediate most of the fast excitatory transmission in the vertebrate central nervous system. They are critical in determining the strength of transmission at glutamatergic synapses, and tight regulation of their function allows for use-dependent and input-specific adaptations of synaptic strength. Their function is influenced by composition, posttranslational modifications and by protein-protein interactions. We have identified a novel brain specific AMPAR receptor interacting protein (AIP47) by mass spectrometry of AMPAR receptor complexes and we are currently studying the role of this protein in regulating AMPAR-receptor mediated synaptic transmission and plasticity of glutamatergic synapses.

**NMDA receptors neuronal plasticity and vulnerability**

The NMDA receptor, a subtype of the glutamate receptor family, is critical for the induction of different forms of plastic changes in the brain. Anatomical and functional characterization of NMDA receptors subtypes has revealed that pyramidal neurones co-express the two NMDA receptor subtypes NR2A and NR2B. The differential developmental regulation of these two NMDA receptor subtype expression with respect to brain areas and cell types exerts an important function in the change of neuronal plasticity during brain maturation. Projects pertaining to this research programme aim at cell type-specific ablation of the NR2B subunit to study the function of the ‘young’ receptor form in the adult brain. The analysis of the genetically modified mice is performed using electrophysiological and behavioural studies.
Top publications


Structure of the Group

Group Leader: Hannah Monyer
Senior Scientist: Andrei Rozov
Postdoctoral fellows: Julieta Alfonso, Rosa Arribas Prat, Antonio Caputi, Elke Fuchs, Kaneko Hiroshi, Anne Herb, Alexey Ponomarenko, Corentin Le Magueresse, Jakob von Engelhardt
PhD-Students: Christina Göngrich, Vogt Angelika, Aleksandar Zivkovic
Scientists: Maria Blatow
Undergraduates: Seda Ballikaya, Michael Barbe, Panagiotis Bargiotas, Christine Bark, Christina Bocklisch, Irena Brinkmann, Golovko Tatiana, Khrulev Sergey, Jennifer Lee, Attila Racz, Olga Voinova
Ulrike Müller

Functional genomics of neurodegenerative diseases; Alzheimer’s disease, physiological and pathological function of APP family proteins

Research Summary

Our research focuses on the molecular mechanisms of synaptic transmission disorders and the pathogenesis of neurodegenerative diseases, in particular Alzheimer’s disease. Our aim is to unravel the physiological and pathogenic function of key genes and mechanisms that trigger disease.

Curriculum Vitae

Degrees: 1985 Diploma, University of Munich  
1989 Dr. rer. nat., University of Munich  
1999 Habilitation in Molecular Biology  
University of Zurich  
1989-1991: Postdoc, Medical School,  
University of Manchester, UK  
1991-1997: EMBO long term fellow and Group Leader,  
Institute for Molecular Biology, University of Zürich  
Head of the Neurogenetics group, MPI for Brain Research, Neurochemistry, Frankfurt  
Since 2005: Professor for Functional Genomics, Department of Bioinformatics/ Functional Genomics, IPMB, University of Heidelberg

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Current Research

Alzheimer’s disease (AD) is the most common neurodegenerative disorder and is characterized by synaptic disfunction, neuronal loss and cognitive decline. The major lesions found in the brains of AD patients are neurofibrillary tangles and neuritic plaques that are mainly composed of the β-amyloid peptide (Aβ) derived via proteolysis from the amyloid precursor protein APP. APP is a single pass transmembrane protein that is processed in two different ways: α-secretase cleaves APP within the Aβ region, thereby precluding Aβ formation and releasing the APPsa ectodomain; in the amyloidogenic pathway APP is sequentially cleaved by β- and γ-secretase, leading to Aβ formation. Whereas the mechanisms governing Aβ generation have been intensely studied, the physiological role of APP and of its numerous proteolytic fragments and the question of whether a loss of these functions contributes to AD are still unknown.

Knockout mice with individual or combined gene deficiencies of APP-family proteins

Determining the in vivo functions of APP in mammals is complicated by the presence of two APP-related genes, APLP1 and APLP2. APP and APLPs share two conserved domains in the extracellular region (E1 and E2) and one in the cytoplasmic domain, whereas the β-amyloid peptide is lacking in APLPs. Thus, functional redundancy may compensate for the loss of essential gene functions, e.g. in knockout (KO) models. Indeed, by generating various KO mutants we could demonstrate that the extensive structural similarities between APP and APLPs are also reflected at the functional level. Mice in which APP, APLP1, or APLP2 is inactivated are viable and APP-KO mice revealed reduced brain and body weight, reduced grip strength, altered locomotor activity, increased susceptibility to seizures and a defect in spatial learning and LTP. In contrast
to the viable single mutants, combined APLP2⁻/⁻-APP⁻/⁻ and APLP2⁻/⁻-APLP1⁻/⁻ double mutants die shortly after birth indicating that APP family proteins serve redundant functions that are essential for viability (Heber et al., 2000). Whereas the brains of double knockout animals exhibit no obvious morphological defects, triple mutants lacking the entire APP gene family showed cranial dysplasias resembling human type II lissencephaly (Herms et al., 2004). Within affected areas neuronal cells from the cortical plate migrated beyond their normal positions and protruded into the marginal zone and the subarachnoid space. Thus, APP/APLPs play a critical role in neuronal adhesion and positioning. This role in cell adhesion is also supported by data from a recent collaborative study demonstrating that APP family proteins form cis- and trans-dimers involved in cellular adhesion and may thus play a role in synaptic differentiation/function (Soba et al. 2005). Collectively, our data revealed an essential role for APP-family members in normal brain development and early postnatal survival. Work is in progress to circumvent early lethality and assess functions postnatally by generating tissue specific knockouts.

**The role of APP and its fragments for neuronal morphology and synaptic function**

Recently, a role of APP and APLP2 at the neuromuscular synapse has been described. Thus, ongoing work in the lab is directed to assess whether APP/APLP deficiency is also associated with related defects of neuronal morphology and/or synaptic function within the CNS. To this end we are analyzing organotypic hippocampal cultures of knockout and knockin mice with regard to morphology and (in collaboration) for their electrophysiological characteristics (basal synaptic transmission, synaptic plasticity).

**Role of APP-dependent gene expression for Alzheimer disease**

The proteolytical processing of APP is very similar to that of Notch and the APP intracellular domain AICD has been suggested to function as a transcriptional regulator. Nevertheless, the nature of the relevant target genes is
still under debate (see e.g. Pardossi-Picard et al., 2005 and Hebert et al., 2006). Using a microarray/qPCR based approach we identified novel differentially expressed genes (e.g. involved in cytoskeletal remodeling, endocytosis, cell adhesion and neurotransmitter systems). In this context we are particularly interested to clarify whether these target genes are directly regulated at the mRNA level via AICD acting in a Notch-like manner, or are more indirectly affected by the absence of APP-family proteins.

### Regulation and molecular pathology of the inhibitory glycine receptor

Glycine receptors (GlyRs) are ligand activated chloride channels composed of α- and β subunits forming a pentamer. GlyRs are involved in the control of spinal motor and sensory pathways, but little was known about the biological roles of different GlyR subtypes. Recently we showed that GlyRα3 subunits are distinctly expressed in superficial laminae of the dorsal spinal cord, the first site of synaptic integration in the pain pathway (Harvey et al., 2004). At this site, glycinergetic neurotransmission is inhibited by prostaglandin E2 (PGE2), a pivotal mediator of inflammatory pain sensitization. By generation of GlyRα3 knockout mice we could show that this receptor subtype plays a crucial role in spinal nociceptive processing. Mice deficient in GlyRα3 not only lacked the inhibition of glycinergetic neurotransmission by PGE2 seen in wild-type mice, but also showed a reduction in pain sensitization induced by spinal PGE2 injection or peripheral inflammation (Harvey et al., 2004). Thus, GlyRα3 may provide a novel molecular target in pain therapy.

**Fig. 2:** Transverse section through wild type spinal cord. Double labeling shows that GlyRα3 (green) is restricted to the dorsal horn, and gephyrin (red) is expressed throughout the gray matter. (adapted from Harvey et al., 2004)

### Top publications

- Ring, S, et al. (2007).The secreted APPsα domain is sufficient to rescue the anatomical, behavioral, and electrophysiologi- cal abnormalities of APP deficient mice. J. Neurosci. 27, 7817-7826

### Structure of the Group

**Group Leader:** Ulrike Müller  
**Postdoctoral fellows:** Viola v. Bohlen, Mikhail Filippov, Jakob Tschäpe  
**PhD-Students:** Dorothee Aydin, Sabine Ring, Sascha Weyer  
**Technicians:** Diana Bundschuh, Julia Gobbert, Michael Neumann, Frankziska Stöckling
Current Research

It is now commonplace that principles guiding embryonic development in humans and in animals are very similar on a molecular level and that genes involved in development also play a role in human disease. The Division of Molecular Embryology is studying mechanisms regulating embryonic cell differentiation in *Xenopus* and mouse. Our aim is to characterize molecular mechanisms relevant for the formation of the embryonic body axis. To this end, we identify developmental control genes, investigate what their biological role and biochemical mode of action is and how they are regulated. We specifically address the following two main topics: I. Molecular mechanisms of Wnt/β-catenin signalling during early vertebrate development. Elucidation of the functions of Dickkopf (Dkk) proteins, a class of Wnt inhibitors, is a major focus. II) Molecular mechanisms of embryonic reprogramming, with the aim to elucidate molecular mechanisms regulating embryonic pluripotency.

Fig. 1: *Xenopus* embryos at 4-cell stage.

Christof Niehrs

Molecular Embryology

Research Summary

The Division of Molecular Embryology is studying mechanisms regulating cell differentiation. The aim is to characterize molecular mechanisms relevant for the formation of the body axis in frogs and mice. To this end, we are identifying developmental control genes and investigating how these are regulated and what their functions are. Our special interest is devoted to investigating the molecular characteristics of a region of the embryo called Spemann organizer. Another focus is the systematic analysis of gene activity during early embryonic development.

Curriculum Vitae

Degrees: 1985 Diploma (M.Sc.)
1990 Ph.D.
1997 Habilitation

1986-1990: Thesis work at EMBL, Heidelberg
1990-1993: Postdoctoral fellow, University of California, L.A., USA

since 1994: Group Leader of the division: “Molecular embryology” at the German Cancer Center (DKFZ), Heidelberg

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Fig. 1: *Xenopus* embryos at 4-cell stage.
Mechanisms of Wnt signaling in early vertebrate development

The Wnt/β-catenin pathway plays an eminent role in development and disease. We showed that in Xenopus embryogenesis, Wnt/β-catenin signaling plays an important role in antero-posterior patterning of the early central nervous system. Our results demonstrated a posteriorizing gradient of Wnt signalling, which regulates dose-dependently positional information from the forebrain to spinal cord. Importantly, we revealed an endogenous antero-posterior gradient of Wnt/β-catenin signalling in the presumptive neural plate of the Xenopus gastrula. Together with other data this led to the proposal of perpendicular activity gradients of Wnt and BMPs, which regulate early CNS patterning (Fig. 2).

We previously identified an important regulator of Spemann’s organizer, dickkopf1(dkk1), member of a new family of secreted proteins. Dkk1 encodes a Wnt inhibitor and its functions in embryonic head development (Fig. 3). While the gene was initially characterized as a developmental regulator, dkk1 is gaining increasingly medical attention, since it has been implicated in bone physiology and myeloma by others. We currently study the role of Dickkopf genes and their receptors Kremen and LRP6 during Xenopus and mouse development, including CNS. Towards this end we identify interacting proteins of these proteins and elucidate their role in Wnt signalling and early development. This led to the recent discovery of Rspondins and Casein kinase 1 gamma as novel Wnt regulators, which are also involved in CNS patterning.

Reprogramming

Another line of research in our laboratory is devoted to the question of reprogramming i.e. the artificial process of transformation of a somatic into a pluripotent cell. The interest is two-fold. First, by identifying regulatory genes that control the state of pluripotency we hope to learn
how the differentiated vs. pluripotent state is regulated. Second, this knowledge may be used to generate human isogenic pluripotent stem cells for regenerative medicine. Towards this end we have developed partial embryonic reprogramming of entire somatic cells by using *Xenopus* egg extracts. Screening for factors required for reprogramming identified the chromatin remodelling ATPase BRG1.

Furthermore, we have identified a molecular mechanism that is involved in demethylation and re-activation of pluripotency genes, such as oct4. This mechanism involves the stress response gene Gadd45, which acts by recruiting DNA repair to sites of demethylation. Methylated cytosines are excised and replaced by unmethylated nucleotide, thereby leading to demethylation. This is a novel epigenetic mechanism of gene activation. We currently study the role of this process during early *Xenopus* development and we screen for factors that mediate the site specific targeting of Gadd45 to sites of demethylation in the genome.

**Top publications**

- Kazanskaya, O., et al. (2004). R-Spondin2 is a Secreted Activator of Wnt/beta-Catenin Signaling and Is Required for Xenopus Myogenesis. Dev Cell. 7(4), 525-34.

**Structure of the Group**

**Group Leader:** Christoph Niehrs

**Scientists:** Gary Davidson, Mathias Gierl, Andrei Glinka, Emil Karaulanov, Olga Kazanskaya, Bisei Ohkawara, Cristina Sirrenberg-Cruciat

**PhD-Students:** Kristina Ellwanger, Wolfram Gruhn, Ya-Lin Huang, Malte Paulsen, Andrea Schäfer, Jinlong Shen, Lilian Sitter, Yuliya Sytnikova

**Technicians:** Gabriele Döderlein, Ursula Fenger,
Sabina Pauen

Early childhood brain and cognitive development

Research Summary
Using behavioural as well as neurophysiological data (heart rate, ERPs), we explore lower and higher order cognitive functions (e.g. intermodal perception, categorization, memory formation, causal and functional understanding, social cognition) in early childhood development. Furthermore, we are interested in the relation between emotional and cognitive self-regulation and how it is influenced by early childhood experience.

Curriculum Vitae

Degrees: 1988 Diploma (M.Sc)  
1992 Ph.D.  
1999 Habilitation  
1985-1988: University of Marburg (Psychology Diploma)  
1990-1991: University of Giessen - DFG Research assistant  
1991-1993: University of Tübingen - Research assistant  
1993-1994: Cornell University - DFG Postdoctoral fellow  
1994-1999: University of Tübingen - Research assistant  
2000-2001: University of Magdeburg  
Leader DFG-Junior Research Group  
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Current Research

Categorization in infancy

Categorization in infancy is based on bottom-up processes (i.e. perceptual abstraction) as well as on top-down processes (i.e. memory activation). As work conducted in our lab has shown, top-down processes play an important role even at a preverbal age. Infants perform a global-to-basic-level shift, with more abstract categories (i.e. animates vs. inanimates) developing earlier than basic-level categories like dogs, cats, chairs or tables (Pauen, 2002a). As indicated by follow-up studies, these categorical distinctions reflect conceptual knowledge (Pauen, 2002b). So far, only behavioural measures have been used to study infant categorization. In our lab, we also use heart rate measure (Elsner, Pauen & Jeschonek, 2006) and ERP-measures (see Figure 1) to validate behavioural data. Corresponding studies demonstrate that even the brains of 7-month-

Fig. 1: Infant prepared to conduct an EPR-Study on categorization.
old infants respond differently to animal and vehicle pictures. Furthermore, we found that 12-month-olds show different brain responses when looking at pictures of artefacts or animals accompanied by matching vs. non-matching sounds. Taken together, our studies provide first neuropsychological evidence for the early emergence of a knowledge-based animate-inanimate distinction.

**Causal and functional reasoning in infancy**

This line of research focuses on the question what kind of knowledge about objects infants acquire during the first year of life. One of the key attributes of animates is self-initiated movement. Using newly developed experimental paradigms, we have shown that even 7-month-olds are able to attribute the cause of a given motion to animates rather than inanimates. When watching an unfamiliar animal moving around together with a ball, they attribute the cause of this motion to the animal rather than the ball (see Figure 2).

Yet another line of research focuses on how infants use functional knowledge to guide their categorization of artefacts. Based on the finding that 12-month-olds categorize objects differently after their functional use has been demonstrated than without a corresponding demonstration (Träuble & Pauen, 2007) we now explore in more detail the conditions that support this kind of functional learning (social cues, objects cues; e.g. Elsner & Pauen, 2007).

**Relation between early cognitive development and language acquisition**

In early lexical acquisition, noun understanding emerges quite early. To better understand how preverbal categorization and noun comprehension interact, we investigate the impact of labelling on categorization performance in infants 7 to 12 months of age. Results reveal that in very young infants, nouns increase general attention for objects, but do not change the pattern of categorization, whereas for older infants who are about to learn basic-level categorical distinctions, nouns can indeed help to make these distinctions within a given global domain. Furthermore, we are interested in studying whether early preverbal categorization skills have prognostic value for later intelligence. Investigating the relation between verbal and non-verbal measures of intelligence for preschoolers, we found that non-verbal categorization skills in a basic-level task at 11 months of age and noun comprehension at 12 months of age (assessed via parental questionnaires) covariate. Furthermore, recent data from our German Language Development Study reveals that verbal and non-verbal measures of intelligence in 4- to 5-year olds are more closely related that originally thought.

**Development of analogical reasoning**

This line of studies focuses on the beginnings of analogical reasoning in human infants. We approach this issue by conducting comparative studies with infants, monkeys and chimpanzees in collaboration with primate labs at the MPI in Leipzig as well as the monkey-lab at the University of Rome. Our studies and collaborations focus on three related topics: (1) intermodal integration of dynamic...
displays, (2) perceptual understanding of the sameness and differentness relation, and (3) tool-use as well and relational mapping. Infants are shown dynamic displays presenting one upward and one downward moving circle, accompanied either by a tone of rising or descending pitch. Using a preferential-looking paradigm, we will find out whether intermodal relational mappings typically found in adults (i.e. an upward movement is associated with a rising pitch) are rooted in basic intermodal perceptual integration of the brain from birth on, or can better be explained by learning processes occurring later in life. In similar ways, we plan to explore other intermodal relations, such as the relation between luminance and pitch.

One very basic perceptual relation that plays a crucial role in categorization is the relation of sameness / differentness. Existing animal studies suggest that monkeys are capable of judging sameness and differentness, when provided with at least 8 to 16 pictures that either look identical or different from each other. This leaves open the question whether they really understood the underlying concept or solved the task by simply recognizing that the elements of some complex display either showed a graphical pattern or did not. Ruling out this methodological problem, the present study will compare monkey and infant performance in a response-match-to sample task, using only two simple graphic figures per display that are either the same or different from each other.

Analogical reasoning plays a crucial role in problem solving. Together with Rome we designed a tool-use study in which monkeys and infants learn to use one of three sticks, differing in the appearance of their handles as well as in the length of the sticks, to push some reward out of a tube. Only the longest of the three sticks reaches the reward in the tube – thus providing an effective tool. Following a training phase, the infants and animals will get a new set of tools. All three sticks have the same length as before, but the handles are exchanged. It will be tested whether the infants / monkeys focus on the functionally relevant feature (i.e. stick length) or the perceptually salient cue (i.e. the handle) when choosing their tool.

Top publications


Structure of the Group

Group Leader: Sabina Pauen
Postdoctoral fellows: Birgit Elsner, Gudrun Kane, Janna Pahnke, Birgit Träuble, Eva Vonderlin
Scientists: Lyset Babocsai, Deise Desch, Alenka Hribar, Susanna Jeschonek, Anna Ropeter, Cornelia Schrauf, Isa Valentina, Andrea Wittke
Current Research

Our research is focused on the question how axons (the long extensions sent out by developing and regenerating nerve cells) are able to protrude, extend, and navigate towards their targets where they will ultimately form synapses. At the tip of each axon is a motile, sensory structure, the growth cone, which is able to sense growth permissive and non-permissive cues in its environment and to react accordingly. Important molecules in the environment as well as in the growth cone membrane are cell adhesion molecules (CAMs) which hence act both as external guidance cues and as axonal receptors by interacting with each other. The external signals are transformed into an adequate growth cone reaction (turn towards or turn away; stop, retraction or advance) by intracellular signalling cascades which ultimately act on the local stability of the cytoskeleton. The growth cone cytoskeleton thus is the structure which defines the future growth direction of the axon: The cytoskeleton is stabilized on one side of the growth cone and destabilized on the other which leads to a local collapse and protrusion formation, respectively, so that the axon in the following turns to the side where the growth cone is net stabilized. This differential stabilisation is mainly modulated by microtubule binding proteins (MBPs) which are capable of enhancing microtubule growth and stability.

In particular, our research concentrates on the roles of two CAMs of the immunoglobulin superfamily, DM-GRASP and NrCAM, for extending axons since they are both axon-specific and expressed during early axon growth. CAMs not only mediate adhesion but also elicit intracellular signalling pathways; this way, CAMs have an downstream impact on cytoskeletal dynamics. We thus also analyse the functional impact of MBPs, in particular MAP1B and APC, on the stability of the microtubule system in the growth cone and the consequences for axonal navigation. Moreover,
we study the modulators of the MBPs which activate or inactivate their microtubule stabilizing properties and thereby mediate between plasma membrane receptors and cytoskeleton.

Our model system is the developing visual system of the avian embryo. The retina is the best accessible part of the central nervous system since it is basically the only structure not covered by bone. Due to its extra-uterine development, the avian embryo is a higher vertebrate embryo which can be readily manipulated and observed in the intact egg over long time periods. In addition, the avian embryo model system provides a series of culture techniques which allow for the study of navigating axons in their natural histotypic environment, e. g. in eye organ culture or in retina flat-mount culture. We concentrate on extension and navigation of retinal ganglion cell (RGC) axons which are the only axons to leave the retina; they dive into the optic nerve head and project to the optic tectum of the midbrain.

Roles of the CAMs DM-GRASP and NrCAM for axonal growth and pathfinding

The spatio-temporal expression analyses which we performed for DM-GRASP and NrCAM in the embryonic visual system revealed that both CAMs are exclusively present on extending, fasciculating RGC axons which form the innermost optic fibre layer in the retina and regional subsets in the optic nerve, chiasm, optic tract, and optic tectum, indicating their function for early axon growth and navigation. Using an in vitro assay system mimicking this restricted presence of DM-GRASP and NrCAM in the growth cone environment by narrow substrate lanes coated on glass cover slips, we could show that both CAMs are able to guide RGC axons (Fig. 1a). Moreover, both CAMs enhance axon growth on laminin substrate, indicating that the presence of these CAMs could speed up RGC axons in vivo. Both CAMs could be demonstrated to contribute crucial to the correct routing of RGC axons into the optic nerve head by inhibition experiments in the intact retina (Fig. 1b). Also the focussing of the RGC growth cones towards the optic fissure and the limitation of their probing activities away from the correct growth direction depends on the presence of the CAMs as visualized by laser scanning microscopy 3D reconstructions (Fig. 1c). Time lapse analysis in retina flat-mount cultures moreover revealed that the RGC axons grow slower and meander more on their way to the optic nerve head if DM-GRASP or NrCAM is blocked. Together these findings show for the first time that these two CAMs have an important impact on axonal growth and navigation.

Fig. 1: Impact of CAMs on axons. (a) NrCAM offered as substrate lanes (N) is preferred over laminin (L) by RGC axons. (b) Blocking of DM-GRASP results in RGC axons crossing the optic fissure (OF) and growing into the opposite retina side. (c) In contrast to the slim growth cones focussed towards the OF (upper panel), blocking of NrCAM (lower panel) leads to perpendicularly probing complex growth cones.

Roles of microtubule binding proteins MAP1B and APC

Growth cone behaviour such as advance, pause, turn, and retraction and thereby the growth direction of the axon is largely determined by the microtubule system which is modulated in its dynamics by MBPs. In growth cones induced to turn at a substrate border, we could show that a special phosphorylated form of the axon-specific MBP microtubule-associated protein 1B (MAP1B) is only found in the stable region of the growth cone, i. e. in the side of the future growth direction. Kinase Cdk5, which performs this type of MAP1B phosphorylation, is present in the entire growth cone. The activator of Cdk5, P35, however, is only found in the stable part of the growth cone; thereby
a local activation of MAP1B phosphorylation can lead to a
differential stabilisation/collapse of growth cone regions.
We could thus demonstrate a crucial role of MAP1B and its
modulators Cdk5/P35 for growth cone turning responses
and thereby axonal navigation. We also investigated
how APC, another MBP present in the growth cone (Fig.
2a), affects the dynamics of microtubules and thus the
behaviour of the growth cone. We neutralized domains of
the large, multifunctional protein APC by chromophore-
assisted laser inactivation (micro-CALI) in one half of the
growth cone. Inactivation of the N-terminal domain (which
is crucial for APC’s dimerisation and hence conceivably
for microtubule bundling/stabilisation) results in growth
cone collapse and turn away of the entire axon (Fig. 2b).
In contrast, neutralisation of the 20 amino acid repeat
domains in the middle region (which are necessary for
APC’s integration into a degradation complex) leads to the
formation of protrusions and turn of the axons towards this
side. This shows for the first time the role of APC for a local
and domain specific modulation of microtubule dynamics
in growth cones, thus affecting axonal steering.

![Fig. 2: Role of the microtubule system in growth cones. (a) Laser scanning microscopy visualizes APC and microtubules in the growth cone. (b) Local laser inactivation of the N-terminal region of APC in one growth cone half leads to a turn of the axon away from this side whereas inactivation of the middle region of APC results in a turn towards this side as seen by the growth cone trajectories depicted for the first 10 min after laser treatment (10 axons each).]

### Top publications

### Structure of the Group
- **Group Leader:** Gabriele Elisabeth Pollerberg
- **Postdoctoral fellows:** Christoph Knab, Karsten Thelen
- **PhD-Students:** Jan Hegner, Francisco Ropero, Steffen Jährling, Christian Hahn, Michael Köster, Bettina Maier
- **Undergraduates:** Helen Desirée Krause, Friderike Ewald, Fabian Roger, Xiaorui Sun, Jakob Villoth
- **Technicians:** Susanne Bergmann, Claudia Brandel, Monika Zieher-Lorenz
**Gudrun Rappold**

**Molecular pathogenesis of genetic disorders**

**Research Summary**

The focus of our research is the molecular elucidation of human disease, especially growth and neuronal disorders. To uncover the causes of these disorders, our work employs different cell culture and animal models and differentiated embryonic stem cells. We would like to understand how mutations correlate with disease, how genes are regulated and how they contribute to differentiation and development.

**Curriculum Vitae**

Degrees: 1980 Diploma (M.Sc.) University of Heidelberg  
1984 Ph.D. University of Heidelberg  
1993 Habilitation  
1974-1980: Biology and Chemistry  
(Stanford, USA, Konstanz and Heidelberg)  
1980-1984: Doctoral thesis in Human Genetics, Heidelberg  
1984-1985: DAAD Scholarship at the Medical Research Council, Mammalian Genome Unit, Edinburgh, Scotland  
1985-1987: Postdoctoral fellow at EMBL, Heidelberg  
1987-1988: Postdoctoral fellow at the Imperial Center Research fund (ICFR) London, England  
1989: Group Leader at the Institute of Human Genetics, Heidelberg  
2004: Full Professor and Chair of Department of Human Molecular Genetics, University of Heidelberg

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**Current Research**

**Homeodomain transcription factors SHOX and SHOX2**

Homeodomain proteins play a fundamental role during embryogenesis and development by regulating pattern formation and organogenesis. SHOX is a member of the paired-related homeobox family, highly conserved among vertebrate species, but absent in mouse and rat. SHOX is best known as a master controller of human height. Defects in SHOX cause syndromal (Léri-Weill, Langer and Turner syndrome) as well as idiopathic growth failure. Together, SHOX defects probably represent the most common known genetic cause of short stature in humans. Furthermore, expression in muscle, vascular tissue and brain suggests that SHOX also plays a role in myogenesis, angiogenesis and neural development. The SHOX gene is regulated both at the transcriptional and translational level. To understand the regulation of gene expression in a spatial and temporal manner, the study of tissue-specific regulatory elements and its consequence with respect to the associated phenotypes will be carried out in model systems.

The SHOX protein acts as a transcriptional activator which binds to specific DNA sequences. Crucial functional domains for SHOX activity (DNA binding, dimerisation, nuclear translocation) have been defined and characterised by mutant variants, providing a mechanistic understanding of the function of this key gene. Phosphorylation on Ser 106 has been shown to play an important role in regulating SHOX biological activity by modulating its transcriptional activity.

SHOX induces cellular growth arrest and is expressed in human growth plate chondrocytes. It is expressed in human and chicken embryos from an early stage onwards with high expression in the developing limbs and represents a marker for chondrocyte maturation in the growth plate. Up to now, there is very little data on the molecular pa-
Identification of upstream regulators and downstream targets will help to understand the pathways in which this gene functions.

On the clinical/translational side, we have established the genotype-phenotype correlation in more than two thousand children with short stature, set up an interactive SHOX database, accompanied a controlled, multi-center trial treating children with SHOX deficiency with recombinant growth hormone. In 2005, the results of this trial were given orphan drug status by the FDA and in 2007, the treatment on SHOX disorders was approved by the Federal authorities in the US and Europe.

For Shox2, its importance in embryonic development was recently shown by demonstrating that its complete loss of functions in “knock-out” mouse models is incompatible with postnatal life and analyses of Shox2 deficient embryos revealed highly specific defects within the sinus venosus of the developing heart as the likely cause of embryonic lethality. Using this mouse model, we are trying to understand the basic functions of Shox2 during early organogenesis. Based on the extraordinary high degree of evolutionary conservation, we are furthermore able to investigate Shox2 functions in diverse animal models including Chicken, Xenopus and Zebrafish.

Our cell and molecular biological analyses include individual steps of transcriptional and post-transcriptional regulation, interacting proteins and downstream targets using the following experimental approaches: studies using primary chondrocytes and differentiated mesenchymal stem cells, Yeast-two-hybrid analysis, GST-pulldown, Co-IP assays, Microarray hybridisation, quantitative RT-PCR, Reporter gene assays and animal as well as cell culture models.

**Serotonin 5-HT Receptor Genes**

Serotonin (5-hydroxytryptamine, 5-HT) controls a variety of physiological functions in the central and peripheral nervous system. Serotonin action is mediated by a multitude of 5-HT receptor subtypes divided into seven main classes (5-HT1R to 5-HT7R). Except for the 5-HT3 receptor, which is a ligand-gated ion channel, all serotonin receptors represent G-protein coupled binding proteins.

Our previous work comprised the analysis of HTR3A and B genes as candidates in the etiology of psychiatric disorders. In more recent years, we successfully isolated several novel serotonin receptor 5-HT3-genes, which can help unravelling the 5-HT3 receptor diversity in humans. One of the novel genes (HTR3E) represents an excellent candidate for the investigation of gastrointestinal diseases such as irritable bowel syndrome and eating disorders (bulimia nervosa and anorexia nervosa) and might shed light upon the pathomechanism of these particular disorders. Analyses of the HTR3 genes are carried out on an electrophysiological, pharmacological, biochemical as well as cytological level to investigate the possible molecular make-up of the respective receptor subtypes and its response to specific drugs.

**Functional Role of the RhoGAP gene MEGAP in neuronal development**

Mental retardation is a developmental disorder characterised by a global deficiency in cognitive abilities. It is a common clinical disorder affecting about 2-3% of the population. We have found that haploinsufficiency of a RhoGAP gene, MEGAP, is associated with mental retardation in several patients. The Rho family of GTPases, and in particular MEGAP, plays an important role in various aspects of neuronal development, including neurite outgrowth and differentiation, axon pathfinding and dendrite spine formation and maintenance.
MEGAP, also called srGAP3, is highly expressed in the developing and mature mammalian nervous system. We are interested in the question of how mutations in MEGAP that alter Rac1 and Cdc42 signalling result in abnormal neuronal development and deficient cognitive functioning in human and mouse. We are studying the mechanisms of MEGAP regulation during development in primary neurons and axonal growth cones with regard to actin and microtubule dynamics and growth cone guidance. We also analyse MEGAP binding partners and further characterise the role of MEGAP in the Slit-Robo signalling pathway. To study the normal and pathological role of MEGAP, a targeted gene disruption of the mouse ortholog has been carried out (collaboration with Prof. Dusan Bartsch). The analysis of the knock-out and wildtype mice including analysis of brain sections during different stages of development, behavioural testings and cultures of primary hippocampal neurons, may enable us to better understand the pathomechanism leading to mental retardation in patients with MEGAP haploinsufficiency.

Top publications


Structure of the Group

<table>
<thead>
<tr>
<th>Group Leader</th>
<th>Gudrun Rappold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postdoctoral fellows</td>
<td>Claire Bacon, Jianjun Chen, Volker Endris, Beate Niesler, Katja Schneider</td>
</tr>
<tr>
<td>PhD-Students</td>
<td>Eva Decker, Claudia Durand, Anne Glaser, Christian Hammer, Johannes Kapeller, Lydia Haussmann, Sandra Puskaric, Simone Steinbrecht</td>
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<td>Technicians</td>
<td>Elke Fenner, Ralph Roeth, Birgit Weiß</td>
</tr>
</tbody>
</table>
Current Research

Neuromagnetic representation of temporal and spectral pitch in the auditory cortex

Temporal integration in the auditory system within 30 milliseconds plays a crucial role in pitch processing. Current models suppose that pitch perception is based on the processing of (i) the temporal regularity of a sound and (ii) its spectral envelope. Although, the representation and integration of both characteristics remains unclear, the latency of the late AEFs exhibit a high correlation to the inverse of the perceived pitch (Gutschalk et al., 2002; Ritter et al., 2005, 2007; Rupp et al., 2005). In an interdisciplinary project (Institut für Theoretische Physik Heidelberg, Prof. Dosch, and the Centre for the Neural Basis of Hearing, Department of Physiology in Cambridge, Prof. Patterson) we are developing critical stimuli by manipulating the temporal regularity as well as the temporal and spectral envelope of sounds. Spatio-temporal source analysis will be applied to locate pitch-related centers in the auditory cortex and to investigate the temporal course of the AEF. These experiments will be carried out in subjects who perceive dominantly the fundamental pitch of an uncomplete harmonic complex sound and a complementary group of listeners, who dominantly perceive specific harmonics of such sounds. The first group exhibits larger AEF and larger grey matter volumes in the left hemisphere while the latter shows the opposite behaviour. The choice of these subjects will provide valuable information to investigate the dependency of pitch perception on temporal and spectral aspects.

Differences in auditory evoked fields and grey matter volume of the left and right Heschl’s gyrus between musicians and non-musicians

The extensive research on auditory fields and morphological characteristics (Schneider et al., 2002; 2005) showed...
that musicians exhibit enhanced P30 components (located in the primary auditory cortex, i.e. medial Heschl’s gyrus) and P50-components (located in lateral Heschl’s gyrus) compared to non-musicians. Furthermore, the magnitude of these signals are correlated with (i) the absolute grey matter volume of these areas and (ii) a psychometric test to assess musicality. Currently, these investigations will be continued in a cross-sectional and longitudinal design in children and adolescents to further investigate the influence of training on the plasticity of these components, because the P50 amplitude is strongly correlated to the long-term duration of professional training while the P30 amplitude is affected to a much lesser degree.

**Early representation of the auditory nerve spike pattern in the primary auditory cortex**

Alternating the phases of a harmonic tone produces pure-tone masked thresholds differing by more than 20 dB. This effect is due to the characteristics of the auditory filters on the basilar membrane which differently affect ringing within channels. Based on the analysis of early

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![Fig. 1](image1.png)

Fig. 1: Simulations of the neural activity in the auditory nerve of a harmonic complex sound $f_0=250$ Hz (a, tonotopic axis with high frequencies at the top and low frequencies at the bottom), and the stabilized auditory image (b) that results from an alignment across channels due to a non-linear strobing mechanism. This computational stage results in a buffer with a decay of excitation within 32 ms. The distance between the ridges corresponds to the perceived pitch of a tone and the height of the ridges determines the salience of pitch. (c) The magnitude of the N100 evoked by tones with different temporal envelopes (ramped vs. damped with different half-life-times) as derived from sources in the lateral Heschl’s gyrus correspond to both, (d) the psychoacoustically determined salience of these tones when compared to each other, and (e) the height of the first ridge of the stabilized auditory image.
AEFs and basilar membrane simulations (Rupp et al., 2002), we analyze in a collaboration with Prof. Dau (DTU Oersted, Denmark) the representation of such peripheral effects in the auditory cortex. First results indicate that neuromagnetic responses are highly consistent with perceptual properties obtained with the same stimuli and with results from simulations of neural activity at the output of cochlear preprocessing. This suggests that the activity wave in the auditory nerve keeps its across-frequency timing structure travelling to the auditory cortex and that the AEF that is reflected in the MEG response is strongly related to the timing structures. Due to the high correlation of basilar membrane characteristics and the morphology of the auditory evoked fields, we are currently optimizing semi-realistic models of the cochlea to enhance the validity of spike simulations in the auditory nerve (Sieroka et al., 2006). Such investigations might support the development of hearing aid algorithms that simulate the compressive behaviour of the cochlea which is found in normal hearing subjects.

**Top publications**


**Structure of the Group**

Group Leader: André Rupp
Postdoctoral fellows: Steffen Ritter
Undergraduates: Martin Andermann, Johannes Hack
Technicians: Barbara Burghardt, Esther Tauberschmidt
Martin Schmelz

Translational pain research

Research Summary

In this research group sensitization of primary afferent nociceptors is investigated as one mechanism for chronic pain and neuropathy. We focus on translational studies using single fiber recording techniques in chronic pain patients, human volunteers and large animals (pig) combined with functional and structural investigations of skin innervation in vivo and in cell culture.

Curriculum Vitae

Degrees: 1991 M.D. University of Erlangen
1999 Habilitation
1985-1991: Medical school
1991-1992: Internship at the Department of Occupational Medicine, University of Erlangen
1993-1999: Postdoctoral fellow at the Department of Physiology, University of Erlangen
1999-2002: Assistant Professor at the Department of Physiology, University of Erlangen
since 2002: Karl-Feuerstein Professor, Department of Anesthesiology Mannheim, University of Heidelberg, Heading the section for Experimental Pain Research
since 2007: IZN Investigator

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Current Research

Cellular porcine model

Patch-clamp and histochemistry of porcine dorsal root ganglion cells to characterize different nociceptor classes. Development of in vitro model of nerve endings separated from the cell body and coculture with keratinocytes.

Porcine single fiber recordings

Characterization of different afferent nerve fiber classes and modulation of axonal excitability using standard teased fiber techniques in the pig saphenous nerve. Effects of locally applied growth factors on excitability of nerve endings and axonal excitability.

Porcine neurogenic inflammation

Development of experimental models of peripheral sensitization by UVB irradiation with the objective readout of axon reflex erythema measured by laser Doppler imaging. Microdialysis in the sunburn to assess levels of inflammatory mediators involved in peripheral sensitization.

Human pain models

Characterization of human pain models for peripheral (UVB irradiation) and central (electrical pain and hyperalgesia model) sensitization by pharmacological intervention. Objective assessment of cutaneous unmyelinated innervation by electrically induced axon reflex erythema and electrically induced axon reflex sweating.

Chronic pain patients

Microneurographic characterization of neuropathic changes in primary afferent fibers linked to chronic pain. Correlation of functional and structural changes in neuropathic pain by using skin biopsies, quantitative sensory testing, and electrically induced axon reflex measurements.
Fig. 1: Two-compartment *in vitro* model of piglet DRG neurons with somata and processes separated by a diffusion barrier. Microphotographs after 6 days in cell culture. PGP9.5 staining.

**Top publications**


Fig. 2: Corresponding patterns of activity dependent slowing of conduction velocity (360 stimuli at 2Hz, followed by 40 stimuli at 0.25Hz) in respective C-fiber classes in humans (microneurography) and pig (teased fiber technique). cmi: mechano-insensitive nociceptors, cm: polymodal nociceptors, symp: sympathetic efferent, cold: cold nociceptors.

**Structure of the Group**

- **Group Leader:** Martin Schmelz
- **Senior scientists:** Marlen Petersen
- **Postdoctoral fellows:** Roman Rukwied
- **Scientists:** Martin Dusch, Otilia Obreja, Marcus Schley
- **Technicians:** Andreas Klusch, Elmar Forsch
Gerhard Schratt

The role of microRNAs in synaptic development and plasticity

Research Summary
The local translation of mRNAs near synapses is crucial for various forms of synaptic plasticity. We recently found that microRNAs, an extensive class of small non-coding RNAs, regulate synaptic protein synthesis and dendritic spine development in neurons. Future experiments aim at the identification of the full complement of synaptic microRNAs and their target mRNAs, as well as microRNA function in memory-related processes in vivo.

Curriculum Vitae
Degrees: 1998 M.Sc. (Diploma) University of Tübingen 2002 Ph.D. University of Tübingen
1998-2002: Thesis work, Interdisciplinary Institute of Cell Biology, University of Tübingen
2002-2006: Postdoctoral fellow at the Division of Neuroscience, Children’s Hospital and Department of Neurobiology, Harvard Medical School, Boston, USA
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Current Research

Genome-wide identification of microRNAs that function during synapse development

MicroRNAs are a class of non-coding RNAs (18-25 nt) that act as post-transcriptional regulators of gene expression. In the mammalian system, the majority of microRNAs bind to 3’UTR regions of target mRNAs, thereby inhibiting the translation of a large set of target mRNAs. In recent years, microRNAs have been attributed a flurry of cellular functions, including the regulation of cell differentiation, survival, and metabolism (Bartel, 2004). The function of microRNAs in the nervous system is still largely elusive. However, the complete lack of microRNAs in the brain leads to defects in morphogenesis and survival. In addition, examples of individual microRNA functions in neurons have been reported, in particular during early stages of neuronal fate determination (miR-9, miR-124) and neurite outgrowth (miR-132) (Kosik, 2006). Recently, we found that a brain-specific microRNA, miR-134, is expressed in post-mitotic neurons and involved in morphological regulation of dendritic spines, the major sites of excitatory synaptic transmission (Schratt et al., 2006). This finding led to the hypothesis that a microRNA regulatory network could control the expression of critical synaptic proteins during synaptic development and plasticity.

In an attempt to characterize the full complement of microRNAs in the synaptodendritic compartment, the synaptic “microRNome”, we embarked on a large-scale expression screen using microarray profiling of microRNAs isolated from rat synaptosome preparations (Siegel et al., 2009). Thereby, we obtained a list of microRNAs that were significantly enriched in synaptosomes compared to whole brain preparations. Subsequent loss-of-function experiments revealed that a subset of these microRNAs is involved in bi-directional regulation of dendritic spine size.
One of the identified miRNAs, miR-138, appears to control spine size by regulating the palmitoylation status of critical synaptic proteins. These results will provide a roadmap for future experiments to determine the role of individual miRNAs in synaptic plasticity in vivo (see below).

**Activity-dependent regulation of microRNA expression and function**

Synapse development and plasticity are highly regulated by neuronal activity. Interestingly, we recently discovered that expression of the synaptic miR-134 is induced by depolarization of the neuronal membrane (Fiore et al., 2009). miR-134 is a member of a large microRNA cluster that consists of more than 40 miRNAs, and it appears that the entire cluster represents one transcriptional unit that is co-regulated by a common calcium sensitive regulatory element. Currently, we are trying to identify the cis-acting regulatory factor(s) that couple miRNA cluster expression to neuronal activity, and to understand the role of calcium-induced miRNA expression in activity-dependent processes such as dendrite growth, synaptogenesis and plasticity.

**Identification of microRNA-associated protein complexes in neurons**

We recently found that the inhibitory activity of miR-134, in addition to calcium-dependent transcription, is regulated at the post-transcriptional level by the neurotrophin BDNF. This regulation likely involves post-transcriptional modification of a miR-134 associated protein/RNA complex, since miR-134 binding to its target mRNA Limk1 appears not be altered by BDNF (Fig. 2). To get a handle on the protein components of the complex we currently perform a large-scale RNA interference screen, targeting neuronal RNA-binding proteins that might participate in microRNA-dependent gene regulation. This approach will be complemented by the biochemical characterization of the miR-134 associated protein complex and the functional characterization of RNA-binding proteins in dendritic spine development.

**Large-scale identification of physiological microRNA target mRNAs in neurons**

The functional characterization of microRNAs is still hampered by the limited knowledge of physiological microRNA target mRNAs. Bioinformatic algorithms have been generated to predict targets based on sequence complementarity and accessibility. These algorithms however do not take into account cell-type specific expression and subcellular localization of microRNAs and their target mRNAs. We plan to exploit the fact that miRNAs primarily regulate mRNA translation at the level of initiation to elucidate microRNA targets. Therefore, polysome-bound mRNAs from neurons will be profiled (Schratt et al., 2004), and those mRNAs that display differential polysome association as a function of microRNA activity will be screened for potential microRNA binding sites.

**In vivo functional analysis of neuronal microRNAs**

Although the evidence for a role of microRNAs in postmitotic neurons is growing, the *in vivo* function of individual miRNAs in synaptic development and function is still completely unknown. We plan to pursue two complementary approaches to unravel the physiological role of candidate miRNAs that we recently identified in...
cultured neurons: i) virus-mediated delivery of microRNAs or their inhibitors into mice using intracranial injection. ii) classical site-directed mutagenesis in the mouse, using the Cre-loxP system to specifically inactivate microRNAs in the postnatal brain. Neurons from virus-infected or genetically modified mice will be subsequently analyzed at the morphological and electrophysiological level. In addition, these mouse models will allow the performance of behavioural experiments related to learning and memory.

**microRNAs as novel targets for therapeutic intervention**

Many neurological disorders are characterized by synaptic dysfunction, including mental retardations, autism-spectrum and mood disorders. Given our findings from cultured neurons, we speculate that microRNA function might also be frequently disturbed in these cognitive diseases. In collaboration with Santaris Pharma, Denmark, we are currently developing oligonucleotide inhibitors directed against synaptic microRNAs for the delivery into the rodent brain *in vivo*. In the future, such agents could represent a novel avenue for therapeutic intervention.

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**Fig. 2: Activity-dependent regulation of dendritic microRNA complexes.**

Under basal conditions (left), dendritic microRNAs such as miR-134 recruit miRISC, leading to translational inhibition of dendritic mRNA targets (i.e. Limk1) and restricted spine growth. Neuronal activity (right) promotes the release of BDNF, which triggers the activation of the mTOR signaling pathway. This in turn leads to the release of miRISC inhibition by an unknown mechanism, allowing the translation of dendritic target mRNAs and spine growth. Adapted from Schratt et al., 2006.

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**Top publications**

- Fiore, R. et al. (2009). Mef2-mediated transcription of the miR379-410 cluster regulates activity-dependent dendritogenesis by fine-tuning Pumilio2 protein levels. Embo J. 28, 697-710

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**Structure of the Group**

**Group Leader:** Gerhard Schratt  
**Postdoctoral fellows:** Roberto Fiore  
**PhD-Students:** Guney Akbalik (Erasmus), Silvia Bicker, Mette Christensen (visiting), Sharof Khudayberdiev, Gabriele Siegel  
**Undergraduates:** Matthias Veith  
**Technicians:** Tatjana Wüst
Current Research

Our research targets the physiological, cellular and molecular mechanisms underlying experience-dependent synaptic plasticity in *Drosophila*. Fundamental for this research are two complementary experimental approaches:

A) The neuromuscular junctions (NMJs) of *Drosophila* larvae represent exceptionally well accessible glutamatergic synapses, which allow *in vivo* behavioral stimulation and a highly resolved physiological, morphological and molecular analysis of the mechanisms underlying experience-dependent synaptic potentiation.

Fig. 1: Development of larval NMJs of *Drosophila*. Developing neuromuscular junction of a *Drosophila* embryo (A, 12 h after egg laying) and larvae (B-D) at different developmental stages (B: 24 h after egg laying; C: 2 days after egg laying, D: 4 days after egg laying). (A) Growth cone of the motoneuron aCC extends dorsally towards its target muscle 1. (B) The growth cone has transformed to presynaptic specialisations of NMJs. These NMJs harbour functionally mature synapses. (C, D) Growth of NMJs during further larval development. NMJs were labelled with an antibody recognising the cell adhesion molecule Fasciclin II. Scale bars: 10 µm (A), (B-C); 20 µm (D). (from Schuster et al., 1996a)

Christoph Schuster

Mechanisms of experience-dependent synaptic plasticity, learning & memory and memory extinction

Research Summary

The physiological, cellular and molecular characterization of synaptic plasticity and higher brain functions such as learning & memory is often hindered by the high complexity of mammalian brains. We therefore apply powerful genetic, physiological and behavioral tools established in the fruit fly *Drosophila melanogaster* to study experience-dependent synaptic potentiation of larval glutamatergic synapses with high resolution as well as long-term memory (LTM) formation and LTM-extinction using an olfactory conditioning paradigm in adult flies. Our research aims at facilitating the identification of the principal mechanisms underlying higher brain functions.

Curriculum Vitae


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B) Olfactory fear conditioning of adult flies is a well established paradigm to elicit and analyze various forms of memory (including long-term memory; Fig. 2) and memory modification (such as extinction).

Both approaches greatly benefit from the powerful genetic tools available in Drosophila and the possibility to transfer the mechanisms identified in the high-resolution model NMJ to higher brain functions and vice versa.

**Experience-dependent potentiation of synaptic transmission**

The crawling activities of Drosophila larvae show large individual differences over time. These differences in crawling profiles are associated with differences in the usage of the glutamatergic neuromuscular synapses and can therefore be used to systematically assess potential experience-dependent synaptic changes. Based on this strategy we have recently shown that the strength of glutamatergic transmission can undergo robust and long-lasting potentiation in an experience-dependent manner.

This potentiation is mediated by several different synaptic mechanisms, which based on their temporal appearance define a hierarchy of several discrete phases of experience-dependent synaptic potentiation [4]. In this project we characterize the physiological and molecular mechanisms underlying experience-dependent synaptic potentiation. We are currently focusing on the following topics:

- Experience-dependent regulation of presynaptic quantal size
- Role of presynaptic mGluRs in the regulation and release of large vesicles
- Experience-dependent regulation of the functional balance of postsynaptic GluRs
Christoph Schuster

- Experience-dependent regulation of postsynaptic NO-synthase (NOS) activity
- Presynaptic NMDARs and their effect on the probability of vesicle release
- Ca^{2+}-dynamics in the pre- and postsynaptic terminal during experience-dependent potentiation
- Role of NOS-activity in the structural organization of synapses
- Experience-dependent synaptic protein synthesis and morphological consolidation of synaptic potentiation
- Development of a computational model of a simple network of glutamatergic synapses

**Long-term memory formation and LTM extinction in Drosophila**

Animals can store information based on their individual experiences. Yet not all information is stored for long periods of time. Rather, it is the most intense or even traumatic events, or the most repeated information, that is eventually encoded in long-term memory (LTM). LTM itself and/or access to the stored information is continually modified by experience, re-enforced through reconsolidation or diminished through extinction. Despite of an increasing general interest in these phenomena the underlying cell biological or molecular mechanisms are poorly understood. The fruit fly *Drosophila* has served as a model system for studying various forms of learning and memory, particularly for those evoked by Pavlovian conditioning, largely because of the power of its genetic tools, its smaller central nervous system and fewer molecular redundancies when compared to mammals. Identifying the principal mechanisms underlying LTM formation, consolidation, recall and extinction should facilitate a better understanding of similar processes in mammals and may guide towards novel treatments of psychopathological conditions. Based on established olfactory fear conditioning paradigms we are currently focusing on the following topics:

- Signaling events involved in the formation, consolidation and recall of LTM
- Mapping of LTM traces in the fly brain
- Role of NMDARs in LTM
- Characterization of LTM extinction
- Mapping of circuits and neurons involved in LTM extinction
- Signaling pathways involved in the formation of extinction memory
- Pharmacological and molecular interference with LTM extinction

**Top publications**


**Structure of the Group**

- **Group Leader:** Christoph Schuster
- **Postdoctoral fellows:** Matthias Knirr, Carla Margulies, Jonathan Rojo-Ruiz
- **PhD-Students:** Jean-Louis Thomas, Lucas Vicuña
- **Undergraduates:** Matthias Heindorf, Jon Leevmann, Friedrich Meyer, Roland Svensson
- **Technicians:** Emilia Sancho-Vargas
**Research Summary**

To understand the role of nuclear receptors, mutations in the mouse including cell-specific and inducible mutations have been generated. This approach allowed to define e.g. the role of the glucocorticoid receptor in control of body weight and its function in the brain (Figure 1), of the mineralocorticoid receptor in behavioural plasticity, and established the mechanism of positive feedback of the estradiol receptor in the brain. The orphan receptor tailless is crucial for neurogenesis in the adult and is involved in brain tumor formation (Figure 2).

**Curriculum Vitae**

**Degrees:**
- 1967 MD
- 1979 Habilitation (Physiological Chemistry)
  Free University of Berlin

**1966-1967:** Thesis work, Institute of Physiological Chemistry,
  University of Marburg,

**1967-1969:** Internship, Free University of Berlin

**1969-1974:** Postdoctoral fellow and research associate,
  Columbia University, New York, USA

**1974-1975:** Assistant Professor,
  Columbia University, New York, USA

**1975-1980:** Head of an Independent Research Group,
  Max-Planck-Institute of Molecular Genetics, Berlin

**Since 1980:** Head of the Division “Molecular Biology of
  the Cell I”, German Cancer Research Center,
  Heidelberg, and Professor, Faculty of Biology,
  University of Heidelberg

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**Current Research**

**I. Nuclear Receptor Function**

**Genetic approaches to define the role of the estradiol receptor α in the regulation of the reproductive axis**

To define the role of the G protein-coupled receptor GPR54 in the estrogen-mediated feedback regulation of GnRH synthesis we follow two approaches. GPR54 expression is controlled by the decapeptide Kiss1 synthesized in the AVPV neurons expressing the estradiol receptor α. Since germ line mutants of GPRR54 are infertile and have a similar phenotype as the ERα forebrain-specific mutants we reason that ERα leads to increased synthesis of Kiss1 which binds and activates the GPR54 receptor in GnRH neurons. To test this hypothesis we use GPR54-/− mice (obtained from Schering Plough) in which we express GPR54 under control of the GnRH gene. We also generate mice with a floxed allele of the GPR54 gene which we will cross with forebrain-specific Cre-expressing mice. With these experiments we hope to provide conclusive evidence that the critical positive feedback action of estrogens upon GnRH neurons are mediated via the Kiss1/GPR54 system and that the action of the receptor is indirect.

**Evaluation of corticosteroid receptor function in the brain**

Corticosteroid hormones regulate a variety of developmental, physiological and pathological processes by interacting with specific receptors, the glucocorticoid and mineralocorticoid receptor. Using genetic technologies we have generated a panel of tissue-specific and function-selective mutations of the genes for these two corticosteroid hormone receptors in the mouse. These mouse models have allowed us to gain important insights in corticosteroid hormone function in the animal.
Using these technologies we have been able to investigate steroid hormone receptor function, both in a tissue- or cell type-selective manner since germ line mutations for the glucocorticoid and mineralocorticoid receptor lead to lethality. We therefore have had a strong interest to develop conditional alleles for these two receptors. For example, using hepatocyte-specific mutations in the mouse we could show that the glucocorticoid receptor and Stat5 in hepatocytes are essential for normal postnatal growth. Surprisingly, the glucocorticoid receptor does not bind to DNA but its activity is mediated through interaction with the Stat5 protein. To identify the function of the glucocorticoid receptor in allergic skin conditions we have analyzed contact hypersensitivity in various specific glucocorticoid receptor mutant mouse strains. We could establish that macrophages and neutrophils are the targets for immune suppression of glucocorticoids in contact allergy responses. To generate mutations of the gluco- and mineralocorticoid receptor in the adult brain we have developed mice which express an inducible Cre recombinase in neurons of the forebrain (Figure 1). These mice with inducible mutations of the gluco- as well as the mineralocorticoid receptor, alone or in combination, are presently investigated to define the role of these receptors in functions like learning and memory, hypothalamic feedback control, and the process of addiction. Function-selective mutations combined with gene expression profiling will help to clarify the transcription mechanism involved in the action of corticosteroid hormones in vivo in the brain.

The nuclear receptor tailless (Tlx) is required for generation and maintenance of adult neural stem cells and participates in brain tumor formation

The tailless (Tlx) gene encodes an orphan nuclear receptor which is expressed in the periventricular neurogenic zone during mouse embryonic development. Mutant mice survive but display specific anatomical defects in the cortex and the limbic system. In particular late developing structures such as the upper cortical layers and the dentate gyrus are reduced in size due to depletion of progenitor cells in the subventricular zone.

To determine the cell types which express the Tlx gene we have chosen an approach where a Cre fusion protein is used as a reporter for the Tlx gene. We have shown that the Tlx gene is expressed exclusively in adult neural stem...
cells, the B cells, but not any more in progenitors (Figure 3). Cell fate mapping experiments showed that Tlx-expressing cells are multipotent which can differentiate into neurons, astrocytes as well as into oligodendrocytes. Using BrdU-incorporation, GFAP and Cre staining we could show that these cells are able to self-renew. Thus, Tlx is specifically expressed by long-term self-renewing neural stem cells. Tlx-expressing cells also express CD133, a marker of brain tumor stem cells. Furthermore, we could show that loss of Tlx leads to upregulation of PTEN in the subventricular zone compatible with its function in control of neural stem cell proliferation. These findings establish Tlx as an indicator for and regulator of adult neural stem cells.

Fig. 3: The Cre recombinase fusion protein is expressed exclusively in B cells expressing GFAP but not in C or A cells expressing EGFR or doublecortin (DCX), resp.

II. A New Model For Parkinson’s Disease

Disruption of nucleolar function leads to compromised mitochondrial activity

We have reported that disruption of nucleolar integrity based on the ablation of the gene for the transcription initiator factor TIF-IA results in stabilization of p53 and p53-mediated apoptosis. These findings are extremely interesting since a crucial role for p53 has been debated in several neurodegenerative diseases. Disruption of nucleolar integrity in dopaminergic neurons following ablation of the transcription initiation factor TIF-IA generated mice with the major hallmarks of Parkinson’s disease: progressive and differential loss of dopaminergic neurons in the Substantia nigra and Ventral Tegmental Area, depletion of striatal dopamine content and responsiveness to L-DOPA treatment. The observation that constitutive and inducible mutations in the TIF-IA gene mimic so closely Parkinson’s disease symptoms, stimulated us to ask whether nucleolar impairment affects mitochondrial activity and induces oxidative stress. Ablation of TIF-IA in dopaminergic neurons leads to disruption of nucleolar organization as reflected by altered distribution of the protein nucleophosmin, which is specifically found in the nucleolus of wild type mice but distributed throughout the entire nucleus in the mutants. Further, disruption of nucleolar integrity due to loss of TIF-IA is associated with the deficiency in the activity of cytochrome c oxidase (COX), the terminal enzyme complex of the mitochondrial respiratory chain. We therefore concluded that nucleolar disruption following TIF-IA ablation leads to impairment of mitochondrial functions. As signs of oxidative damage we find a strong increase in the number of dopaminergic neurons positive for markers of nitrosylated proteins, neuroketals, which are products of oxydised membrane fatty acid components and oxydised DNA. We reason that p53 overexpression mediates the effects of nucleolar disruption on mitochondria.
Top publications


Structure of the Group

Group Leader: Günther Schütz
Postdoctoral fellows: Stefan Berger, Andrii Domanskyi, Gitta Erdmann, Milen Kirilov, Witold Konopka, Grzegorz Kreiner, Hai-Kun Liu, Rosanna Parlato, Jan Rodriguez Parkitna, Caroline Ronzaud, Ying Wang
PhD-Students: Daniel Habermehl, Claus Rieker, Martin Novak
Technicians: Heike Alter, Tabea Arnsperger, Dagmar Bock, Katharina Sowodniok, Stefanie Stotz, Andrea Takacs
Markus Schwaninger

Gene regulation in cerebral ischemia

Research Summary
Stroke is a common and devastating disorder but still there is no effective therapy for the majority of patients. Because delayed mechanisms of ischemic brain damage such as neuroinflammation, apoptosis, and neurogenesis, rely on gene expression, we investigate gene regulation in the context of cerebral ischemia. Genetic and pharmacological tools are combined with the long-term aim to improve stroke therapy.

Curriculum Vitae

Degrees: 1987 MD 2000 Ph.D.
1983-1987: Thesis work in the Institute of Pharmacology, University of Freiburg
1991-1995: Postdoctoral fellow, Department of Molecular Pharmacology, University of Göttingen
1996-2007: Attending physician, Department of Neurology, University of Heidelberg; Group Leader “Molecular Neuropharmacology”
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Current Research

Transcriptional control of ischemic neurodegeneration by NF-kB (Oliver Herrmann, Waleed Barakat, Melanie Neubert, Sajjad Muhammad, Gertrud von Wilpert)
Apoptosis and inflammation are regulated at the transcriptional level. An essential transcriptional regulator is NF-kB. Our previous work has shown that NF-kB is activated in neurons after stroke. Interference with NF-kB signalling reduced the infarct size (Schneider et al., 1999; Herrmann et al., 2005). Future work will define the relevant target genes of NF-kB and how the NF-kB signalling cascade is activated in cerebral ischemia. Furthermore, we will explore pharmacological tools to interfere with NF-kB signaling in stroke.

TWEAK in cerebral ischemia (Marion Schölzke, Sasidhar Murikinati, Nadine Gehrig)
TWEAK is a cytokine of the TNF family. It binds to the membrane receptor Fn14. In cerebral ischemia, there is a marked up regulation of both the ligand TWEAK and the receptor Fn14. Interference with TWEAK signalling reduced the infarct size two days after onset of ischemia (Potrovita et al., 2004). However, for clinical application further characterization of TWEAK signalling in cerebral ischemia is important.

Neurogenesis in stroke (Marion Schölzke, Ming-Fei Lang, Lars Werner, Sasidhar Murikinati, Ira Maegele, Christine Stanek)
Stroke triggers adult neurogenesis. New born neurons are found in brain areas, in which no neurons are born under normal conditions. Preliminary evidence suggests that the close vicinity to endothelial cells in the vascular niche favours neurogenesis. However, the regulation of ischemia-induced neurogenesis is incompletely understood and
evidence for the functional relevance of neurogenesis is only correlative (Schölzke and Schwaninger, 2007). To explore neurogenesis in cerebral ischemia, we are working on a transgenic approach to target the relevant cell types in vivo.

Fig. 1: ATP binding site of a kinase up-stream of the transcription factor NF-κB.

Fig. 2: Expression of the recombinase Cre (red) in endothelial cells of the cerebellum. Green, endothelial cell marker CD31. Blue, nuclear staining by DAPI.

Top publications


Structure of the Group

Group Leader: Markus Schwaninger
Postdoctoral fellows: Dirk Ridder, Antje Krenz
PhD-Students: Waleed Barakat, Christoph Leib, Ming-Fei Lang, Sasidhar Murikinati, Melanie Neubert, Lars Werner
Technicians: Nadine Gehrig, Ira Maegele, Christina Stannek
Top publications:


Structure of the Group

Group Leader: Peter H. Seeburg
Senior scientists: Miyoko Higuchi, Georg Köhr, Rolf Sprengel
Postdoctoral fellows: Alexander Kolleker, Yair Pilpel, Martin Schwarz
PhD-Students: Stefan Bonn, Ali Cetin, Florian Freudenberg, Noam Pilpel
Technicians: Horst Großkurth, Sabine Grünewald, Joachim Hopisch, Judith Müller, Margarita Pfeffer
Horst Simon

Differentiation and survival of mesencephalic dopaminergic neurons

Research Summary

Degeneration of dopaminergic neurons in the substantia nigra is the hallmark of Parkinson’s disease. We examine the molecules, which determine the properties of these cells, regulate their differentiation, ensure their survival during development, and play a role in their maintenance during adulthood.

Curriculum Vitae

Degrees: 1989 M. Sc. (Diploma in biochemistry)
1993 Ph.D.
1986-1989: Diploma in Biochemistry and Molecular Biology, ETH Zürich, Switzerland
1989-1993: Thesis work at King’s College, University of London, UK
1993: Postdoctoral fellow at King’s College, University of London, UK
1994-1999: Postdoctoral fellow at The Salk Institute for Biological studies, La Jolla, USA
1999: Leader of the Biofuture group, University of Heidelberg

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Current Research

Functional characterization of the Engrailed transcription factors

The Engrailed genes are homeobox transcription factors which participate in neuronal specification. They are expressed in mesencephalic dopaminergic (mes-DA) briefly after they become postmitotic and critically determine their survival. In mouse embryos deficient of the two genes (En1 and En2), mesDA neurons are generated, start to express their neurotransmitter phenotype, but then disappear (Alberi et al., 2004; Simon et al., 2001). The Engrailed requirement for the survival of these neurons is gene-dose dependent and cell-autonomous. Interestingly, in one of the genotypes (En1-/-; En2-/-), which is viable and fertile, the nigral DA neurons are gradually and specifically lost during the first two postnatal months (Fig.1). The disappearance of the cells leads to diminished storage and release of dopamine in the dorsal striatum (caudate putamen) and to motor deficiencies which are reminiscent of akinesia and bradykinesia, two cardinal symptoms of Parkinson’s disease (PD) (Sgado et al., 2006).

Death of Engrailed-deficient mesDA neurons is caused by the activation of the mitochondrial pathway of apoptosis, a molecular mechanism, which is shared with in neurotoxin based models for PD, intoxication with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone and 6-hydroxydopamine (6-OHDA). An over-expression experiment in a neuronal cell line demonstrated that the Engrailed genes repress p75NTR, a neurotrophin receptor. Several lines of evidence now suggest that elevated p75NTR expression is causal to the death of engrailed deficient mesDA neurons. Direct interference with p75NTR by a function-blocking antibody or by RNA interference using penetratin-coupled oligos rescues the mutant neurons in vitro. Markedly, the cell death induced by P75 is mediated by the suppression of the Erk1/2 MAPK signalling pathway. (Alavian et al. sub-
mitted). We currently investigate this issue further in vivo and vitro, by using mutant mice, viruses and pharmacological approaches.

Fig. 1: Slow progressive loss of nigral DA neurons in mutant mice heterozygous null for En1 and homozygous null for En2 (En^HT). P0 (A, B), P30 (C, D) and 3 months old wild-type (A-F) and En^HT (A'-F') mice. TH immunostaining on the level of SN (A, C, E) and VTA (B, D, F).

The role of K-ATP channel activity for the sensitivity of mesencephalic dopaminergic to mitochondrial insult

K-ATP channels couple the metabolic state of the neuron to its membrane potential by sensing the ATP/ADP ratio. The channel opens, when the intracellular ATP concentration decreases, leading to an outflux of potassium ions and to hyperpolarization of the membrane, thus reducing the excitability of the cells. In mesDA neurons, the channel consists of four inner-core forming Kir6.2 molecules and four surrounding Sur1 molecules. We have shown that genetic inactivation of the channel does not change the survival rate of mesDA neurons during the entire lifespan of null mutants for Sur1 and Kir6.2 (Fig. 2). On the contrary, the in vivo loss of function of the channel results in rescue of nigral DA neurons in two mechanistically distinct mouse models of nigral degeneration, intoxication with MPTP and the weaver mouse (Liss et al., 2005). In our own experiments, we have demonstrated that the same can be achieved by employing channel blockers like the sulfonylurea tolbutamide. Sulfonylureas are widely used to treat diabetes type 2 in humans. We are currently examining whether these pharmacological findings can be employed to rescue nigral DA neurons from degeneration in models for PD. For this purpose, we use Alzet mini-pumps to chronically administer K-ATP channel blocking compounds in mouse and rat.

Fig. 2: K-ATP channel component Kir6.2 and Sur1. (A) Scheme of K-ATP channel. (B) Cell count of 18 months old wild type and null mutants for Kir6.2 and Sur1. (C) Expression of tyrosine hydroxylase (TH), Sur1 and Kir6.2 in nigral DA neurons.
Top publications


Structure of the Group

- Group Leader: Horst Simon
- PhD-Students: Kambiz N. Alavian, Lavinia Alberi, Lavinia Bhatt, Daniel Gherbassi, Christian Scholz, Paola Sgado, Sandrine Thuret
- Undergraduates: Hima Chandra
- Technicians: Gabi Döderlein
Molecular mechanisms mediating regulated exocytosis

Research Summary
Intracellular membrane fusion involves the assembly of cognate v-SNAREs and t-SNAREs between opposing membranes. At the neuronal synapse, a cascade of components and reactions controls SNARE complex formation and couples the triggering signal to the fusion machinery. To elucidate the molecular function of the regulatory machinery, we are attempting to reconstitute neurotransmitter release in vitro.

Curriculum Vitae
Degrees: 1986 M. Sc. (Diploma in Biology) 1991 Ph.D.
1982-1986: Diploma in Biology, Ludwig-Maximilians University Munich
1987-1991: Thesis work at the Institute for Physiological Chemistry, Biochemistry and Cell Biology, Ludwig-Maximilians-University Munich
1991-1993: Research fellow, Cellular Biochemistry and Biophysics, Sloan-Kettering Institute, New York, USA
1994-1997: Assistant Laboratory Member, Cellular Biochemistry and Biophysics, Sloan-Kettering Institute, New York, USA
1998-2004: Assistant Professor, Cellular Biochemistry and Biophysics and Cell Biology programs, Sloan-Kettering Institute, New York, USA
2004-2005: Associate Professor, Cell Biology, Sloan-Kettering Institute, New York, USA
since 2005: Full Professor at the Biochemistry Center, University of Heidelberg

Current Research
Neurotransmitter release is the paradigm for regulated exocytosis and distinct components acting at different steps have been identified (see Figure 1 for a brief overview). Membrane fusion is initiated by the interaction of the v-SNARE VAMP2 on synaptic vesicles with its cognate t-SNARE, consisting of syntaxin1 and SNAP25 on the presynaptic plasma membrane. SNARE proteins assemble into a stable four-helix bundle. In vitro assays have shown that this protein folding reaction drives membrane fusion. However, in vivo, SNARE complex assembly is tightly regulated and involves multiple steps and numerous regulatory components that either accelerate or arrest the formation of distinct reaction intermediates. The initial tethering of synaptic vesicles to the active zone of the neuronal synapse does not depend on v-/t-SNARE interactions, but likely requires small GTP-binding proteins such as Rab3 and its effectors. Further, the t-SNARE component syntaxin1 and its binding partner Munc18-1 have been implicated in vesicle docking. Thus, the vesicle tethering machinery is directly linked to the downstream fusion machinery and a multi-step, multi-component process controls SNARE complex assembly. The primed pool of synaptic vesicles seems to be docked by partially assembled SNARE complexes and might be arrested at a hemifusion step. Calcium binding to the calcium sensing machinery, which is coupled to the SNAREs, opens the fusion pore. Fusion pores have two fates: they can reversibly close or fully dilate resulting in the complete incorporation of the vesicular components into the plasma membrane. SNAREs are subsequently recycled by an energy consuming reaction, involving the hexameric ATPase NSF. Endocytosis regenerates the synaptic vesicles.

To analyze the dynamic assembly of the neuronal exocytosis machinery and to dissect the distinct molecular mecha-
nisms, we are using completely and semi-reconstituted fusion assays (Figure 2). These assays allow us to monitor content and lipid mixing and to detect hemifusion intermediates. In addition, we measure regulated exocytosis in vivo by using a pH-sensitive GFP targeted to secretory vesicles. Cryo-electron microscopy will be employed to analyze the architecture of reconstituted fusion pores.

**Specific projects:**

**Role of lipids and membrane microdomains in exo- and endocytosis**

t-SNAREs have been found in membrane microdomains and a perturbation of these microdomains inhibits exocytosis. Furthermore, the local lipid environment at the fusion site could significantly affect the recruitment of regulatory components, the membrane curvature, and fusion pore dynamics. Indeed recent results indicate that a local lipid turnover is required for exocytosis. Therefore we are analyzing the role of protein-lipid interactions and distinct lipids at different steps of the fusion reaction. Furthermore we will test, whether the unique lipid composition of synaptic vesicles facilitates the sorting of synaptic vesicle components and thus provides a platform for efficient endocytosis.

**Role of regulatory proteins (Rim1, Rab 3, Munc18, Munc13, complexins, synaptotagmins, Vo-ATPase, and other regulators)**

Numerous regulators directly bind SNARE proteins, but in many cases their molecular functions are unclear and the regulatory network is poorly understood. We study these proteins as individual components and in various combinations. Therefore, these regulators are expressed as recombinant proteins in E.coli, or insect cells, purified to homogeneity, and analyzed in *in vitro* fusion assays. In biochemical assays, we measure the fusion of an entire population of reconstituted SNARE-liposomes (Figure 2A).
imaging assays, the docking, hemifusion, and full fusion of individual SNARE-liposomes can be resolved (Figure 2B). In *in vivo* assays, the exocytosis of individual secretory vesicles is studied in living cells (Figure 2C). In this method, the secretory granules contain a pH-sensitive marker (pHluorin) in their lumen. Upon triggering exocytosis, fusion pore opening and content release is detected by an increase in fluorescence. Using siRNA technology, proteins involved in exocytosis can be down regulated and replaced by mutant copies. Thus, the biochemical results obtained in the reconstituted assays can be directly tested and verified under physiological conditions. These combined analyses shall reveal the sequential order and the entire assembly line that generates “ready to fuse” vesicles.

**Structural and functional organization of fusion pores**

At the electrophysiological level, fusion pores are well defined, but their structural organization is unclear. The factors that determine reversible fusion pore opening/closure or full dilation are largely unknown. Thus we are attempting structural analyses of reconstituted fusion intermediates by cryo-electronmicroscopy.

**Top publications**


**Structure of the Group**

**Group Leader:** Thomas Söllner  
**Postdoctoral fellows:** Jörg Malsam  
**PhD-Students:** Susanne Kreye, Simone Paulsen, Patricia Rusu, Yvette Schollmeier, Florian Seiler  
**Technicians:** Jean Michel Krause
Current Research

We are using newly established models to generate alcohol/or drug-dependent rats or mice. Behavioural, neurochemical and molecular examinations on alcohol and drug dependent rodents will help us to understand the neurobiological mechanisms of addictive behaviour. Studies with mutant mice (also derived from an ENU screen) and rats will help us to identify genes involved in the initiation of drug-seeking behaviour. In addition, an organbank with different alcohol-prefering rat lines has been established. The aim of the organ bank is the characterisation of molecular cascades involved in alcohol-derived diseases. In a comparative approach an organbank from alcohol dependent patients is used. Using massive microarray approaches and proteomic analysis from the material deriving from this organbank, we will be able to pin down molecular networks that trigger the pathological condition.

Rainer Spanagel

The neurobiology of drug addiction

Research Summary

In the Department of Psychopharmacology our major interest is in drug abuse research. In particular, we are working on alcohol dependence and the co-morbidity to anxiety and depression. We have also several projects on cocaine, opioids, cannabinoids and nicotine. Our close collaboration with the Clinic of Addictive Behaviour at the CIMH (Prof. K. Mann) enables us to rapidly translate our preclinical findings into alcohol/drug dependent patients. A further translational arm concerns human genetic studies in combination with neuroimaging.

Curriculum Vitae


Contact

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Fig. 1: We are in the course of establishing a central animal and human organbank from alcohol dependent individuals for conducting genomics, transcriptomis and proteomics in liver, pancreas and brain tissue.
The primary goals of our investigations are (i) the identification of risk alleles in the development of addictive behaviour, (ii) the characterisation of neuronal networks mediating drug-taking behaviour (mainly by ph-MRI methods), and (iii) the development of new anti-relapse compounds. Linking genetic and pharmacological findings we finally aim for an individually adapted pharmacotherapy. In doing this, alcohol-dependent animals will be separated into different behavioural and neurobiological phenotypes (e.g. by the use of animal MRI) and will then be treated with a corresponding anti-relapse compound. Treatment responses will finally be correlated with specific genotypes and this pharmacogenetic information will then be translated into alcohol dependent patients.

In comparison, we are studying neuroplastic changes within the reward pathway induced by psychostimulants, opioids, nicotine, and cannabinoids and relate these changes to the observed behaviours such as behavioural sensitisation, conditioned place preference, intravenous self-administration and reinstatement of drug-seeking behaviour.

Currently, we are running 12 different research projects in DFG, BMBF and EU-funded networks. In the following section one project is described in more details.

One research project focuses on the involvement of clock genes in the modulation of drug-induced behaviours. A link between the neurobehavioural effects of drugs of abuse and period gene activity has been first established in *Drosophila*. Flies show behavioural sensitisation following repeated cocaine administration - a phenomenon that has been implicated in drug craving. Thus, they exposed the flies to volatilized free-base cocaine which produces a set of behaviours similar to those observed in rodents, including grooming and enhanced motor activity. Flies mutant in the period gene did not behaviourally sensitise after repeated exposure to cocaine whereas wild-type flies showed a strong sensitised response. This finding was further supported in mutant mice lacking functional Per genes. Thus, following repeated cocaine injections, a sensitised behavioural response did not occur in Per1 mutant mice. In contrast, Per2 mutant mice exhibited a hyper-sensitised response to cocaine. Conditioned place preference experiments revealed similar results: Per1 mutant mice showed a complete lack of cocaine reward, whereas Per2 mutants displayed a strong cocaine-induced place preference. The role of the Per1 gene in the development of cocaine sensitisation has been confirmed in successive studies conducted in different rodents. Currently, these mice are tested for intravenous cocaine self-administration and reinstatement behaviour. In *vivo* microdialysis is performed in parallel in order to correlate extracellular dopamine and glutamate levels in the reward pathway with the observed behaviours.

Per1 and Per2 mutant mice have now also been studied
in alcohol self-administration experiments. Using operant conditions, Per1 and wild type mice were trained to self-administer alcohol. Furthermore, extinction sessions were introduced, followed by reinstatement measures of ethanol-seeking behavior. In another set of animals, the mice were exposed to voluntary long-term alcohol consumption, ensued by a two-month deprivation phase, after which the alcohol deprivation effect - which is used as a measure of relapse - was examined. Mutant mice did not display a significantly divergent number of reinforced lever presses than wild type animals.

Furthermore, no significant differences between groups were obtained regarding reinstatement of ethanol-seeking behavior. Similar results were obtained in the two bottle free choice paradigm. Specifically, no genotype differences concerning consumption and preference were observed over a broad range of different ethanol concentrations. Moreover, after the deprivation phase, both groups exhibited significant alcohol deprivation effects, yet no genotype differences. These data do not suggest a relationship between the circadian clock gene Per1 and ethanol reinforcement, -seeking and relapse behavior. In contrast, compared to wild type animals, Per2 mutant mice exhibit an enhanced alcohol intake and preference when pharmacologically relevant concentrations are offered.

Alterations in the brain reinforcement system of these mutant mice might drive an enhanced incentive motivation to consume more alcohol than control animals. The mesolimbic reinforcement system is modulated by various glutamatergic input pathways and in a series of experiments it was found that Per2 mutant mice have a hyper-glutamatergic state, especially in the nucleus accumbens. Regarding the large evidence given in the literature for an involvement of enhanced glutamate levels or alterations of the glutamatergic system in excessive alcohol consumption, one would expect a massive impact of the Per2 gene mutation on alcohol consumption via alterations within the glutamatergic system. This idea has been further confirmed by examining the effects of acamprosate in these mice. Acamprosate is used in the clinic for relapse prevention and it is suggested that acamprosate acts mainly on a hyper-glutamatergic state, yet having only little effect on a “normal” glutamatergic state. Therefore, acamprosate should be more effective in reducing alcohol consumption in Per2 mutant than in wild type mice. Indeed, following repeated acamprosate treatment, mutant mice showed decreased alcohol consumption along with a normalization of extracellular glutamate levels in the nucleus accumbens.

These new findings provide a clear link of the mouse Per2 gene, the glutamatergic system, and excessive alcohol consumption. However, future animal research ought to address the question of whether the Per2 gene, and other clock genes, are also directly implicated in alcohol...
sensitivity, tolerance, withdrawal and most importantly in alcohol relapse behaviour. Most importantly, however, the link between Per2 and excessive alcohol consumption in mice could already been translated to humans. Thus, association studies in different samples have demonstrated that specific genetic variations of the human PER2 gene are associated with high alcohol consumption.

**Top publications**


**Structure of the Group**

- **Group leader:** Rainer Spanagel
- **Senior scientists:** Peter Gebicke-Haerter, Cornelius Pawlak, Wolfgang Sommer
- **Postdoctoral fellows:** Ainhoa Bilbao, Anita Hansson, Anna Molander, Stephanie Perreau-Lenz, Miriam Schneider, Valentina Vengeliene
- **PhD-Students:** Chris Maria Feichtinger, Briac Halbout, Fernando Leonardi-Essmann, Nina Reinmuth, Peggy Schneider
- **Technicians:** Sabrina Koch, Katja Lankisch, Elisabeth Röbel, Claudia Schäfer
Current Research

Correlation between odor discrimination performance of mice and odor representation in the olfactory bulb

Odors can be discriminated by mice within a few hundred milliseconds. Using an automated olfactometer the discrimination time (DT) can be measured for various odor pairs. We compare the DT with the physiological representations of odors on the level of the olfactory bulb (OB), as measured using in vivo intrinsic optical signal imaging, calcium dye imaging, and voltage sensitive dye imaging. We search for predictors of behavioral performance within the measured neuronal activity. Manipulations that change behavioral and physiological responses (e.g. odor adaptation) are used to further test correlations between representations / processing on one side and behaviour on the other side. (Fig. 1). (Cooperation with Nixon Abraham, Thomas Kuner, Andreas Schaefer)


Spike triggered averaging of spontaneous electrical activity in the neo-cortex

In order to understand cortical information processing it is crucial to understand the functional integration of individual neurons into the cortical network. Voltage sensitive dye imaging with high spatial and temporal resolution in the neocortex emphasizes mainly sub-

Hartwig Spors

Spatio-temporal patterns of neuronal activity in the healthy and diseased brain

Research Summary

We examine spatio-temporal stimulus representations in vivo. Using a combination of behavioral tests, electro-, and optophysiological techniques we study how spatial and temporal aspects of these stimulus representations drive downstream neurons and finally predict behavior. A genetic model for human epilepsy allows us to extend these measurements to determine changes of population activity in the diseased brain.

Curriculum Vitae


Contact

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with action potentials of individual neurons and what aspects of the spatio-temporal patterns are predictive of action potential firing of the individual neurons. (Fig. 2).


threshold electrical activity of layer 2/3. The combination with tetrode recordings in layer 2/3 allows us to correlate the optically measured input to a neuronal population over a wide cortical region (e.g. 4 x 4 mm) with action potentials of several neighboring neurons. We ask if specific patterns and temporal sequences of population activity correlate

Fig. 1: Olfactory bulb activation patterns predict odor discrimination times. (A) Examples of activation patterns measured on the dorsal surface of the olfactory bulb for 4 odor pairs: (+) Carvon vs. (-) Carvon (C+/C-); (+) Octanol vs. (-) Octanol (O+/O-); Eugenol vs. Cineol (Eu/Cin); Ethylbutyrate vs. Amylacetate (EB/AA). (B) Pattern difference (Euclidean distance) of the activation patterns of the odor pairs for two odor concentrations (100 ml/min or 25 ml/min odorized air) as function of the discrimination time. The difference values are significantly anti-correlated with the discrimination time ($r^2 > 0.9, p<0.05$).

Fig. 2: Spike triggered patterns of electrical sub-threshold activity differ for two neighboring neurons. Top: Sub threshold population activity, measured with the voltage sensitive dye RH1691, around ($\pm$ 12.5 ms) spontaneous APs of two different neighboring neurons was averaged. The minimum and maximum color scale values for each image are given in per mille on the top left in each image. Scale bar 1 mm. The position of the tetrode (star in the center) and of the whisker barrels were overlaid post hoc. Bottom: The similarity across frames triggered on APs of the same neuron (black) is higher than the similarity of frames triggered on all APs (red) ignoring the neuron identity.
In vivo characterization of a mouse model carrying a point mutation (G2R43Q) that causes absence epilepsy in humans

While animal models for epilepsy are abundant, only recently genetic mouse models became available that carry mutations which cause epilepsy in humans. Mice with a point mutation in the Gamma2 subunit of the GABA-A receptor display absence seizures and lowered seizure threshold as do their human counterparts. We set out to determine changes on the network level in vivo measuring spontaneous and evoked population activity before and after challenging the animals with a low dose of the epileptogenic drug pentylentetrazol. Cortical opto- and electrophysiological measurements are combined with targeted single unit recordings in the thalamus in order to localize network changes to the cortex and / or the thalamus. (Fig. 3). (Cooperation with Steven Petrou, University of Melbourne)


Top publications


Fig. 3: Pentylentetrazol (PTZ) enhances whisker-evoked cortical responses in G2R43Q mice barrel cortex. (A) Voltage sensitive dye imaging signal amplitude increases after PTZ administration in G2R43Q (note different color bars). Average of 32 stimulus responses. (B) Time course of response amplitudes pooled over all animals (G2R43Q (+/d) n=8; wild type (WT) n=12) normalized to values before PTZ.

Structure of the Group

Group Leader: Hartwig Spors
Postdoctoral fellows: Frederic von Wegner
Undergraduates: Rebecca Böhme, Nilufar Shahshahani, Dmitrij Turaev
MD students: Daniel Golkowski, Thomas Künzting, Jens Witsch
Rolf Sprengel

The role of glutamate receptors in hippocampus mediated learning, emotional behaviors and mood disorders

Research Summary

NMDA receptor induced increase of AMPA currents at hippocampal CA1 cell synapses is one basic mechanism underlying spatial learning and memory in the rodent. By genetic removal of NMDA and AMPA receptor subtypes in specific brain regions we dissect different forms of memories to identify underlying physiological processes.

Curriculum Vitae

Degrees: 1981 M.Sc. (Diploma), University of Heidelberg
1983 Ph.D. University of Heidelberg
1983-1996: Postdoctoral fellow, Department of Microbiology, University of Heidelberg; Department of Microbiology and Immunology, University of California, San Francisco, USA; MPI for Biochemistry, Munich; Center for Molecular Biology, University of Heidelberg
1996-2001: Research associate, Department of Molecular Neurobiology, MPI for Medical Research, Heidelberg
since 2001: Research Group leader, Department of Molecular Neurobiology, MPI for Medical Research, Heidelberg

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Current Research

Our major goal is to monitor and to visualize molecular changes which underlie learning and memory processes in the adult mouse brain. We use different learning paradigms in the mouse and conditional ‘Knockout’ mouse models, which are impaired in different forms of learning as basic tools in our studies. In the genetic background of these learning impaired mice we introduced by transgenic technologies or by virus mediated gene transfers indicator genes, which are then used to monitor the molecular changes before, during and after learning in brain slices and in two photon live imaging. Primary neuronal cultures and organotypic slice cultures are used for in vitro studies.

Memory deficiencies coupled to selective AMPA or NMDA receptor dependent plasticity (in defined principal cell layers of the hippocampus)

NMDA receptor induced increase of AMPA currents at hippocampal CA1 cell synapses is one basic mechanism underlying spatial learning and memory in the rodent. By genetic removal of NMDA and AMPA receptor subtypes in specific brain regions we are able to dissect different forms of memories and to identify underlying physiological processes. With global GluR-A knockout mice we made a provocative finding that spatial reference memory can be formed without spatial working memory. To understand both memory forms at the physiological and molecular level in more detail we would like to approach the following major questions:

• Can we dissect different forms of memory formation in fear conditioning?
• Can we detect physiological parameters that are correlated with either spatial working or spatial reference memory?
• How can a spatial reference memory be formed without working memory?
• How is LTP connected to information storage?

The role of glutamate and glutamate receptors in mouse models for emotional behaviors and mood disorders

The neurotransmitter glutamate is involved in the pathophysiology and treatment of mood disorders. The goal of our studies is to dissect the role of glutamate in mouse models for affective disorders. We subject different genetically modified mice with impaired glutamate homeostasis and glutamate signaling to behavioral, neuroendocrinological, molecular and pharmacological studies. A variety of mutant mice with specific deficits in glutamate uptake (EAAT-1 and EAAT-2 transporters) or glutamatergic neurotransmission, e.g. of ionotropic (AMPA- and NMDA-type) glutamate receptors (GluR-A, GluR-C, NR-1, NR-2A) will be analyzed. By restricting the gene deletions to specific areas in the brain we will identify the relevant brain regions. Glutamatergic drugs that shape emotional behavior in murine depression models will also be tested in these mice.

• Alterations in molecular/biochemical/cellular signaling pathways that have been postulated for the pathogenesis or pathophysiology are investigated.

Fig. 1: Memory performance of mice is analyzed in (A) T-maze, (B) Y-maze and in (C, D) conditioning chambers.

Fig. 2: The gene for the NMDA receptor subunit NR1 is specifically removed in the gyrus dentatus of the hippocampus. (A) The expression of Cre recombinase is restricted to the granular cells of the gyrus dentatus by the CamK2A/Grin2C promoter which controls the transcription factor (itTA) that is needed for Cre expression. In Cre expressing cells the gene segments which are flanked by loxP sites (black triangles) are removed. The loss of intact NR1 expression in the gyrus dentatus region can be monitored by in situ hybridization (B) or by anti-NR1 antibodies in immunocytochemical stainings (C, lower panels). (C, upper panels) The gyrus dentatus specific Cre expression is visualized by anti-Cre antibodies which show a strong labeling of the granular cell layer. Membrane depolarization results in a transient increase of pHluorin fluorescence at single vesicle fusion sites (compare left panel with 2 right panels, s = seconds).

Functional changes in neuronal networks in mice with selective loss of AMPA or NMDA receptors

We have developed viral-mediated gene expression systems for rapid and precise delivery of proteins, including genetically-encoded fluorescent calcium indicator proteins (FCIPs), into neurons for recording activity at a population scale. Our goal is to characterize by optical imaging spatiotemporal activity patterns of a group of neurons activated by sensory experience. We will try to establish the essential role of NMDA- and AMPA receptors in map plasticity.
Transcriptional and posttranscriptional modification of AMPA receptor complexes

We investigate AMPA receptor complexes from brain tissue of rats addicted to alcohol. Particularly, the expression and posttranscriptional modification of genes which participate in trafficking, stability and synaptic localization of AMPA receptors will be quantified in specific regions of the brain.

- Are changes in AMPA receptor signaling correlated with the development of addictive behavior?

Top publications


Structure of the Group

<table>
<thead>
<tr>
<th>Group Leader:</th>
<th>Rolf Sprengel</th>
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<tbody>
<tr>
<td>Postdoctoral fellows:</td>
<td>Simone Giese, Liliana Layer</td>
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<tr>
<td>PhD-Students:</td>
<td>Thorsten Bus, Godwin Dogbevia, Wannan Tang, Yiwei Cheng, Dario Arcoz-Diaz</td>
</tr>
<tr>
<td>Technicians:</td>
<td>Hans Gaugler, Annette Herold, Simone Hundemer, Martina Lang</td>
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Current Research

An essential role for primary cilia in the development of the forebrain

Primary cilia have recently been implicated as crucial sites of signal transduction and protein processing that are important for a wide range of developmental functions (Fig. 1). We have found an essential role of primary cilia in forebrain development. The recessive mutation cobblesone (cbs)

![Image of primary cilia](image)

Fig. 1: Primary cilia project into the dorsolateral telencephalic ventricles (V) of 12.5 d.p.c. mouse embryos. (A,B) Transmission electron microscopy showing a cilium cut longitudinally (A) and in cross section (B), the latter revealing the characteristic “9 + 0” ciliary morphology. (C) Scanning electron microscopy of cilia (indicated by arrows) lining the ventricle (V) of embryonic brain. Scale bars: A,B: 200 nm, C: 1000 nm.

Kerry L. Tucker

Early events in neurogenesis and nerve development in the central and peripheral nervous systems

Research Summary

Our laboratory is concerned with several aspects of neurogenesis and nerve outgrowth in the developing murine nervous system. In the cortex, we are working with several mutants involved in the trafficking of developmentally-relevant signalling molecules within primary cilia. We are also investigating the role that histone deacetylases play in the development of the forebrain. In the periphery, we employ an organotypic slice culture system to manipulate and image spinal nerve innervation into the forelimb.

Curriculum Vitae

Degrees: 1990 B.A. at Harvard College, Cambridge, USA
1997 Ph.D. Massachusetts Institute of Technology, Cambridge, USA
1993-1997: Ph.D. research, Whitehead Institute for Biomedical Research, Cambridge, USA
1997-2003: Postdoctoral fellow, MPI for Neurobiology, Martinsried, Germany and Friedrich Miescher Institute, Basel, Switzerland
2003: Sabbatical, Biogen Idec, Inc, Cambridge, USA
Since 2003: Junior Group Leader, IZN, University of Heidelberg, Germany

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was identified in an ENU-based mouse mutagenesis screen and is distinguished by cortical “heterotopias”, appearing at 10.5 d.p.c. as protrusions from the pial surface of the dorsal forebrain. Homozygous mutants showed defects in the formation of the dorsomedial telencephalon, the evagination of folds at the ventricular zone of the cortex and thereby to the formation of the heterotopias (Fig. 2). Later embryonic stages show a failure to form superficial cortical layers such as the subplate, the cortical plate and the marginal zone.

In situ analysis indicated the presence of the choroid plexus, cortical hem and hippocampal anlage, but the morphology of these structures was severely disturbed. In contrast, development of the ventral forebrain appeared largely normal. Standard genetic mapping approaches and classical complementation analysis have identified cbs as a mutation in the Ift88 gene. The Ift88 protein plays an important role in the construction and maintenance of both primary and motile cilia, acting in a complex that is responsible for the intraflagellar transport of protein cargos. Northern blot, real time RT-PCR, and Western blot analysis showed a 70-80% decrease in levels of the Ift88 mRNA and protein, respectively, indicating a hypomorphic allele. Altered processing of the transcription factor Gli3 has been observed in the brains of cbs mutants, while other developmental pathways causing this pleiotropic phenotype are currently under investigation.

Histone deacetylases control neurogenesis in embryonic brain

Histone-modifying enzymes are essential for a wide variety of cellular processes dependent upon gene regulation. Histone deacetylases (HDACs) lead to the compaction of chromatin and subsequent silencing of gene transcription, and they have recently been implicated in a diversity of postnatal functions and dysfunctions in the brain including ocular dominance plasticity, the consolidation of memory in the hippocampus, epileptic seizures, and depression. We have investigated their role in the development of neurons in embryonic mouse brain. As a wide variety of HDACs are expressed in differentiating neural progenitor cells, we have taken a pharmacological approach to inhibit multiple family members. Inhibition of class I and II HDACs in developing mouse embryos with trichostatin A resulted in a dramatic reduction in neurogenesis in the striatum and a modest increase in neurogenesis in the cortex. A reduction in neurogenesis in striatum-derived neural precursors was accompanied by an increase in the production of immature astrocytes. We have shown that HDACs control neurogenesis by inhibition of the bone morphogenetic protein BMP2/4 signaling pathway. HDACs function at the transcriptional level by inhibiting and promoting, respectively, the expression of Bmp2 and Smad7, an intracellular inhibitor of BMP signaling. Inhibition of the BMP2/4 signaling pathway restores normal levels of neurogenesis and astrogliogenesis to both striatal and cortical cultures in which HDACs are inhibited. Our results demonstrate a transcriptionally-based regulation of BMP2/4 signaling by HDACs both in vivo and in vitro that is critical for striatal neurogenesis and that modulates
cortical neurogenesis. This suggests that HDACs may regulate the developmental switch from neurogenesis to astrogliogenesis that occurs in late gestation. We are pursuing this question through identification of the responsible HDAC genes, their interaction partners, and their molecular targets.

**Imaging of peripheral nerve outgrowth in slice culture**

Newborn neurons elaborate an axon that undertakes a complicated journey to find its ultimate target in the brain or periphery. Although major progress in the study of this process has been made by examination of dissociated neurons in vitro, one would like to observe and manipulate axonal outgrowth and pathfinding as it occurs in situ, as fasciculated nerves growing within the tissue itself. We have developed a simple technique to do this, through cultivation of embryonic mouse slices from the tauGFP mouse line that expresses EGFP specifically in newborn neurons. This system allows for imaging of outgrowth of peripheral nerves into structures such as the developing limb (Fig. 3).

With this technique we can reproduce normal innervation patterns by spinal nerves derived from spinal cord motor neurons and sensory neurons of the dorsal root ganglia. The slices can be manipulated pharmacologically as well as genetically, by crossing the EGFP-expressing line with lines containing targeted mutations in genes of interest. We are exploiting the latter possibility with a mutant in the gene encoding Semaphorin3A, a key regulator of early spinal nerve outgrowth.

**Transgenic mouse lines expressing modulators of Rho GTPase function**

We have generated a series of mouse lines in which all postmitotic neurons express modulators of Rho GTPase function. The first line we have derived expresses a dominant negative inhibitor of RhoA in which amino acid 19 has been substituted to asparagine (N19-RhoA). Through an unknown mechanism, this results in an overrepresentation of neurons in all layers of the cerebral cortex, when analyzed at maturity. As we have not found defects in layering identity so far, we believe the cause to lie in the regulation of developmentally-occurring postnatal apoptosis, and this is currently being examined.

**Top publications**


**Structure of the Group**

**Group Leader:** Kerry Tucker

**Visiting Scientists:** Dean O. Smith, Sidney Cambridge

Isabel Brachmann, Christian Gojak, Kathrin Weissmüller, Marc Willaredt

**PhD-Students:** Kristin Bobsin, Valentin Esvyukov, Silke Herzer, Veronika Kremer, Hannah Meyer, Dmitry Rusanov, Xiao-Rui Sun, Xiao Shen, Markus Stahlberg
Klaus Unsicker

TGF-β, FGF and neurotrophins in neural development and functions

Research Summary

We are interested in the functions of three major families of growth factors in the developing and adult nervous system. We focus on the development of neural crest derivatives, functions of limbic areas and mesostriatal/mesolimbic systems in health and disease. An important topic in the research of the laboratory is the molecular understanding of neuronal survival and death. Methodologies include mouse mutants, cell and tissue culture, biochemistry, molecular biology, histology, and electrophysiology.

Curriculum Vitae

Degrees: 1968 MD in Histology, University of Kiel
1978-1992: Full Professor and Head of Department, Anatomy and Cell Biology, University of Marburg
1983-1984: Visiting Professor, Department of Biology, University of California, San Diego, USA
1989-1990: Visiting Professor, Laboratory of Chemoprevention, NCI, NIH, Bethesda, USA
2006: Visiting Professor, Institute of Biotechnology, University of Helsinki, Finland
since 1992: Full Professor and Director, Department of Anatomy and Cell Biology, University of Heidelberg
since 2000: Director, IZN, University of Heidelberg

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Current Research

Generation of cell diversity in the sympathoadrenal cell lineage of the neural crest

The neural crest (NC) gives rise to different types of neurons, glial, endocrine, and mesenchymal cells and, hence, is an excellent model for exploring mechanisms underlying the generation of cell diversity. We focus on neuroendocrine (chromaffin) derivatives of the NC (see Fig. 1). We have shown that, contrary to a classic hypothesis, glucocorticoid hormones and adrenal cortical cells are not required for most aspects of chromaffin cell differentiation [1, 2]. Currently, we study the role of BMP-4 and its receptors in the induction of chromaffin cell fate and differentiation. BMP-4 is an essential factor for inducing a catecholaminergic phenotype in NC cells. It is secreted by cells in the wall of the dorsal aorta and surrounding mesenchyme, rapidly downregulated in sympathetic ganglionic anlagen, but persistent in adrenal cortical cells [7]. This raised the question whether BMP-4 might be important in the induction and differentiation of the chromaffin phenotype. In a series of loss- and gain-

Fig. 1: In situ hybridisation showing TH mRNA (red) in adrenal chromaffin cells and BMP4 mRNA (blue) in adrenal cortical cells of an E9 chick embryo.
of-function experiments in chick embryos we found that BMP-4 did not switch neuronal to chromaffin cell fate, but significantly promoted further differentiation of chromaffin cells. By GFP electroporation into neural tube and NC cells we try to analyze the temporal sequence of delamination of distinct progenitor subpopulations. Preliminary results suggest that the vast majority of single NC cells can give rise to both, sympathetic neurons and neuroendocrine chromaffin cells.

Development of a CNS-peripheral nervous system circuitry

Neurons located in the lateral spinal cord and in the brainstem link the central and peripheral portions of the autonomic nervous system. These neurons innervate peripheral autonomic ganglia and chromaffin cells. Their trophic regulation is not well understood. We have recently discovered that cardiotrophin-1 and the LIFRβ are crucial for the postnatal maintenance of this neuron population [3].

By comparing neurons of the pre- and paravertebral sympathetic ganglia we found marked differences, as e.g. in NGF dependence. It is possible that prevertebral in contrast to paravertebral ganglia receive a second neurotrophic signal from their innervation targets (enteric nervous system and gut). If so, neurons in the prevertebral ganglia should, in addition to trkA, express a further neurotrophic factor receptor. To test this, we currently started an in situ hybridization analysis using different probes for trophic factor receptors (e.g. neurotrophin receptors and GFR-α receptors).

Neuron survival and the roles of ERK

A classic perception of the molecular bases of neuron death implies ERK as an important regulator of neuron survival. We have now found that ERK has also a key role in promoting neuronal death of cerebellar granule cells induced by K⁺ withdrawal [4, 5]. Specifically, neuronal death mediated by plasma membrane damage is accompanied by a late and sustained activation of ERK. Inhibition of ERK activation results in a dramatic reduction of neuron death. Classic growth factors, as e.g. IGF-1, induce an early and transient ERK activation (15min to 2h), and also abrogate the appearance of late and sustained ERK (6 to 24h) suggesting that IGF-1 can positively and negatively regulate the ERK pathway [4].

Functions of a novel TGF-β in neuronal development and maintenance

GDF-15 is a novel distant member of the TGF-βs, originally identified as a potent trophic factor for midbrain dopaminergic neurons. We have generated a GDF-15 knockout mouse, which exhibits motoneuron and neural stem cell phenotypes. There is a progressive postnatal loss of hindbrain and spinal cord motoneurons from 3 to 6 months of age resulting in an approx. 20% deficit. In addition, mutant mice have revealed hypermyelination of axons and increased expression of myelin proteins.

Fig. 2: Alpha-synuclein accumulating neurons in the SNpc of an aged trkB/C(+/−)/(+/−) mouse (cell nuclei are stained in blue by DAPI; alpha-synuclein immunoreactivity is shown in red).

This would be consistent with Schwann cells as a source and a role of GDF-15 in regulating myelination. However, mechanisms underlying motoneuron death still remain to be explored. Neural stem cells (NSC) express high levels of GDF-15 mRNA, and GDF-15 KO mice have less EGFR expressing NSC that wt mice. Details of GDF-15 functions in NSC proliferation and differentiation are currently under investigation.

TrkB and trkC neurotrophin receptors: spine morphology and dopamine neurons

Current analyses of adult and aged heterozygous trkB and trkC mice as well as of young adult conditional CamKII-
trkB knockout mice have revealed the importance of these receptors for the maintenance of dendritic spine numbers and dendritic spine morphology in the hippocampal field CA1 [6]. These analyses of adult and aged heterozygous trkB and trkC mice also showed that these receptors are crucially important for the maintenance of the dopaminergic nigrostriatal system in aged mice. The aged heterozygous knockout mice showed a reduction in the number of dopaminergic neurons in the substantia nigra (SN). This was accompanied by a massive accumulation of alpha-synuclein in the remaining neurons of the SN (Fig. 2), underscoring the significance of trk mediated signaling for preventing degeneration and death of this neuron population.


Top publications

Current Research

Hematopoietic stem cells as vehicles for a gliomas-directed therapy

This project aims at elucidating the molecular mechanisms of lesion-tropism of hematopoietic stem cells (Tabatabai et al. 2005 & 2006). Independent subprojects in this project are:

- mechanism of endothelial transvasation of hematopoietic stem cells
- comparison of hematopoietic and mesenchymal stem cells for the delivery of therapeutic molecules
- development of a cell-based antiangiogenic therapy for malignant gliomas
- optimization of an anti-transforming growth factor (TGF)-b therapy with stem cells

Functional characterization of invasion-related proteins induced by chronic non-lethal hypoxia

Malignant gliomas are hypoxic tumors and this contributes to the resistance to therapy and putatively also to the invasive phenotype. In a proteome study several proteins have been identified to be differentially expressed under hypoxic treatment compared to normoxic conditions and could be confirmed by orthogonal methods. Of these candidates N-myc downstream regulated gene 1 protein (NDRG1) and neuroenolase (ENO2) will be analysed. Silencing of the corresponding candidate genes and reexposing these cells to hypoxia in the invasion/apoptosis and angiogenesis paradigms will underscore the functional relevance of the candidates for the induction of an invasive phenotype or gliomas angiogenesis. Applying proteomics techniques, additionally involved proteins are looked for in cells harboring the silenced candidate gene to find downstream molecules that potentially serve as therapeutic targets for an anti-angiogenic therapy.

Wolfgang Wick

Biology and experimental therapy of malignant glioma

Research Summary

The putative origin of malignant gliomas from neuronal or other brain-derived stem cells challenges several aspects of current concepts in brain tumor biology and therapeutic approaches. Further key propensities of gliomas, such as migration and invasiveness as well as angiogenesis need further molecular clarification. Consequent experimental therapies involve vaccination approaches and delivery by hematopoietic and mesenchymal stem cells.

Curriculum Vitae

Degrees: 1998 MD 2003 Habilitation
1994-1997: Thesis work, Dep. of Neuropathology, University of Bonn
1998-2003: Postdoctoral fellow and resident in Neurology, Dep. of Neurology, University of Tübingen
2004-2006: Group Leader of the Neurooncology Group, Tübingen
2007: Full Professor, University Hospital of Heidelberg, Neurooncology

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Novel functions of BCL-2 family proteins in glioblastomas - invasiveness and autophagy

Since this subproject focuses on invasion analyses, apoptotic and non-apoptotic cell death mechanisms, and orthotopic glioma animal models. In glioblastomas, the BCL-2 and BCL-xL proteins contribute to an overall resistance to apoptosis which correlates with the clinically relevant chemo- and radioresistance. Our recent data demonstrate that BCL-xL specifically promotes the invasiveness of glioma cells in vitro and in vivo (Weiler et al. 2006). This novel BCL-xL function is mediated by altered gene expression and does not depend on the direct anti-apoptotic effect of BCL-xL through sequestering pro-apoptotic BCL-2 family members. Moreover, BCL-2 and BCL-xL were recently described to be major regulators of autophagic cell death (type II cell death). There is increasing evidence that autophagy plays a crucial role in the tumorigenesis and therapy resistance of glioblastoma.

Fig. 1: Adult hematopoietic stem cell exhibit a TGF-β/CXCL-12-dependent tropism for gliomas in vitro and in vivo. Images 1 - 3 depict an experimental LNT-229 intracranial glioma (nuclei DAPI stained (1-2) or H&E staining (3)) invaded by hematopoietic stem cells (PKH26). Image 4 shows that there are no stem cells in the non-tumor hemisphere.

Fig. 2: Free floating human glioblastoma tumor spheres of the tumors 323 and 325 cultured in NSC-M after excision and homogenisation and respective adherent non-sphere-forming cells.

- Development of a protein kinase C inhibitor for the therapy of malignant gliomas (Tabatabai et al. 2007) and experimental autoimmune encephalomyelitis.
- Evaluation of anti-glioma vaccination.
- Description and functional characterization of gliomas-initiating cells.
**Top publications**


**Structure of the Group**

**Group Leader:** Wolfgang Wick  
**Senior scientist:** Michael Platten  
**PhD Students:** Ulrike Litzenburger, Christiane Optiz, Phillip Pfenning, Markus Weiler, Lorna Whyte  
**Undergraduates:** Sebastian Boch, Anke Funke-Kaiser, Sebastian Luger  
**Technicians:** Petra Rübsmann
Otmar D. Wiestler

Molecular neuropathology of human brain tumors / surgical neuropathology of CNS tumors

Research Summary

- Molecular Neuropathology of Human Brain Tumors
- Surgical Neuropathology of CNS Tumors
- Reconstructive Neurobiology
- Molecular Neuropathology of Focal Human Epilepsies

Curriculum Vitae

Degrees 1984 MD, University of Freiburg
1984-1987: Postdoctoral fellow at the Department of Pathology, University of California, San Diego, USA
1987-1989: Residency training in Neuropathology, Institute of Neuropathology, Department of Pathology, University of Zürich, Switzerland
1989-1992: Senior resident in Neuropathology, Institute of Neuropathology, Department of Pathology, University of Zürich, Switzerland
1992-2003: Professor of Neuropathology and Head of the Department of Neuropathology, Medical Center, University of Bonn
1994-2003: Head of the German Brain Tumor Reference Center
since 2004: Chairman and Scientific Member of the Management Board, German Cancer Research Center (DKFZ), Heidelberg

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Research interests

Surgical and Molecular Neuropathology of Human Brain Tumors

Based on a large number of referrals to The German Brain Tumor Reference Center at the University of Bonn Medical Center, our group has carried out extensive studies on the morphological and molecular characterization of human CNS neoplasms. Critical information has also been derived from therapeutic trials for which the center served as reference neuropathology laboratory.

The 2007 WHO Classification of Brain Tumors, for which the consensus conference was held in Heidelberg in 2006, serves as the international standard for the diagnosis and characterization of nervous system cancers.

Fig. 1: Ganglioglioma with binucleated neuron and strong immuno-reactivity for synaptophysin.
Molecular Neuropathology of Human Gliomas and Medulloblastomas

In cooperation with Andreas von Deimling (Heidelberg) and Torsten Pietsch (Bonn), human gliomas and medulloblastomas have been subjected to a systematic molecular and cellular analysis. The studies yielded important novel insights into molecular pathways in the formation of these tumors some of which have been introduced in the diagnostic repertoire.

In the case of childhood medulloblastomas, a combination of molecular and cell biological experiments made it possible to unravel the origin of these embryonal tumors from distinct cerebellar progenitors and to associate these subtypes with distinct molecular alterations.

Molecular Neuropathology of Epilepsy-associated Neural Tumors

Patients with chronic, focal epilepsies often display low-grade neoplasms with distinct morphological and molecular properties. Characteristics include high differentiation, presence of both glial and neuronal components, a potential origin from malformative lesions and a pattern of molecular changes distinct from other CNS neoplasms.

Top publications

- Hartmann, W., et al. (2006). Phosphatidylinositol 3’-kinase / Akt signaling is activated in medulloblastoma cell proliferation and is associated with reduced expression of PTEN. Clin. Cancer Res. 12, 3019-3027.
Research Summary

In vertebrates, patterning of the anterior neural plate culminates in the defined expression of the evolutionarily conserved transcription factors Six3 and Pax6. In the region where Six3 and Pax6 expression overlap, retinal fate is specified. Under the influence of midline signalling the retinal anlage is split into two retinal primordia. Six3 is also required in this process. The two retinal primordia require the homeobox containing transcription factor Rx3 for their evagination to form the optic vesicle. Those are further subdivided to give rise to neural retina, retinal pigmented epithelium and optic stalk respectively. In anamniotes, the ciliary margin of the neural retina contains a stem cell population that gives rise to all retinal cell types and facilitates live long growth of the eye.

Curriculum Vitae

Degrees: 1987 M.Sc.
1990 Ph.D.
1999 Habilitation (Cell Biology and Developmental Biology)
Technical University of Braunschweig
1987-1990: Thesis work, MPI for Biochemistry, Martinsried
1995-1998: Group Leader, MPI for Biophysical Chemistry, Göttingen
1999-2007: Group Leader, EMBL Heidelberg
Since 2007: Director at the Institute for Genetics and Toxicology, Center of Research, Karlsruhe
Since 2007: Full Professor, Institute for Zoology, University of Heidelberg

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Current Research

While our focus in the first period at EMBL (1999-2002) was mainly on early patterning, the second period (2003-2007) is characterized by key findings in optic vesicle (Rembold et al., 2006) and optic cup (see below) morphogenesis.

Our gain of function experiments had indicated that the homeodomain containing transcription factor Six3 is sufficient for ectopic eye formation (Loosli et al., 1999). In a loss of function analysis we showed that its activity is also necessary for the formation of the entire forebrain and eyes (Carl et al., 2002). Interestingly Six3 also plays subsequent roles related to the proximo-distal patterning of the eye field. Our analysis indicates that, depending on the interactor, Six3 determines different fates along the proximo-distal axis (Tessmar et al., 2002) and, by direct interaction with the replication initiation complex, positively acts on proliferation (Del Bene et al., 2004). This interaction interestingly shows the direct interference of a transcription factor with the cell cycle and conversely allows the cell cycle to modulate the transcriptional potential of a key player in eye development. In the absence of a battery of Six3 transcriptional targets the experimental basis for this far-reaching possibility was however thin. We have further pursued this issue and have identified Six3 target genes by ChiP from FAC sorted Six3-positive cells out of the embryonic context. In collaboration with colleagues from the Genome Institute of Singapore (Yijun Ruan, Chia-Lin Wei, GIS) we analyzed Six3 targets in a genome wide survey and (among many others) could show the direct binding of Six3 to its own upstream regions.

Eye Morphogenesis

Optic vesicle evagination, the subsequent step in eye development, is impaired in the eyeless (el, medaka) and chokh (chk, zebrafish) mutants (Loosli et al., 2003; Winkler...
et al., 2000). The gene affected is another homeodomain containing transcription factor, Rx3 (Loosli et al., 2003; Loosli et al., 2001). Our analysis facilitated the generation of transgenic lines (in medaka and zebrafish) that express GFP specifically in the eye field of wild type and mutant embryos. These lines allowed following optic vesicle formation \textit{in vivo} by 4D confocal analysis (Huisken et al., 2004; Rembold et al., 2006), one of our milestones in the past four years. In these studies we unraveled that organ morphogenesis crucially depends of the migratory activity of cells that, in contrast to the text-book view, migrate as individual cells in the context of eye formation (Rembold et al., 2006).

**Eye Evolution**

The work on Rx genes had led us to also investigate their role in basal Prototomia. We found that in the larva of the basic Lochtrophozoan \textit{Platynereis}, Rx is expressed in ciliary photoreceptors, as in the eyes of Deuterostomia. These photoreceptors that are not part of the eye, are found in a complex network within the conserved axonal scaffold. This and other data led us to propose that the body plan of Urbilateria was quite elaborated (Arendt et al., 2001). It contained already a visual complex at the anterior end of a conserved axonal scaffold that served as the evolutionary substratum from which the eyes of Proto- and Deuterostomia emerged (Arendt et al., 2004).

**Medaka Genomics**

To further develop medaka into a competitive model system in an efficient and economical way, it was of key importance to strengthen our contacts to the Japanese medaka community. We have been successfully collaborating with the Kondoh differentiation project and completed the first description of mutants from a joint mutagenesis screen published in the “Medaka issue” of Mechanisms of Development (June/July 2004). This

![Fig. 1: Overview of the eye of a double transgenic medaka fish at 4 days post fertilization. Green cells are expressing a membrane localized YFP under the control of the ath5 promoter, labeling the retinal ganglion cell layer. Ciliary marginal zone, Müller glia and photoreceptors are labelled in red by H2B-RFP under the control of the rx2-promoter. The image is a maximum projection of a confocal stack recorded with the Leica SP5 and a 20x glycerol objective.](image1)

![Fig. 2: Time-lapse montage of lyn-tandem tomato expressing cells in the retina under the control of the vsx3 promoter. Columns of precursor-cells develop from a vertical to a horizontal network forming the inner plexiforme layer in the retina. Cells were imaged live and \textit{in vivo} using a Leica SP5 and a 20x oil immersion objective.](image2)
and other activities catalyzed the initiation of a genome project that covers all aspects of medaka genomics. The medaka genome has now been released and was published in Nature. With the expected publication of the zebrafish genome in the near future, almost 150 million years of evolution will be experimentally amenable in these fully developed model systems, putting fish into a unique position among the vertebrates.

We have started to establish ourselves in the field of bioinformatics to complement and direct bench work. At the moment we focus on mining the genomic information available in the context of gene and genome evolution (Martinez-Morales et al., 2007) and transcriptional networks related to eye development and evolution (Ettwiller et al., 2005; Henrich et al., 2003; Henrich et al., 2004; Henrich et al., 2005) in order to establish a virtuous cycle between bench and computer to direct future experimental work in a more system wide context.

**Top publications**


**Structure of the Group**

**Group Leader:** Joachim Wittbrodt  
**Postdoctoral fellows:** Lazaro Centanin, Petra Haas, Daigo Inoue, Mirana Ramialison, Stephanie Schneider  
**PhD students:** Annette Schmidt, Philipp Keller (joint with E. Stelzer), Robert Reinhardt  
**Technicians:** Claudia Müller, Beate Wittbrodt  
**Animal technicians:** Aldona Nowicka, Patrycja Grabowska

Fig. 3: Reconstruction of the zebrafish digital embryo. The right half of the embryo is shown as the microscopy data, where nuclei are labeled using H2B-GFP (yellow/red LUT). The left half shows the segmented and rendered data with colors encoding movement directions of the individual cells (Keller, et al. 2008).
Current Research

Detailed Modelling of Signal Processing in Neurons

Three main aims of contemporary brain science with respect to functions of the cerebral cortex are a quantitative understanding of

1. Coding of sensory perceptions or motor actions.
2. Structure of the cortex at subcellular resolution.

As paradigm for studying these questions we choose a cortical column, the smallest functional unit in the mammalian brain. We address these questions with a hierarchical approach starting from spatially resolved models of a single neuron, including detailed mathematical description of the most relevant physico-chemical processes via local circuits up to ensembles of several thousands of neurons in the whole cortical column. These models are developed in close co-operation with experiments. Detailed mathematical simulations based on first principles of physics will lead to novel effective descriptions of neurons and ensembles of neurons. These effective descriptions allow the simulation of the behaviour of large collections of neurons by advanced numerical simulation techniques. The results of the different approaches will be compared with each other and with data from especially designed experiments for validation.

To that end, we have to accomplish several sub-tasks:

First, we need to extract geometries and connectivities of neurons from two-photon microscopy data, used to scan cells inside the brain of a living animal. To that end, we developed two software tools. The Neuron Reconstruction Algorithm, NeuRA, is a tool for the automatic extraction of

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<th>Gabriel Wittum</th>
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Computational Neuroscience as part of the Chair Simulation in Technology

Research Summary

Main focus of our work is modeling the signal processing in neurons and networks of neurons in order to obtain a quantitative understanding of neuronal coding, structure of cortex at subcellular resolution and plasticity. To that end we develop models, algorithms and software in the framework of cooperative projects. An important platform for this cooperation is the newly established Bernstein-Group DMSPiN.

Curriculum Vitae

Degrees: 1983 Diploma in Mathematics and Physics, University of Kalsruhe
1987 Ph.D. (Dr. rer.nat.) in Applied Mathematics, University of Karlsruhe
1991 Habilitation, University of Heidelberg
1984-1987: Research assistant, Computer Science, University of Kiel
1987-1991: Postdoctoral fellow at SFB 123, Univ. of Heidelberg
1991: Professor for Numerics, University of Heidelberg
1995: Chairman of the GAMM committee “Scientific Computing”
1996: Co-founder of the SFB 412
1999-2000: Dean of Mathematics and Computer Science, University of Heidelberg
1996-2006: Head of Competence Center for HLRS since 1998: Chair for Simulation in Technology, University of Heidelberg

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neuron geometries from two-photon data, [1]. Based on this approach, the following Projects are run in the framework of our newly established Bernstein-Group “Detailed Modeling of Signal Processing in Neurons (DMSPiN)”.

1. Calcium signaling from synapse to nucleus (with H. Bading)

2. Realistic modeling of presynaptic transmitter content and dynamics and its implications for synaptic plasticity (with A. Draguhn)

3. Development and function of basic networks (with C. Schuster)

4. Modelling of gap junction coupled interneurones (with H. Monyer)

The projects are on the level of a single cell. On the level of larger ensembles of neurons, we developed an approach based on compartmental models. Here the key are the two programs NeuGen, generating a network of realistic neurons, and NeuSim, simulating compartmental models on this network on parallel computers.

Fig. 1: Left: Spiny stellate from layer four of a rat’s cortex. Data by J. Waters (NW University, formerly MPI Heidelberg), reconstruction by A. Heusel (SiT, Univ. Heidelberg).

Fig. 2: Right: Simulation of signal transduction on a branch of a dendrite, C. Vossen, SiT.
Top publications


Structure of the Group

Group Leader: Gabriel Wittum
Senior Scientists: Michael Heisig
Postdoctoral fellows: Vadym Aizinger, Alfio Grillo, Markus Knodel, Michael Lampe, Dimitrij Logaschenko
Veit Witzemann

Molecular anatomy of the developing neuromuscular junction

Research Summary
The formation of the neuromuscular junction involves reciprocal interactions between the presynaptic nerve terminal and the postsynaptic muscle fiber. We generate genetically manipulated mouse models to modulate synaptic activity by changing the functional properties of the postsynaptic signaltransducers, the acetylcholine receptors (AChR) or by inactivating conditionally other synaptic regulators. These studies lead to the analysis of disorders that are caused by defective neuromuscular junctions.

Curriculum Vitae

Degrees: 1971 Diploma in Biology, University of Freiburg
1974 Ph.D. University of Constance
1988 Habilitation in Biochemistry, University of Constance
2008 Apl Professor, University of Constance

1974-1975: Postdoctoral fellow, University of Constance
1975-1978: Research fellow, California Institute of Technology, Pasadena, USA
1978-1987: Research associate, Dept. of Neurochemistry, MPI for Biophysical Chemistry, Göttingen
1987-1989: Group Leader, Dept. of Cellphysiology, MPI for Biophysical Chemistry, Göttingen
1989: Group leader, Dept. of Cellphysiology, MPI for Medical Research, Heidelberg

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Current Research

AChR-mediated activity determines early steps in synapse formation

During early postnatal development fetal-type AChR (AChRγ) become replaced by adult-type AChR (AChRε). The physiological significance of this conversion is not understood. We generated by homologous recombination mice that express during embryonic development receptors (AChRγ/ε) that have adult-type properties (Koenen et al., 2005). We showed that AChRγ are not required to preserve myoblastfusion, muscle and end-plate differentiation since mice that express the modified, adult-type AChRγ/ε during embryonic development are viable and display no obviously changed phenotype. However, the positioning of endplates is changed dramatically (Fig. 1): Endplates in mutant mice are spread over a much broader territory than in wildtype mice suggesting that one function of the fetal type of AChR is to ensure an orderly innervation pattern of skeletal muscle.

Adult-type AChRε are required to maintain and stabilize the postsynaptic architecture (Schwarz et al., 2000). This has been demonstrated by generating mice that express genetically engineered fetal-type AChR throughout postnatal development. The AChRs with “fetal”-like properties induce a “de-differentiation” of the postsynaptic architecture and cause mild symptoms of muscle weakness, indicating that ultrastructure and function of neuromuscular junctions in adult muscle depend specifically on the expression of adult-type AChR (Witzemann et al., in preparation).

In order to understand the regulatory role of AChR-mediated activity during embryonic development we generated mice that express structurally intact but functionally “silent” AChR. As described in Peter et al. (2005), we used a mutation located in the subunit gene that was
found to cause a fast channel congenital myasthenic syndrome in human patients. Preliminary results show that the εP121L subunit is assembled into AChR complexes that are targeted to the postsynaptic membrane. Further analysis will clarify whether AChR-mediated activity is necessary for the formation and stabilization of synaptic contacts during embryonic development.

In another mouse model we express GFP-labelled γ subunits and thus green fluorescent embryonic-type AChRγ-GFP.

We demonstrate that muscle-specific programs of receptor subunit gene transcription control AChR replacement. Analysis of the dynamics of the embryonic AChRγ to adult AChRε conversion at the neuromuscular junction shows, in contrast to previous reports, that conversion does not occur simultaneously for all endplates of the diaphragm muscle. Furthermore, we were able to visualize for the first time channel conversion at distinct endplates. The conversion proceeds in a directed manner in which new AChRε are integrated from peripheral to central regions for individual endplates (Yampolsky et al., 2008).

**Synaptic regulators for initial steps in synapse formation and final differentiation of the NMJ**

We showed that MuSK kinase activity is sufficient to determine early postsynaptic specialization prior to innervation (Sander et al., 2001). We also showed that MuSK kinase is essential for the continuous supply of AChR to the postsynaptic membrane. Conditional inactivation of MuSK in adult muscle causes the disintegration of synapses and induces extensive axonal growth and sprouting. This indicates that both MuSK and AChR maintain the functional and structural integrity of the NMJ (Hesser et al., 2006).

**Inherited Channelopathies**

Congenital myasthenic syndromes (CMS) represent a group of disorders that are caused by inborn pre- or postsynaptic defects of neuromuscular transmission. The genetic heterogeneity of mutations in the AChR subunit genes leads to variable AChR deficiency and a variable degree of muscle weakness. The molecular basis of postsynaptic CMS is analysed in mouse models lacking AChR or expressing AChR carrying mutations that have been detected in human patients suffering from muscle weakness. A new heteroallelic mutation has been detected in the muscle-specific kinase (MuSK) of a human patient. We generated a mouse model carrying the same mutation. The mice develop severe symptoms of muscle weakness (Fig. 2) similar to human patients. Thus they represent not only a valuable tool to dissect MuSK signaling pathways but also to study MuSK-induced pathophysiology of CMS (Chevessier et al., 2008).
With our mouse models we can investigate in living animals experimentally induced and clearly defined perturbations of signal transduction at an as yet unknown resolution. Biochemical, ultrastructural, and electrophysiological changes can be followed in vivo. We employ direct gene transfer to modulate signal cascades, initiated by AChR-mediated activity or by MuSK-induced signals and quantitative PCR, and siRNA technology to analyse changes in gene expression. Finally, we visualize synapse degradation and synapse formation by in vivo imaging of individual neuromuscular junctions.

Fig. 2: Heteroallelic mutation in musk causes CMS. The transgenic mice will help to understand MuSK-induced pathophysiology of CMS at the molecular level. Mouse mutant at P 40 and P 75 displays progressive shrinkage of pelvic and scapular muscles and appearance of severe thoracolumbar kyphosis.

With our mouse models we can investigate in living animals experimentally induced and clearly defined perturbations of signal transduction at an as yet unknown resolution. Biochemical, ultrastructural, and electrophysiological changes can be followed in vivo. We employ direct gene transfer to modulate signal cascades, initiated by AChR-mediated activity or by MuSK-induced signals and quantitative PCR, and siRNA technology to analyse changes in gene expression. Finally, we visualize synapse degradation and synapse formation by in vivo imaging of individual neuromuscular junctions.

**Top publications**


**Structure of the Group**

Group Leader: Veit Witzemann
Postdoctoral fellows: Frédéric Chevessier, Pessah Yampolsky
PhD-Students: Pier-Giorgio Pacifici
Technical Assistance: Ulrike Mersdorf, Susi Zobeley
Teaching
IZN Teaching Program

The Major ‘Neuroscience’ in the MSc program ‘Molecular Biosciences’

To prepare students for PhD programs in neuroscience, the IZN offers a neuroscience course as part of the MSc program ‘Molecular Biosciences’ at the Faculty of Biosciences. After finishing the BSc, students may enrol in this 2-year course and receive intensive training in neuroscientific theory and cutting-edge lab technology. The program is taught in English and welcomes international students. With a strong emphasis on experimental approaches, the program’s aim is to prepare students for a career in the neurosciences. The MSc can be completed in either 3 or 4 semesters.

The program:

1st semester:
• Frontiers of Biosciences I + II (Lectures in molecular biosciences, including molecular neurobiology)
• Lab class ‘Modern methods in neurobiology’ with seminar
• Lab class ‘Axon growth, synaptogenesis, and synaptic plasticity’ with seminar

2nd semester:
• Focus Bioscience I: ‘Neuronal structures and molecules’ (Lectures, lab rotation and seminar)
• Focus Bioscience II: ‘Neuronal networks and computation’ (Lectures, lab rotation, seminar)

3rd semester:
• Biolab: Neuroscience lab rotation program
• Working in Biosciences: Lab rotation program of the student’s choice

4th semester:
• Master’s thesis in a neuroscience lab.

Instruction covers a wide spectrum of neuroscientific research, ranging from molecular neurobiology to brain physiology as well as cognitive and computational neuroscience. The MSc program is organized by the following IZN neurosciences lecturers:

• Prof. Dr. Hilmar Bading (Institute for Neurobiology)
• Prof. Dr. Joachim Kirsch (Institute for Anatomy and Cell Biology)
• Prof. Dr. Thomas Kuner (Institute for Anatomy and Cell Biology)
• Dr. Frank Möhrlen (Institute for Zoology)
• Prof. Dr. Elisabeth Pollerberg (Institute for Zoology)
• Prof. Dr. Christoph Schuster (Institute for Neurobiology)
• Prof. Dr. Rainer Spanagel (Central Institute of Mental Health)
• Dr. Rolf Sprengel (Max-Planck-Institute for Medical Research)
• Prof. Dr. Klaus Unsicker (Institute for Zoology)
• Prof. Dr. Andreas Draguhn (Institute for Physiology and Pathophysiology)

IZN PhD Program

Established in April 2004, the doctoral program at the Interdisciplinary Center for Neurosciences leads to the degree of Dr. rer. nat. (in the Faculty of Biological Sciences) or of Dr. med. (in the Faculty of Medicine).

The program provides research opportunities in the fields of Neuroanatomy, Neurobiology, Clinical Neurobiology, Neurophysiology, and Medical Cell Biology. With the new structure of the IZN additional topics of Neuroscience (Behaviour, Modelling, Neurodegenerative Diseases, Pain, Psychiatric Disorders etc.) will be covered.

It also includes doctoral students from the Graduate College 791 ‘Neural Developmental and Degenerative Processes: Basic Research and Clinical Implications’ which is currently in its second funding period.

Presently, the program comprises 45 doctoral students, 17 of whom are funded by the Graduate College 791, with the remainder receiving support from various stipends and institutional funds.

The program provides students with a variety of lectures and seminars, as well as with the possibility to participate in several of the following practical courses offered by members of the IZN.

• Preparation and culture of primary neurons (H. Bading)
• Video-imaging of neuron cultures (H. Bading)
• Electrophysiology (H. Bading)
• Transmission electron microscopy (H. Bading)
Pre- and Postgraduate Teaching Programme

Bachelor Biology
Bachelor Molecular Cellbiology
Seminars, Practical Courses, Lectures

Master Molecular Biosciences
Major Neurosciences
Seminars, Practical Courses, Lectures

HBIGS
Selection, Admission, Administration

IZN PhD Programme

Graduate College 791
SFB 636 Graduate Programme

Medical Faculty
Dr. med.

Faculty of Bioscience
Dr. rer. nat.

MD-PhD Programme of the Medical Faculty and the Faculty of Biosciences

Graduate College 791


Teaching

- Multiple electrode arrays (H. Bading)
- Confocal laser scanning microscopy (H. Bading)
- Isolation and *in vitro* culture of neural stem cells (F. Ciccolini)
- Fluorocytometry (F. Ciccolini)
- Associative learning and memory (C. Schuster)
- *Drosophila* molecular and classical genetics (C. Schuster)
- Electrophysiology – Intracellular current clamp recordings (C. Schuster)
- Functional Imaging – calcium and FM 1-43 (C. Schuster)
- *In vitro* and *in vivo* electrophysiological recording in the hippocampus (H. Monyer)
- Paired recordings from connected neurons in brain slices (A. Rozov)
- Preparation and culture of primary neurons (J. Kirsch)
- Video-imaging of neuron cultures (J. Kirsch)
- Transmission electron microscopy (J. Kirsch)
- Confocal laser scanning microscopy (J. Kirsch)
- Transmission electron microscopy (K. Unsicker)
- Neuronal cell culture (K. Unsicker)
- Non-radioactive *in situ* hybridisation on tissue slices (U. Ernsberger)
- Visualisation of the developing mouse nervous system by GFP (K. Tucker)
- Transfection, imaging, and morphological analysis of primary neuronal cultures (G. Schratt)
- Immunohistochemistry on floating brain sections (H. Simon)
- Fluorescence-imaging and patch clamp electrophysiology in cultured neurons (U. Misgeld and A. Draguhn)
- Patch clamp recording from identified neurons in brain slices (U. Misgeld and A. Draguhn)
- Measurement and analysis of neural network oscillations (U. Misgeld and A. Draguhn)

At the IZN’s annual retreat, PhD students have the chance to present a poster to the assembled members of the center and invited symposium speakers.

Several IZN Investigators are also members of ‘The Hartmut Hoffmann-Berling International Graduate School of Molecular and Cellular Biology Heidelberg’ (HBIGS) which is part of the ‘Exzellenzinitiative’ approved in October 2007.

With its new structure, the IZN integrates 51 IZN Investigators and thus provides a context in which students in the PhD program will have extensive opportunities to enhance their knowledge in the fields of behavioral/systems and translational neurosciences.
Diploma Theses 2003-2008

**Bading**

**Weislogel, Jan** (2003)
Calcium imaging using recombinant Ca\(^{2+}\) probes in primary hippocampal neurons

**Wiegert, Simon** (2004)
(I) Live Imaging of ERK Nuclear Translocation and (II) Analysis of the Role of Gene Transcription in Activity Induced Enhancement of Synaptic Efficacy in Hippocampal Neurons in Culture

**Hoffmann, Tina** (2006)
Nuclear Translocation of the CREB Coactivator TORC2 (Transducer of Regulated CREB Activity 2) and Examination of CREB mediated Activity-Dependent Neuronal Survival in Cultured Hippocampal Neurons

**Krieger, Markus** (2007)
Effects of nuclear Ca\(^{2+}\) and CaMKIV signalling on Nucleus Accumbens-gated Behavior in the Rat

**Vicinus, Benjamin** (2007)
Interfering with nuclear ERK1/2-signaling in cultured hippocampal neurons

**Ditzel, Désirée** (2008)
 Imaging of spacially distinct calcium signal using recombinant calcium probes

**Schlüter, Jana** (2008)
Calcium imaging in *Hydra vulgaris*

**Tröster, Philip** (2008)
Calcium signaling and activity-dependent gene expression in hippocampal neurons

**Bartsch**

**Panke, Jutta** (2007)
Rho and MAPK signal transduction pathways in the MEGAP knockout mouse

**Ciccolini**

**Hundeshagen, Phillip** (2007)
Effect of Neural Activity on the Differentiation of Neural Stem Cells

**Draguhn**

**Lehmann, Alexander** (2007)
Actions of Aβ-peptides on synaptic transmission

**Duhme, Nana** (2008)
Characterisation of normal and mutant human inwardly rectifying potassium channels

**Oehmen, Martin** (2008)
Effects of presynaptic GABA-A-receptors on inhibitory synaptic transmission in cultured hippocampal neurons

**Kameke, Alexandra von** (2008)
Optical imaging of fast network activity

**Flor**

**Caumans, Indra** (2003)
Dysfunktionale Aufmerksamkeitsprozesse und Präpulsinhibition bei schizophren erkrankten Menschen

**Cetinkaya, Sevim** (2003)

**Lamberger, Michael** (2003)

**Martin, Veronika** (2003)
Evaluation eines Reizexpositionsverfahrens zur Behandlung alkoholabhängiger Patienten

**Rumpf, Matthias** (2003)
Die Rolle von Lernprozessen und elterlichem Verhalten bei der Entwicklung von sozialen Ängsten

**Someasan, Alexandra** (2003)
Die P50-Suppression schizophren Erkrankter erhoben in einer simultanen P50-PPI-Abteilung

**Stroth, Sanna** (2003)
Somatosensorisch evozierte Potentiale bei chronischen Schmerzen der Skelettmuskulatur

**Wald, Annette** (2003)
Untersuchung des Zusammenhangs der Inhibitory Gating-Maße Präpulsinhibition und P50-Suppression an gesunden und schizophrenen Probanden

**Chaney, Vernon** (2004)
Untersuchungen zur Wahrnehmung und zum Erkennen emotionaler Gesichtsausdrücke bei der sozialen Phobie

**Dos Santos, Vasco** (2004)
Zur Spezifität der Emotionsinduktion bei Patienten mit generalisierter Sozialphobie und nicht ängstlichen Kontrollpersonen in einem Verhaltenstest
Nees, Frauke (2004)
Psychophysiologische Untersuchungen bei alkohol-/nikotinabhängigen Patienten - Analyse der Reaktion auf verschiedene Alkohol- bzw. Nikotinreize

Pfeiffer, Kerstin (2004)
Traumaberichte von Personen mit und ohne PBS: inhaltliche Textanalyse sowie subjektive und psychophysiologische Reaktionen

Scharpf, Katrin (2004)
Validierung einer Druckstimulationsmethode zur experimentellen Schmerzinduktion

Storner, Tina (2004)
Psychophysiologische Untersuchungen bei alkohol-/nikotinabhängigen Patienten - Analyse der Reaktion auf verschiedene Alkohol- bzw. Nikotinhinweisreize

Tuttas, Marie-Luise (2004)
Psychometrische Evaluation von Fragebögen zur Schmerzdiagnostik von Kindern und Jugendlichen

Zur Rolle der Antizipation bei der stressbedingten Aktivierung der Hypothalamus-Hypophyse-Nebennierenrinden-Achse

Balke, Doreen (2005)
Langzeitauswirkungen früher Schmerzerfahrungen auf die Schmerzwahrnehmung in später Kindheit

Dilmac, Kristil (2005)
Soziale Kompetenz bei Subtypen sozialer Phobie

Halbeis, Damaris (2005)
Klassifikation chronischer Gesichtsschmerzen anhand des MPI-D

Herrmann, Sandra (2005)
Psychometrische Evaluation von Fragebögen zur Diagnostik bei Schmerzen und allgemeinen körperlichen Beschwerden im Kindes- und Jugendalter

Heuser, Mark (2005)
Emotionale Reagibilität bei generalisierter sozialer Phobie

Mußgnug, Nadga (2005)
Angstinduktion mittels phobierelevanten und -irrelevanten Stimuli bei nicht-generalisierter sozialer Phobie

Schreiber, Viola (2005)
Emotionale Taubheit in der Posttraumatischen Belastungsstörung

Soekadar, Surjo (2005)
Phantomschmerz und neuronale Plastizität nach Amputation der unteren Extremität: Prävention und Therapie mit Mempoine und Baclofen

Ullrich-Kleinmanns, Jens (2005)
Neuropsychologische Aspekte der Nikotinabhängigkeit: Zur Veränderung der motivationalen Valenz verschiedener Verstärker im Nikotinentzug

Farrugia, Claire (2006)
Quantitative sensory testing and psychological variables in trigeminal neuralgia, trigeminal neuropathy and atypical facial pain

Flach, Florentine (2006)
Der Einfluss von Persönlichkeitsmerkmalen auf die Posttraumatische Belastungsstörung

Hoffmann, Mike (2006)
Wiederauffrischung (reinstatement) - ein Mechanismus zur Aufrechterhaltung der sozialen Phobie

Kehrerberger, Christiane (2006)
Schmerzverarbeitung und Schmerzempfindlichkeit bei Kindern mit rezidivierenden Bauchschmerzen

Koler, Johanna (2006)
Der Einfluss von Delta-9-THC auf Lernen und Gedächtnis

Konieczna, Anna (2006)
Mehrdimensionalität psychophysikalischer Kennwerte experimenteller Schmerzverarbeitung bei Gesunden und chronisch Schmerzkran ken

Krajewski, Robert (2006)
Können endokrinologische Parameter anhand von Stressverarbeitungsstrategien, alltäglicher Belastung, Depressivität und Ängstlichkeit vorhergesagt werden?

Lang, Stefan (2006)
Zum Einfluss stresskorrelierter Muskelanspannung bei Patienten mit Trigeminusneuralgie

Rance, Mariela (2006)
Sensibilisierung bei verschiedenen Stimulationsmethoden

Suppl Angelika (2006)
Mögliche Einflussfaktoren für die Entstehung einer sozialen Phobie

Yimaz, Pinar (2006)
Zusammenhang zwischen quantitativer sensorischer Testung und der Beeinträchtigung bei Patienten mit chronischen muskulöskelettalen Schmerzen

Zahrnan, Assad (2006)
Der Einfluss von Lernerfahrungen auf implizite Assoziationen bei Personen mit sozialer Phobie und nichtängstlichen Kontrollpersonen
Klimm, Sabrina (2006)  
Das Schmerzerleben von Kindern mit rezidivierenden Bauchschmerzen: eine experimentelle Untersuchung unter Verwendung des Kaltwassertests

Greiner, Stefanie (2007)  
Die Rolle der Mutter-Kind-Interaktion während des Kaltwassertests bei Kindern mit rezidivierenden Bauchschmerzen

Lieven, Stefan (2007)  
Wenn die Angst, vor anderen das Gesicht zu verlieren, Menschen aus der Bahn ihres Alltags wirft

Wittenberg, Sandra (2007)  
Gibt es Geschlechtsunterschiede in der Schmerzwar- 
mung von Kindern mit Migräne

Dinu-Biringer, Ramona (2008)  
Elektrodermale Reaktivität und neuronale Korrelate beim aversen Lernen und Verlernen. Vergleich von Cue- und Kontext-Konditionierung im Zusammenhang mit Ängstlichkeit

Thiel, Kathrin (2008)  
Aufmerksamkeitshinwendung auf alkoholassozierte Stimuli: Zusammenhang mit der kognitiven Leistungsfähigkeit und der Inhibition präpotenter Verhaltensreaktionen bei alkoholabhängigen Personen

Frings

Savic, Alexandra (2004)  
Suche nach Ionenkanalblockern für CNG-Kanäle in Schlangen- und Kegelschneckengiften

Drexel, Jan (2004)  
Isolierung und Charakterisierung einer Astacin-homologen Metalloprotease

Immunohistochemische Charakterisierung von Schmerzzellen in der Ratte

Wiedmann, Verena (2004)  
Internetportal der Bioinformatik für Studenten im Grundstudium der Biologie

Klimmeck, Daniel (2005)  
Vitale Gewebeschnitte des olfaktorischen Epithels der postnatalen Maus

Ungerer, Nicole (2005)  
Isolierung und Charakterisierung von Membranproteinen aus Riechzellen der Ratte

Funk, Katharina (2006)  
Entwicklung eines Modellsystems für die Signaltransduktion in Schmerzzellen

Vocke, Kerstin (2006)  
Mutagenese der cAMP-Bindestelle von CNG-Kanälen

Hengl, Thomas (2006)  
Lokalisation von mRNA-Transkripten auf Gewebeschnitten des Riechepithels

Schlabing, Jochen (2006)  
Expression von Calmodulinmutanten

Stavermann, Maren (2007)  
Fluoreszenzoptische Messungen der Riechzellaktivität

Jeridi, Semir (2007)  
Etablierung eines fluoreszenzbasierten Nachweissystems für Ca²⁺-aktivierte Cl⁻-Flüsse

Daiber, Philipp (2007)  
Expression von Bestrophin 2 in olfaktorischen und nozizeptiven Systemen

Holstein

Identifizierung der Interaktionspartner des T-Box Transkriptionsfaktors Brachyury in Hydra

Philipp, Isabelle (2003)  
Cloning and Expression of Cell Polarity Genes in Hydra

Saina, Michael (2003)  
Isolation und Expressionsanalyse von Mitgliedern eines TGF-beta Signalwegs in Nematostella vectensis

Funktionale Charakterisierung von Hydra Chordin zur Vorbereitung von Injektionsexperimenten und Protein-Interaktionsstudien mittels Blau-Nativer PAGE

Anton, Roman (2004)  
Analyse eines BMP2/4 Dpp-Orthologs und eines potentiellen BMP-Antagonisten von Nematostella vectensis (Anthozoa, Edwardsiidae)

Fritzenwanker, Jens (2004)  
Beschreibung der Embryonalentwicklung und Charakterisierung eines Fork Head Homologs aus Nematostella vectensis

Hrach, Jens (2004)  
Mikroinjektionen in Nematostella vectensis

Mättner, Robert (2004)  
Analyse der Transfektion von Hydrazellen mit Transposon enthaltenden Vektoren

Nacak, Tanju (2004)  
Charakterisierung von Signalmolekülen während der Kopfre- 
generation in Hydra vulgaris
Diploma Theses

**Büttner, Andreas** (2005)
Analyse putativer BMP- und Wnt-Anatgonisten mit einem Cystin-Knoten Motiv in *Hydra*

**Krause, AnnKatrin** (2006)
Charakterisierung von Gremlin-ähnlichen Molekülen in *Hydra magnipapillata*

**Steinbronn, Nadine** (2006)
Cadherine in *Nematostella vectensis* - genauere Charakterisierung und Interaktionstudien mit beta-Catenin.

**Veit, Marion** (2006)
Charakterisierung eines PS-1 und eines APP Homologs in *Hydra magnipapillata*

**Christ, Annabel** (2007)
Untersuchungen zur stabilen Transfektion von *Hydra magnipapillata*

**Kins**

**Nesic, Iva** (2002)
Untersuchungen zur subzellulären Lokalisation von APLP1 und APLP2

**Haas, Petra** (2003)
Charakterisierung subzellulärer Sortierungssignale von APP

**Szodorai, Anita** (2003)
Untersuchungen zur Funktion der APP-Proteinfamilie als Kinesin-Membranrezeptoren

**Wagner, Katja** (2004)
Untersuchungen zur Interaktion der APP-Genfamilie mit PSD-95 und Fe65/Fe65L1

**Back, Simone** (2005)
Untersuchungen zur subzellulären Verteilung von APP in Nervenzellen

**Lauffer, Nadine** (2005)
Untersuchungen zur axonalen Transportmaschinerie von APP Familienmitgliedern

**Siehl, Katjuscha** (2005)
RNA Interference Technology Based Knockdown of the APP Familiy Proteins

**Rusu, Patricia** (2005)
Analyses of the Physiological Functions of APP/APPL in *Drosophila melanogaster*

**Stahl, Ronny** (2007)
The influence of APP processing on cell adhesion

**Kirsch**

**Laue, Thomas** (2007)
Lokalisationsstudien des eukaryotischen Elongationsfaktors (eEF1 A) in hippocampalen Neuronen und Etablierung von RNA-Interferenz-Methoden zur Reduktion der Expression von eEF1 A

**Kuner Thomas**

**Vasileva, Mariya** (2005)
Overexpression of synapsin isoforms in the calyx of Held via ATGp

**Reuter, Kirsten** (2006)
Selective Labeling of Presynaptic Protein in the Calyx of Held Mediated by the Genetically Encoded AGT-tag

**Sandikci, Arzu** (2006)
Imaging steady state spatial distribution of chloride in the soma and dendrites of principal neurons using new variants of genetically encoded chloride indicator Clomeleon

**Monyer**

**Schächinger, Thorsten** (2003)
Generation of a DNA construct for the conditional knock-out of the NMDA receptor subunit NR2B gene in *Mus musculus*

**Götz, Thomas** (2004)
Developing a novel method to reversibly modulate neuronal activity in the mouse brain

**Bocklisch, Christina** (2007)
Functional and neurochemical characterization of NR2D-EGFP expressing cells in the hippocampus

**Pollerberg**

Einfluss von mikro- und nanostrukturennten Oberflächen auf Melanozyten und Osteoblasten

**Tchouandong, Leopoldine** (2003)
Produktion und Aufreinigung der rekombinanten Zelladhäsionsmoleküle DM.GRASP u. ALCAM

**Zeiler, Martin** (2004)
Einfluss unterschiedlich nanostrukturierter Oberflächen auf das Verhalten von Osteoblasten

**Blüm, Raphael** (2004)
Durchmusterung einer cDNA-Bank nach extrazellulären Interaktionspartnern von Zelladhäsionsmolekülen

**Souren, Marcel** (2004)
*In vivo* analysis of regulatory elements predicted *in silico*
Georg, Tanja (2005)
Regulation der Endozytose von Zelladhäsionsmolekülen

Krais, Annette (2005)
Einfluss des Zelladhäsionsmoleküls DM-GRASP auf intrazelluläre Signalwege

Bertuch, Stefanie (2006)
Regulation der Endozytose des Zelladhäsionsmoleküls DM-GRASP

Bubis, Andreas (2007)
Untersuchungen zur Interaktion von Zelladhäsionsmolekülen

Geuder, Tanja (2007)
Untersuchungen zur Interaktion zweier integraler, axonaler Membranproteine

Höckendorf, Burkhardt (2007)
Proof of principle for a gene trap approach in medaka using the maize transposable element Ac/Dc

Rupp

Andermann, Martin
Neuromagnetic investigation of instrument size: Influence of musical aptitude and pitch perception

Ibrom, Sophie
Mismatch negativity, the auditory memory trace and musical aptitude

Schuster

Pfenning, Philipp-Niclas (2007)
Die Rolle von TRP-Caliumkanälen und NO-Signalzkaskaden während erfahrungsabhängiger Potenzierung glutamatregierter Synapsen

Leefmann, Jon (2008)
Analysis of synaptic transmission and locomotive behavior in larvae of Drosophila melanogaster by optical control of phosensitive adenyl cyclase and channelrhodopsin-2

Litzenburger, Ulrike (2007)
Die Rolle des Phosphorregulierungsstaus der postsynaptischen Glutamatrezeptoren und die Rolle der NO-Synthese während der erfahrungsabhängigen synaptischen Potenzierung von Drosophila melanogaster

Seeburg

Lentivirus-mediated gene expression in the mammalian cortex

Laudenklos, Sabrina (2004)
Lentiviral-based approach to study dendritic integrative properties of pyramidal neurons in rat barrel cortex in vivo

Spors

Shahshahani, Nilufar (2008)
Odor adaptation and odor discrimination time

Sprengel

Layer, Liliana (2003)
Funktioneller Austausch der endogenen GluR-A-Untereinheit durch GluR-A-Varianten im Hippokampus der Maus

Marx, Verena (2003)
Tetrazyklinregulation GFP markierter AMPA-Rezeptoren im Gehirnpräparat transgener Mäuse

Mihaljevic, André (2004)
mRNA trafficking of the voltage - gated potassium channel subunit Kv4.2 in hippocampal pyramidal neurons.

Bus, Thorsten (2005)
Selektive Steuerung der Genexpression in GnRH-Neuronen.

Tang, Wannan (2005)
In vivo labelling of Tbr1 gene in mitral cells in the olfactory bulb of developing zebrafish, Danio rerio

Strobel, Cornelia (2006)
Analyse des Isolator 40 Elements in transgenen Mäusen

Tucker

Brachmann, Isabel (2005)
Analysis of the central and peripheral nervous systems of the mouse mutant line tauGFP during embryonic development

Schumacher, Stefanie (2006)
Establishment of RNA interference (RNAi) for the reduction of gene expression in neural stem cells from mouse brain and from in vitro-differentiated embryonic stem cells

Weißmüller, Kathrin (2006)
The neurobiological developmental potential of in vitro-differentiated embryonic mouse stem cells in the central and peripheral nervous system of the chick embryo

Shen, Xiao (2008)
Analysis of a cortical layering defect in the postnatal brain of tau::N19RhoA transgenic mice

Unsicker

Lohr, Jennifer (2004)
Die Entwicklung der Nebennieren und sympathoadrenalen Zelllinie bei SF-1 haploinsuffizienten Mäusen
Master / Doctoral Theses

Master Theses 2003-2008

Bading
Aso, Yoshinor (2007)
Activity Dependent Induction of GADD45 Family Genes and Promotion of Survival in Hippocampal Neurons

Burau, Karin (2007)
The morphology and dynamics of the retinal bipolar cell terminals in the zebrafish

Lu, Li (2007)
Characterization of Activity-regulated Fbxo33, a Potential Gene Involved in Synaptic Plasticity

Zou, Ming (2008)
A Nuclear Calcium-Regulated Gene Program for Neuroprotection

Draguhn
Vasileva, Mariya (2007)
Alterations of synaptic transmission after disruption of the APPpathway

Schratt
Khudayberdiev, Sharof (2007)
The transcriptional regulation of a large microRNA cluster at the rat 6q32 domain

Veith, Matthias (2007)
Identification of neuronal microRNA target mRNAs

Tucker
Isabel Brachmann (2005)
Analyse des Zentralen und Peripheren Nervensystems der Mausmutantenlinie tau-GFP während der Embryonalentwicklung

Stefanie Schumacher (2006)
Etablierung von RNA Interference (RNAi) zur Minderung der Genexpression in neuronalen Stammzellen aus dem Mausgehirn und von in vitro-differenzierten embryonalen Stammzellen

Wolff, Steffen (2007)
Nuclear-cytoplasmic shuttling of histone deacetylases and its role in neurogenesis

Doctoral Theses 2003-2008

Bading
Dübel, Jens (2005)
Untersuchung intrazellulärer Chlorid-Konzentrationen in Clomeleon-exprimierenden ON-Bipolarzellen der Mausretina mit Hilfe der Zwei-Photonen-Mikroskopie

Inta, Joana Monica (2005)
TWEAK and NF-kB in Cerebral Ischemia

Buchner, Julia (2006)
Early development of topographically organized activity patterns and GABAergic Interneurons in the zebrafish olfactory bulb

Chen, Jing (2006)
Cerebellar granule cell-specific deletion of the AMPA receptor subunit Glur-D gene

Hartmann, Bettina (2006)
Molekulare Mechanismen synaptischer Plastizität in nozizeptiven Neuronen des Rückenmarks unter Beteiligung von AMPA-Rezeptoren

Wittmann, Malte (2006)
Synaptic and extra-synaptic NMDA receptors in hippocampal neurons: regulation of nuclear shape and cell fate

Zhang, Sheng-Jia (2006)
Specifying molecular determinants of the subcellular targeting of synaptic and extrasynaptic GABA(A) receptors

Generation and analysis of calcium signals in the cell nucleus

Sanno, Hitomi (2007)
Postnatal control of cortical development by Rho GTPases

Weislogel, Jan (2008)
Imaging of spatially distinct calcium-signals using recombinant indicators

Bartsch
Baur, Max (2006)
Charakterisierung tet-kontrollierter, serotonerger oder glialer Gehirnexpression des artifiziellen Transkriptionsfaktors (tTA) mittels doppelt transgener Reporter-Mäuse

Kautt, Sandra (2007)
Expression of MEGP mRNA during embryonic development

Mannhardt, Sönke (2007)
Effect of nifedipine on fear memory extinction
Huppert, Verena (2008)
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<td>Verhaltens- und molekulare Untersuchungen zur Drogenwirkung</td>
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<td>Axon growth, synaptogenesis, plasticity</td>
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<td>Gene transfer to the mouse brain, Purification of the Taq-Polymerase</td>
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<td>Using EGFP to illuminate the mouse nervous system</td>
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<td>Molecular, cellular and organismic studies, Using EGFP to illuminate</td>
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<td>Molecular and genetic tools for the analysis of medaka and zebrafish</td>
<td>Jochen Wittbrodt</td>
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<td>Intensive course at the MPI for Medical Research</td>
<td>Veit Witzemann</td>
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<td>Course for Graduate College</td>
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Lehrerfortbildungsveranstaltungen der
Neurowissenschaftlichen Gesellschaft -

Neurowissenschaften in der gymnasialen Oberstufe' Im Rahmen der 'Brain Awareness Week'

15.03.2004

10.15  Hilmar Bading, IZN, Neurobiologie: Lernen

11.00  Oliver von Bohlen, IZN, Neuroanatomie: Das emotionale Gehirn

13.30  Andrea Ludolph / Joachim Kirsch, IZN, Anatomie & Zellbiologie: Zappelphilippsgehirn – das Aufmerksamkeitsdefizitsyndrom

14.15  Klaus Unsicker, IZN, Neuroanatomie: Wachstumsfaktoren für Hirnzellen

15.00  Horst Simon, IZN, Neuroanatomie: Entwicklungsneurobiologie und Krankheit


Neues vom Gehirn

17.03.2006

10.00  Prof. Andreas Draguhn, IZN, Institut für Physiologie: Funktionsprinzipien von Synapsen

11:00  Prof. Hannah Monyer, Dr. Jakob von Engelhardt, IZN, Klin. Neurobiologie der Neurologischen Klinik: Neubildung von Nervenzellen - ein Mechanismus der Plastizität?

13:00  Prof. Hilmar Bading, IZN, Neurobiologie: Kalzium: Schalter für Veränderungen im Gehirn

14:00  PD Dr. Oliver von Bohlen und Halbach, IZN, Neuroanatomie: Morphologische Aspekte erfahrungsabhängigen Lernens


Neurobiologische Grundlagen kognitiver Leistungen

04.03.2005

10.00  Prof. Andreas Draguhn, IZN, Institut für Physiologie: Informationsverarbeitung in neuronalen Netzwerken

11:00  Dr. Rainer Friedrich, IZN, MPI für Medizinische Forschung: Funktionsprinzipien des Riechsinnes

13:00  Dr. Andreas Frick, MPI für Med. Forschung: Mechanismen der synaptischen Plastizität

14:00  Dr. Oliver Dick, IZN, Institut für Neurobiologie: Das Auge: Einblicke ins Gehirn

15:00  Prof. Herta Flor, IZN, ZI Mannheim: Traumagedächtnis

Signalmoleküle des Nervensystems: neue Techniken und Ergebnisse der molekularen und zellulären Neurobiologie

23.03.2007

10:00  Prof. Dr. Thomas Söllner, BZH/IZN, Univ. Heidelberg: Exo- und Endocytose an der neuronalen Synapse

11:00  PD Dr. Mathias Klugmann, IZN, Neurobiologie: Gentherapie für neurologische Erkrankungen

13:00  Prof. Dr. Gudrun Rappold, IZN, Humangenetik, Univ. Heidelberg: Genetische Grundlagen der geistigen Retardierung

14:00  Prof. Dr. Thomas Kuner, IZN, Medizinische Zellbiologie: Gezielte Eingriffe in die Funktion von Synapsen des zentralen Nervensystems durch viralen Gentransfer

15:00  Versuche zur Neuro- und Sinnesphysiologie im Unterricht: Demonstration mit praktischen Übungen. Ferdi Oberheinrich, Firma ADInstruments, Spechbach b. Heidelberg
Entwicklung des Nervensystems

14.03.2008

10:00 Prof. Dr. Jochen Wittbrodt, Zoologie, IZN, Univ. Heidelberg: Evolution und Entwicklung des Auges

11:00 Prof. Dr. Thomas Holstein, Zoologie, IZN, Univ. Heidelberg: Entstehung des Nervensystems

13:00 Prof. Dr. Joachim Kirsch, Anatomie und Zellbiologie, IZN, Univ. Heidelberg: Entwicklung von zentralnervösen Synapsen

14:00 Prof. Dr. Kerry Tucker, Neuroanatomie, IZN, Univ. Heidelberg: Entwicklung der Anatomie des Gehirns

15:00 Prof. Dr. Christoph Schuster, Neurobiologie, IZN, Uni Heidelberg: Axonale Wegfindung und Plastizität im Nervensystem von Insekten
Seminars and Symposia
IZN Seminar Series

The IZN hosts four seminar series. The bi-weekly ‘IZN Seminars’, that provide doctoral students or postdocs with an opportunity to present their projects, alternate with the ‘Heidelberg Neurobiology Lectures’, in which renowned scientists from abroad talk about their latest research. At the bi-weekly ‘GK 791 Seminars’ and the monthly ‘SFB 488 Seminar: Progress in developmental neurosciences’, IZN Investigators and their group members report on their current projects.

In addition, the IZN organizes special lectures, international symposia and the annual IZN retreat at Kloster Schöntal/Jagst, which has become a tradition for all Heidelberg/Mannheim neuroscientists to meet and discuss science.

IZN Seminars 2003

Hilmar Bading  
Nuclear calcium signaling in neuronal survival

Mascha Blatow  
A novel network of multipolar bursting interneurons generates theta frequency oscillations in neocortex

Karin Burau  
c-ret signaling and neuronal diversification

Antonio Caputi  
Anatomical and physiological characterization of hippocampal calretinin cells

Francesca Ciccolini  
Characterisation of late neural stem cells by direct isolation: uncoupling of acquisition of EGF responsiveness and bias towards glia generation.

Andreas Draguhn  
The role of transmitter uptake and transmitter metabolism at central inhibitory synapses

Jakob von Engelhardt  
Generation of transgenic mice expressing EGFP in cholinacetyltransferase-positive neurons

Elke Fuchs  
Conditional gene ablation in GABAergic interneurons

Ulrich Hoheisel  
Consequences of changes in spinal and supraspinal cGMP for spinal neuronal activity.

Katrin Huber  
The development of the sympathoadrenal cell lineage

Tanja Kögel  
Myosin Va-dependent transport and maturation of secretory granules

Jochen Kuhse  
The regulation of cluster formation of NMDA-receptor NR1-splice variants in spinal neurons

Volker Nimmrich  
High-frequency (~200 Hz) network oscillations in the rodent hippocampus: analysis of cellular and network mechanisms in vitro

Heike Peterziel  
Molecular mechanisms of GDNF/TGF-β cooperativity

Katharina Schindowski  
Growth factors in cerebral ischemia: Regulation and physiological roles of GDF-15, FGF-2, and FGF-5

Andreas Schober  
Neurotrophic factors for preganglionic sympathetic neurons

Christian Scholz  
Development of midbrain dopaminergic neurons in chicken

Kerry Tucker  
A green mouse: Using GFP to study peripheral nervous system development

Peer Wulff  
Cell type-specific modulation of neuronal activity

IZN Seminars 2004

Isabel Aller  
Selective ablation of the GABAA receptor g2 subunit from cerebellar granule cells

Ayla Arslan  
Synaptic and extrasynaptic GABAA receptors

Peter Bengtson  
Synchronised recurrent bursting of cultured hippocampal neurons – a model for investigating long lasting plasticity.

Karin Burau  
Development of cholinergic sympathetic neurons

Sabine Chourbaji  
Behavioural and transgenic approaches in murine animal models for depressive disorders

Francesca Ciccolini  
EGF is a motogen for late development stem cells

Irina Coserea  
Role of NMDA receptor subunits in excitatory cell death
IZN Seminars 2005

Suhua Deng
Functional analysis of plexin-B family members plexin-B1 and plexin-B2

Beril Doganci
Conditional knock-out of the NMDA receptor subunit NR2B

Thomas Dresbach
Targeting proteins to nascent synapses: Routes to branches

Anja Eder
Generating Ca2+ signals by photolysis

Gitta Erdmann
Analysis of glucocorticoid signaling in the mouse brain by gene targeting

Nidhi Gakhar
Calcium Signalling in Neural Precursors

Daniel Gherbassi
Mining the human genome: Identification of genes with potential links to Parkinson's disease

Christine Hassler
Functional screen for interaction partners of Kremen protein in Xenopus Embryos

Ulrich Hoheisel
Inflammatory cytokines and neurotrophins as stimulants for group IV muscle afferents in the rat.

Katrin Huber
Role of Phox2B and MASH-1 in chromaffin cell development

Dragos Inta
In vivo labeling of specific interneuronal populations

Bettina Maier
The role of DM-GRASP in the developing visual system

David McCormick
Rapid activation of recurrent cortical networks: A basic feature of cortical operation?

Corina Popovici
GDF-15 - a TGF-β superfamily member with possible implications in the pathology of malignant gliomas

Hitomi Sanno
The GTPase Rho & nerve development

Caroline Schmitz
Screening for genes controlling axon guidance in C. elegans

Andreas Schober
GDNF/TGF-β synergy in a model of Parkinson's disease

Christoph Schuster
Experience-dependent synaptic plasticity in Drosophila

Paola Sgado
The atypical homeoprotein Pbx1a controls late axonal pathfinding of mesencephalic dopaminergic neurons

Frank Stief
Altered inhibition-excitation-balance in hippocampal interneurons in chronic temporal lobe epilepsy

Jens Strelau
Characterization of growth-differentiation factor 15, a transforming growth factor beta superfamily member

Markus Uhrig
From development to neurodegeneration: Neural transdifferentiation of human adult stem cells? & Gene expression profiling of human neuroblastoma cells exposed to A beta peptides

Wei Zhang
Muscarnic modulation of SK channel activity in nigra neurons

Aleksandar Zivkovic
Characterization of excitatory synaptic transmission in GluR-D knock-out mice

IZN Seminars 2005

Kambiz N. Alavian
Mechanism of cell death in engrailed deficient mesencephalic dopaminergic neurons

Oliver von Bohlen
Role of trkB in the maintenance of dendritic spines

Antonio Caputi
Analysis and characterization of two Calretinin-positive GABAergic cell populations in layer II/III of the mouse neocortex

Francesca Ciccolini
Effect of CREB / CREM transcription factors in neural stem cell proliferation and self-renewal

Geoffrey Drew
Substance P drives endocannabinoid signalling in midbrain periaqueductal grey neurons by enhancing glutamate release

Alexei Egorov
Muscarnic control of graded firing activity in medial temporal lobe structures

Ulrike Engel, Harvard Medical School, Boston
Signaling to the cytoskeleton in neuronal outgrowth: The microtubule plus end binding protein Orbit/CLASP mediates axon guidance downstream of the tyrosine kinase Abl.
IZN Seminar Series

Uwe Ernsberger
Factors for cholinergic development of sympathetic neurons

Kristin Hartmann / Christina Janista
“Regulation of efficacy at GABAergic synapses by presynaptic GABA content”

Ulrich Hoheisel
Tetrodotoxin (TTX) as a tool for studying the spinal connectivity of nociceptive afferents

Matthias Klugmann
CNS gene therapy in a rat leukodystrophy model

Thomas Kremer
Identifying novel active zone proteins

Jochen Kuhse
Activity-dependent shedding of the NMDA receptor glycine binding site by matrix metalloproteinase 3: A novel mechanism of postsynaptic plasticity

Daniela Lambertz
Influence of chronic myositis on spinal field potentials of TTX resistant skin and muscle afferents in rat spinal cord

Heike Peterziel
Cooperativity between members of the TGF-beta superfamily in neuronal cells

Andrei Rozov
LTP (Induction and termination)

Andrei Rozov
Supression of inhibition by a direct action of cannabinoids on ionotropic GABA receptors

Maya Shaked
Neural differentiation of ES cells

Horst Simon
Progressive loss of nigral dopaminergic neurons in postnatal engrailed mutant mice

Jörn Steinert
Are quantal size variations strictly postsynaptic?

Stefan Titz
Ammonium uptake and KCC2 function: Pathophysiological and developmental aspects

Simone Velte
Modulation of SK channel activity in nigral neurons by disinhibition and internal chloride concentration

Simon Wiegert
ERK trafficking in hippocampal neurons

Peer Wulff
Functions of GABA-A receptors on interneurons

Amanda Wyatt
Retrograde NO-signalling activates presynaptic NMDARs at Drosophila NMJs

IZN Seminars 2006

Isabel Aller
The neurobiology of TASK-1 and -3 potassium channels

Martin Both
Specificity of information transfer within the hippocampus

Ali Cetin
Monitoring activity dependent changes in somato-sensory barrel cortex

Jing Chen
Cerebellar granule cell-specific deletion of the AMPA receptor GluR-D gene

Oliver Dick
NMDA receptor regulated shuttling of FOXOs in hippocampal neurons

Geoff Drew
Regulation of synaptic inhibition by glutamate uptake in the midbrain periaqueductal grey

Olivia Dumitrescu
Characterization of 5HT3a-expressing cortical interneurons in a transgenic mouse model

Marina Eliava
Morphological study of gap junctions using Cx36-EGFP transgenic mouse

Uwe Ernsberger
Neuronal differentiation and diversification – the sympathetic system and beyond

Nidhi Gakhar
Modulation of neural precursor cell differentiation by neural activity

Alexander Groh
Targeted expression of fluorescent proteins in layer 5B neurons reveals a strongly depressing corticothalamic giant synapse imparting low-pass filtering of cortical inputs

Frank Hofmann
Microelectrode arrays (MEAs) as a tool to study late phase plasticity
Ulrich Hoheisel
Intracellular recordings of rat dorsal horn neurons in vivo before, during and after intramuscular injections of nerve growth factor

Dragos Inta
Distinct postnatal migratory streams of GABAergic neurons: regulation by serotonin via its ligand-gated ion channel

Dragos Inta
Postnatal pancortical migration of GABAergic neurons modulated by serotonin 5-HT3 receptors

Jarek Jarosik
FGF-2 has antidepressant properties in an animal model of depression

Carla Margulies
Nuclear Calcium Signaling: a green light for long-term memory in Drosophila

Ulrich Misgeld
The functional role of endocannabinoid CB1 receptors on neostriatal medium spiny neurons

Heike Peterziel
F-spondin promotes neuron survival and differentiation

Alexei Ponomarenko
Recruitment of interneurons shapes synchronous states of the intact hippocampus

Hitomi Sanno
Inducible expression of Rho GTPase modulators in the developing murine nervous system

Christian Scholz
K-ATP channels as a pharmacological target to rescue midbrain dopaminergic neurons from toxic insult nervous system

Gerhard Schratt
MicroRNAs in synapse development

Stefanie Schuhmacher
RNA interference in neural stem cells

Jörg Steinert
Role of postsynaptic glutamate receptors in the experience-dependent activation of presynaptic NMDA

Malte Wittmann
Activity-dependent control of the geometry of neuronal nuclei

IZN Seminars 2007

Kambiz Alavian
The role of P75 in the death of engrailed deficient mesencephalic dopaminergic neurons

Florian Bährner
Plasticity of hippocampal neurons in memory-related network oscillations

Waleed Barakat
RAGE in cerebral ischemia

Tiziana Cesetti
Absence of functional GABA-A receptors in stem cells of the postnatal subventricular zone

Uwe Ernsberger
To build a neuron (cont.)

Elke Fuchs
Recruitment of parvalbumin-positive interneurons determines hippocampal function and associated behaviour

Nadine Holter
Functional maturation of developing interneurons in the molecular layer of mouse dentate gyrus

David Lau
Analysis of transcription network involved in neuronal survival

Volker Mack
A novel synaptic protein alters AMPA receptor-mediated transmission

Daniela Mauceri
SAP97: Physio-pathological functions of a cargo protein

Andrei Rozov
Two Calretinin-positive GABAergic cell population in layer 2/3 of mouse neocortex provide different forms of disinhibition

Andreas Schober
Zuckerkanndl’s organ - re-visited

Yongjoon Suh
Effect of Dlx2 on neural precursor cells from subventricular zone and hippocampus

Kerry Tucker
Histone acetylation controls embryonic forebrain neurogenesis

Wolfgang Wick
Molecular basis of a cellular therapy for glioblastoma

Nina Wittenmeyer
Neuroligin 1 promotes maturation of the cytomatrix of active zones via postsynaptic interactions
IZN Seminars 2008

Nixon Abraham
Synaptic inhibition accelerates odor discrimination in mice

Julieta Alfonso
Neurogenesis and widespread forebrain migration of distinct GABAergic neurons from the early postnatal subventricular zone

Raphael Blüm
Glycine receptor activity affects intracellular signaling pathways in cultured neurons

Isabel Brachmann
Imaging of spinal nerve outgrowth in normal and semaphorin 3A mutant mouse embryos

Carmen Carrillo
Growth/differentiation factor (GDF) 15 regulates cell cycle exit of secondary progenitors in the developing mouse ganglionic eminence

Roberto Fiore
Function of a large microRNA cluster in activity-dependent neuronal development

Florian Freudenberg
The role of hippocampal AMPA receptors in an animal model of depression

Lydia Haussmann
Protrusion and Retraction - Implications of the interaction between MEGAP and the Ena/VASP binding protein Lamellipodin in lamellipodial dynamics

Alexander Lehmann
Effects of a defined oligomeric Aβ-species on synaptic activity

Sasidhar Murikinati
CB2 receptor activation in cerebral ischemia

Pier Giorgio Pacifici
Characterization of a mouse model lacking AChR activity during embryonic development

Jan-Marek Weislogel
Visualisation of spatial distinct calcium signals in Hydra

Sascha Weyer
In vivo analysis of APP functional domains

Sabrina Zechel
Putative factors for the development and maintenance of the nigrostriatal dopaminergic system

Heidelberg Neurobiology Lectures 2003

Silvia Arber, Basel
Molecular pathways controlling sensory-motor connectivity in the spinal cord

Elena Cattaneo, Milan
Huntingtin function in Huntington’s Disease

Georg Dechant, Innsbruck
Neurotrophic factors and sympathetic neurotransmitter plasticity

Helmut Haas, Düsseldorf
Histamine in the brain

Uwe Heinemann, Berlin
Excitotoxic injury in nerve cells: involvement of mitochondria

Etienne Hirsch, Paris
Glial cells and apoptosis in Parkinsonian syndromes

Kai Kaila, Helsinki
GABA: an exciting inhibitory neurotransmitter

Philipp Kahle, München
Pathological features of a-Synuclein in Parkinson’s Disease and related disorders

Hans Lassmann, Wien
Basic mechanisms of brain inflammation: their relevance for the pathogenesis of multiple sclerosis and other human inflammatory CNS diseases.

Claudia Lodovichi, Durham
New insights into olfactory system organization

Markus Missler, Göttingen
alpha-Neurexins function as organizer molecules that couple Ca2+ -channels to synaptic transmission

Richard Olsen, Los Angeles
Structure, Function, and Plasticity of GABA-A Receptors

Ole Paulsen, Oxford
Network oscillations and synaptic plasticity in the hippocampus

Frank Pfieger, Strasbourg
Cholesterol homeostasis and function in CNS neurons

Olaf Pongs, Hamburg
M-channels in the central nervous system - determinants of neuronal excitability
IZN Seminar Series

Jochen Roeper, Marburg
To spike or to burst - ionic mechanisms in control of electrical activity in dopaminergic neurons

Dietmar Schmitz, Berlin
Comparison of different forms of synaptic plasticity in the hippocampus

Jörg Schulz, Tübingen
Molecular pathways of neuronal death: From mechanisms to treatment

Marten Smit, Utrecht
Molecular mechanisms of midbrain dopamine neuron development

Eberhard Weihe, Marburg
Chemical coding of neurotransmission: The vesicular transporter connection

Heidelberg Neurobiology Lectures 2004

Eero Castren, Helsinki
Physiological, pathophysiological and pharmacological effects of neurotrophins in adult brain

Richard Dyck, Calgary
Zinc as a neurotransmitter - Implications for plasticity and pathology

David I. Graham, Glasgow
Traumatic brain injury - What is new?

Mike Gutnick, Jerusalem
Thalamocortical axons release serotonin during cortical circuit development

Reinhard Jahn, Göttingen
Molecular mechanisms of neuronal exocytosis

Avihu Klar, Jerusalem
Transcriptional and post translational control of axon guidance

Martin Korte, Martinsried
Neurotrophins and activity dependent synaptic plasticity

Volkmar Lessmann, Mainz
Intracellular targeting and synaptic secretion of neurotrophins

Siegfried Löwel, Magdeburg
Experience-dependent plasticity of intracortical circuitry and functional maps in the visual cortex

Paolo Malatesta, Parma
Glial cells generate neurons: cellular and molecular mechanisms of neurogenesis

David McCormick, Boston
Rapid activation of recurrent cortical networks: a basic feature of cortical operation?

Thomas Misgeld, St. Louis
Imaging the dynamics of axon removal in development and disease

Hans-Werner Müller, Düsseldorf
Long-distance axon regeneration and functional improvement in spinal cord injury

Harald Neumann, Göttingen
Molecular mechanism of inflammatory axonal injury

Juha Partanen, Helsinki
Intercellular signalling at the boundary between developing mid- and hindbrain

Thomas Perlmann, Stockholm
Nuclear receptor signaling in dopamine neuron development and survival

Michael Sendtner, Würzburg
Role of B-raf and BAG-1 in neurotrophin signalling

Esther Shohami, Jerusalem
Targeting intracellular mechanisms: a new approach to treatment of traumatic brain injury

Christine Stichel-Gunkel, Bochum
M. Parkinson: on the way to a new therapy

Roger Traub, New York
Model of a thalamocortical column, exhibiting spindles, gamma oscillations, and a variety of seizure phenomenologies

Antoine Triller, Paris
Diffusion dynamics of the postsynaptic glycine receptor at a single molecule level

Klaus Willecke, Bonn
Expression and functions of connexins in mouse brain, including retina
IZN Seminar Series

Gabriel Wittum, Heidelberg
Reconstruction of neuron geometrics from 2-photon microscopy data

Heidelberg Neurobiology Lectures 2005

Nail Burnashev, Amsterdam
Inhibitory amino acid receptors in the CNS neurons as targets for direct action of cannabinoids

Johan Ericson, Stockholm
Application of developmental determinates to produce authentic midbrain dopamine neurons from stem cells

Bernd Fakler, Freiburg
Charakterisierung und physiologische Bedeutung der Multi-Proteinkomplexe von Kv1- und SK2-Typ Kaliumkanälen

Andreas Faissner, Bochum
Structure and functions of the microenvironment in neural stem cell development and neuron-glia interactions

Kurt Gottmann, Düsseldorf
Role of the synaptic adhesion molecule N-cadherin in presynaptic organization and function

Christian Hübner, Hamburg
Lessons from cation-chloride cotransporter knockout mice

Dimitri Kullmann, London
Synaptic plasticity in hippocampal interneurons: mechanisms and roles in circuit computations

Andreas Lüthi, Basel
Input-specific mechanisms of synaptic plasticity in the lateral amygdala

Marina Pizzi, Brescia
NF-kappaB factors in the control of neuronal cell death

Alain Prochiantz, Paris
Engrailed and Otx2 transcription factors as signaling molecules in axon guidance and synaptic plasticity

Gudrun Rappold, Heidelberg
MEGAP, mental retardation and the cellular basis of cognition

Gal Richter-Levin, Haifa
Stress and Amygdala modulation of memory-related processes in the hippocampus

Heidelberg Neurobiology Lectures 2006

Yves DeKoninck, Québec
Altered chloride homeostasis as a substrate of chronic pain

Michael Frotscher, Freiburg
Laminating the Hippocampus

Toshitaka Fujisawa, Mishima
Peptidomic approach to identify novel neuropeptides

Heiko Luhmann, Mainz
Oscillatory network activity in immature neocortical networks

Yoshiaki Kidokoro, Maebashi
Multiple types of Ca2+ channels involved in exocytosis and endocytosis at the Drosophila neuromuscular junction

Thomas Klausberger, Oxford
Network oscillations and GABAergic interneurons in the hippocampus

Claudio Rivera, Helsinki
There is more to KCC2 than chloride regulation

Björn Scheffler, Gainesville
Neural stem cells: “The good, the bad, and the ugly”

Philippe Vernier, Gif-sur-Yvette
Organization and differentiation of dopamine systems in protochordates and vertebrates: An evolutionary view

Manuela Zaccolo, Padova
Real-time imaging of cAMP: visualization of the spatial and temporal dynamics of intracellular signalling

Heidelberg Neurobiology Lectures 2007

George Augustine, Durham
Synaptic biophotonics: using optogenetic approaches to study brain circuitry

Clive Bramham, Bergen
BDNF and control of LTP consolidation in the intact brain

Emilio Carbone, Torino
Calcium channels in chromaffin cells: new role for T- and L-types

Giorgio Carmignoto, Padova
Astrocyte-neuron dialogue promotes neuronal synchrony

Thomas Deller, Frankfurt
Reshaping the nervous system - dendritic reorganization of dentate granule cells following denervation

Thomas Euler, Heidelberg
Dendritic processing in the retina
IZN Seminar Series

Christian Haass, München
The molecular clockwork of Alzheimer’s Disease

Helmut Kettenmann, Berlin
News from the glial world

Martin Korte, Braunschweig
The Yin and Yang of Neurotrophin receptor signalling in the process of synaptic plasticity: results and fairy tails

Georg Kuhn, Göteborg
Neurogenesis in the adult brain under pathological conditions

Martin Schmelz, Mannheim
C-nociceptors in chronic pain patients - translational studies

Heidelberg Neurobiology Lectures 2008

Laszlo Acsady, Budapest
A fresh view on the thalamus: excitatory and inhibitory control of higher order thalamic relays

Yves Barde, Basel
Using embryonic stem cells to study neural development

Dan Ehninger, Los Angeles
Mouse models of tuberous sclerosis: cognitive and behavioral aspects

Charles ffrench-Constant, Cambridge
Regulation of neural stem and precursor behaviour during development and repair by extracellular matrix

Christoph Kellendonk, New York
Modeling schizophrenia endophenotypes in mice

Andreas Püschel, Münster
How to make a neuron: signaling pathways directing axon formation

André Rupp, Heidelberg
Pitch-Perception: Psychoacoustics, modelling, and neuromagnetic representation in the auditory cortex

Paul Saftig, Kiel
Proteolytic systems and their functions in neurobiology: Lysosomes, autophagy and proteolysis at the plasmamembrane

Andreas Schäfer, Heidelberg
Mechanisms of odor discrimination in mice

Vincent Torre, Triest
Force generation in neurons: elementary events and computational properties

David L. Van Vactor, Boston
Signaling mechanisms that regulate synapse development in Drosophila

SFB 488 Seminars:
Progress in developmental neurosciences

SFB 488 Seminars 2003

Hilmar Bading
MAP kinase signaling in neuronal network plasticity

Dirk Feldmeyer
Structural and functional changes in the developing barrel cortex

Rainer Friedrich
Function and development of olfaction and mechanotransduction in zebrafish

Sheriar Hormuzdi
Neuronal intercellular channel-forming proteins: Molecular investigations, functional implications

Katrin Huber
The development of the sympathoadrenal cell lineage

Rohini Kuner
Expression and functional implications of plexin-family members in the developing nervous system

Bingyu Mao
Kremen2 modulates Dickkopf2 during Wnt/LRP6 signaling

Rosanna Parlato
Generation of CREB mutations in catecholaminergic neurons

Christoph Peter
Generation of a transgenic mouse model for the slow channel congenital myasthenic syndrome

Daniel J. Spergel
Glutamate receptors and the attainment of fertility

Stefan Titz
Does GABA promote the developmental switch of its own response?

Bill Wisden
Building GABAergic synapses

Jochen Wittbrodt
Control of proliferation and differentiation during early vertebrate eye development
IZN Seminar Series

SFB 488 Seminars 2004

Oliver Henschel
MuSK is required to maintain postsynaptic organisation at the neuromuscular junction

Thomas Holstein
Genetic regulation of neurogenesis in cnidarians

Emil Karaulanov
Transcriptional regulation of BMP4 synexpression in Xenopus in vitro, in vivo and in silico analyses

Rohini Kuner
Sema4D-Plexin-B signaling in the development of hippocampal and cortical neurons

Jun Li
Early functional development of chemotopy in the zebrafish olfactory system

Oliver Schlicker
GABAA-receptors in dendritic membrane traffic

Stefan Titz
Functional consequences of KCC2 overexpression in cultured hippocampal neurons

Kerry Tucker
Manipulating axonal outgrowth in mouse nervous system development

Tilmann Weber
Transgenic mouse models of serotonergic deficits in depression

Nina Wettschureck
Gq/G11-mediated signalling is required for endocannabinoid-mediated neuroprotection

Tim Wintermantel
Genetic dissection of estrogen receptor function in the nervous system

William Wisden
Targeting GABA-A receptors to synapses

Jochen Wittbrodt
The role of Rx3 in vertebrate optic vesicle evagination

Sheng-Jia Zhang
Transcriptional profiling of activity-dependent gene expression in cultured hippocampal neurons

SFB 488 Seminars 2005

Dirk Feldmeyer
Neuronal connectivity in the neocortex of reeler mice

Rainer Friedrich
Optical measurements of spatio-temporal activity patterns in the brain

Oliver Henschel
Synapse degradation and formation of new synapses upon conditional inactivation of MuSK

Katrin Huber
Role of the adrenal cortex in chromaffin cell development

Martin Kluska
Functional relevance of the GDP-GTP exchange factor collybistin interaction with the Map4-Kinase4 on the generation and morphology of inhibitory synapses

Rohini Kuner
Semaphorin4D-plexin-B1 modulate neuritogenesis and neuronal migration in the developing forebrain

Ulrich Misgeld
Development of inhibition in substantia nigra

Alexandra Moers
G12/G13 are critically involved in cerebellar development in mice

G. Elisabeth Pollerberg
MAP1B phosphorylation in navigating growth cones

Derya Shimshek
GnRH neuron specific gene manipulations

Kerry Tucker
Reverse & forward genetic analysis of peripheral nerve development

Robert Waltereit
Altered episodic-like memory and impaired synaptic plasticity in a rat model of Tuberous Sclerosis

Bill Wisden
K2P channels and neuronal cell excitability

Jochen Wittbrodt
Triggering neurogenesis in the retina

SFB 488 Seminars 2006

Peter Bengtson
Somatic and dendritic calcium signaling during LTP induction

Gary Davidson
New screen, new gene: identification of an LRP6/Arrow kinase

Volker Endris
Functional characterisation of the mental retardation associated GAP protein, MEGAP
David Engblom  
Analysis of drug addiction using mutations specific to cells of the dopamine system

Corina Guder  
An ancient Wnt-Dickkopf-antagonism in Hydra

Katrin Huber  
The development of the sympathoadrenal lineage

Rohini Kuner  
The role of Plexin-B1 and Semaphorin 4D in branching morphogenesis

Juan-Ramon Martinez-Morales  
The medaka mutation ojoplano disrupts a novel vertebrate gene with a fundamental role in tissue morphogenesis

Alexandra Moehrs  
G-protein mediated signalling in cortical development

Karsten Thelen  
Intracellular impact of cell adhesion molecule DM-GRASP on axon elongation and navigation

Kerry Tucker  
Control of cortico-striatal neurogenesis by histone deacetyl-transferases

SFB 488 Seminars 2007

Hilmar Bading  
A nuclear calcium-regulated genomic survival program

Volker Endris  
MEGAP constitutes a microtubule associated protein widely expressed in the developing nervous system

Roberto Fiore  
Function of a large microRNA cluster in activity-dependent neuronal development

Kristin Hartmann  
Plasticity of GABAergic synapses

Katrin Huber-Wittmer  
Development of the sympathoadrenal lineage

Rohini Kuner  
Role of neuronal plexin-B proteins in migration and pattern formation in vivo

Hai-Kun Liu  
The nuclear receptor tailless (tlx) is expressed in adult neural stem cells and required for their generation

SFB 488 Seminars 2008

Sidney Cambridge  
Doxycycline-dependent, photoactivated gene expression at cellular resolution in eukaryotic systems

Volker Endris  
The inhibitory effects of MEGAP on actin dynamics

Nadine Holter  
Inhibition in the developing dentate gyrus

Milen Kirilov  
Neuroendocrine regulation of reproduction: Role of the estrogen receptor and GPR54

Ulrich Misgeld  
Synaptic and non-synaptic inhibition in juvenile GABA neurons of substantia nigra

Marcel Souren  
Identification of upstream factors for the differentiation of retinal ganglion cells

Konstantin Khodosevich  
Major signaling pathways in migrating neuroblasts

Karsten Thelen  
Role of the 3’UTR of DM-GRASP for local protein translation

Klaus Unsicker  
Development and degeneration of extra-adrenal chromaffin cells: Mode of cell death

Thomas Worzfeld  
Analysis of plexin-B2 signalling in vivo
IZN Seminar Series

Graduate College 791
“Neural Development and Degenerative Processes: Basic Research and Clinical Implications”

2003

Dusan Bartsch
Learning, memory and gene expression

Francesca Ciccolini
Stem cells of the central nervous system

Thomas Euler / Group Winfried Denk
Signal processing in the mammalian retina

Marc Fatar / Group Michael Hennerici
Ultrasound treatment in animal stroke models

Dirk Feldmeyer
Neuronal networks in the neocortex – structural and functional properties

Rainer Friedrich
Synchronization of neuronal ensembles: mechanisms and functions

Tobias Hartmann
Alzheimer’s disease

Fritz A. Henn
Neurogenesis in affective disorders

Harald Hutter
Axon guidance signals: Molecules and mechanisms

Thomas Lemberger / Günther Schütz Group
Genetic dissection of the role of the CREB transcription factor in neuronal survival

Ulrich Misgeld
The developmental change of the GABA response from depolarizing to hyperpolarizing

Christof Niehrs
Mechanisms of antero-posterior axis formation

Stefan Offermanns
G-protein mediated signaling in the developing and adult nervous system

Andrei Rozov
Pre- and postsynaptic mechanism of facilitation

Markus Schwaninger
Acute neurodegeneration in cerebral ischemia

Peter Seeburg
Glutamate receptors in the developing brain

Klaus Unsicker
TGF-βs: Multifunctional growth factors with important roles in neural development and maintenance

Klaus Unsicker
Development of the nervous system and related malformations

William Wisden
Is neurotransmission important for the developing brain?

Veit Witzemann
Neurological diseases at the neuromuscular junction

Veit Witzemann
Formation of synapses at the neuromuscular junction – a change of the neurocentric view

Graduate College 791
2004

Dusan Bartsch
Learning to forget: memory extinction

Guest Speaker: Ralf Baumeister, Freiburg
C. elegans models for the functional analysis of human genes involved in neurodegenerative diseases

Stefan Berger / Group Günther Schütz
Analysis of mineralocorticoid and glucocorticoid receptor function in brain by gene targeting

Francesca Ciccolini
Development of mammalian interneurons

Dirk Feldmeyer
Methods to study neurotransmission

Rainer Friedrich
Topographic maps in the nervous system

Tobias Hartmann
Cellbiological basis for Alzheimer’s disease

Harald Hutter
Transcriptional networks controlling neuronal differentiation

Guest Speaker: Dietmar Kuhl /Molecular Neurobiology, Berlin
Learning about activity dependent genes

Bernd Kuhn /Group Winfried Denk / MPI
Voltage-sensitive dyes: Basic principles and applications
Ulrich Misgeld  
Monitoring KCC2 function during the developmental switch of the GABA response

Hannah Monyer  
Control of development by RNA processing

Guest Speaker: Zoltan Nusser, Budapest  
Short-term plasticity of excitatory and inhibitory synapses

Stefan Offermanns  
Functions and mechanisms of plexin-mediated signalling in the nervous system

G. Elisabeth Pollerberg  
Studies in the avian embryo visual system

Andrei Rozov  
Voltage and ligand gated ion channels

Markus Schwaninger  
Mechanisms of neuronal apoptosis

Peter Seeburg  
Long term potentiation

Guest Speaker: Traub Roger, New York  
Evidence for electrical coupling between the axons of pyramidal neurons, and the role of such coupling in generating oscillations

William Wisden  
New techniques to regulate neuronal activity

G. Elisabeth Pollerberg  
The tip of the axon: Molecules on and in the growth cone

Gudrun Rappold  
Genetic etiology of mental retardation

Andrei Rozov  
Metabotropic receptors and synaptic plasticity

Günther Schütz  
Analysis of nuclear receptor function by gene targeting

Markus Schwaninger  
Clinical problems in basic stroke research

Klaus Unsicker  
The TGF-ß superfamily of growth factors and their roles in the nervous system

William Wisden  
Silencing neurons in development

Veit Witzemann  
The value of toxins in science and medicine

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Graduate College 791 2005

Dusan Bartsch  
Epigenetic regulation of gene expression in the brain

Francesca Ciccolini  
Clinical implication of neural stem cell research

Andreas Draguhn  
High-frequency network oscillations: cellular neuroscience with some cognitive “meaning”?

Guest Speaker: Wolfgang Driever, Freiburg  
Developmental neurogenetics in zebrafish: Cell specification in the dopaminergic and noradrenergic systems

Rainer Friedrich  
Calcium imaging in the brain

Tobias Hartmann  
Neurons, lipids and neurodegeneration

Fritz A. Henn  
The pathophysiology of depression

Fritz A. Henn  
Use and misuse of animal models of brain diseases

Harald Hutter  
The importance of pioneer axons for neuronal circuit formation

Rohini Kuner  
Basic mechanisms in physiological and pathological pain

Ulrich Misgeld  
Can we still learn from (substantia nigra) slices?

Christof Niehrs  
Regulation of antero-posterior neural patterning during early Xenopus development

G. Elisabeth Pollerberg  
Calcium imaging in the brain

Tobias Hartmann  
Neurons, lipids and neurodegeneration

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The tip of the axon: Molecules on and in the growth cone

Andreas Draguhn  
Animal models in psychiatric research

Rainer Friedrich  
Epigenetic regulation of gene expression in the brain

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Graduate College 791 2006

Hilmar Bading  
Calcium signaling in the cell nucleus

Dusan Bartsch  
Animal models in psychiatric research

Dusan Bartsch  
Epigenetic regulation of gene expression in the brain
IZN Seminar Series

Francesca Ciccolini
Effect of neurotransmitter on neural precursor differentiation and proliferation

Gary Davidson / Christof Niehrs group
Mechanisms and regulation of cell movement

Andreas Draguhn
Plasticity of GABAergic synapses - role of transmitter concentration

Rainer Friedrich
Genetic tools for probing and manipulating the function of neuronal circuits

Peter Gass
Genetically induced mouse models of stress-sensitivity and stress-resistance

Ulrich Misgeld
Electrophysiological studies on substantia nigra neurons in slices

Hannah Monyer
GABAergic interneurone diversity in the CNS

Ulrike Müller
Functions of the Amyloid precursor protein gene family

Stefan Offermanns
G-protein mediated signalling in the nervous system

G. Elisabeth Pollerberg
The secret (intracellular) life of cell adhesion molecules: A glance behind the curtain

Gudrun Rappold
Mental retardation

Andrei Rozov
Release probability versus response probability - two dimensions of short-term synaptic plasticity

Günther Schütz
Genetic analysis of steroid hormone receptor function

Peter Seeburg
Excitatory neurotransmission

Markus Schwaninger
Signaling through the transcription factor NF-kappaB

Klaus Unsicker
Transforming growth factor-beta: multifunctional and synergistic signaling in the nervous system

Veit Witzemann
Signals from nerve and muscle that regulate the development of neuromuscular junctions

Graduate College 791

Hilmar Bading
Nuclear calcium signaling and activity-regulated adaptive responses in the nervous system

Dusan Bartsch
Memory extinction

Andreas Draguhn
Analysis of neuronal networks

Andreas Draguhn
Mechanisms and meaning of high-frequency network oscillations

Guest Speaker: Julietta Uta Frey
Cellular memory consolidation: associative requirements

Peter Gass
Neurobiological concepts of depressive disorders

Guest Speaker: Martin Korte
Learning and memory: What’s LTP got to do with it?

Guest Speaker: Martin Korte
The Ying and Yang of Neurotrophin receptor signalling in the process of synaptic plasticity: results and fairy tails

Ulrich Misgeld
SK channels control the excitability of juvenile GABA output neurons in substantia nigra slices

Ulrich Misgeld
Synaptic inhibition in substantia nigra

Hannah Monyer
Development of GABAergic interneurones

Guest Speaker: Klaus Nave
Molecular mechanism of axon-glia interactions and myelin disease

Guest Speaker: Klaus Nave
Mouse models of neurological diseases

Christof Niehrs
Early embryonic neural patterning in Xenopus

Stefan Offermanns
Mechanisms and roles of semaphorin/plexin signaling in the nervous system

G. Elisabeth Pollerberg
Inside axons: The role of the cytoskeleton

Gudrun Rappold
New insights into neurological disorders
Günther Schütz
The role of the nuclear receptor tailless in neurogenesis and brain tumor formation

Markus Schwaninger
Anoxic tolerance in turtles and other vertebrates. What can we learn for neurological diseases?

Markus Schwaninger
Mechanisms of brain damage and repair in cerebral ischemia

Peter Seeburg
Excitatory neurotransmission

Klaus Unsicker
Specification of neuronal and endocrine derivatives of the neural crest

Veit Witzemann
Synaptic plasticity at neuromuscular junctions

Graduate College 791 2008

Hilmar Bading
Nuclear calcium signaling in learning and survival

Dusan Bartsch
Voltage gated calcium channels in normal and pathologic brain function

Francesca Ciccolini
Characterization of SVZ neural stem cells

Andreas Draguhn
Different recording methods and typical data in cellular electrophysiology

Jakob von Engelhardt / Hannah Monyer group
Synaptic plasticity

Peter Gass
Translational models in psychiatry

Guest Speaker: Helmut Kettenmann, Berlin
“Concepts in neuroscience” lessons from history

Guest Speaker: Edvard Moser, Trondheim, Norway
Grid cells and spatial representation in entorhinalhippocampal neural networks

Ulrike Müller
Mouse models of neurodegenerative diseases

Christof Niehrs
Molecular mechanisms of early antero-posterior patterning

G. Elisabeth Pollerberg
Signalling inside and outside of growth cones

Gudrun Rappold
New insights into mental retardation

Günther Schütz
Estrogen receptor function in neuroendocrine regulation of reproduction

Markus Schwaninger
NF-κB signaling in health and disease

Peter Seeburg
Molecular determinants of fast synaptic neurotransmission

Klaus Unsicker
GDF-15, a novel TGFβ with functions in postnatal neuron survival and myelination

Klaus Unsicker
Recent progress in understanding neural functions of GDF-15

Veit Witzemann
Receptor subunit switches are universal components of synapse development

Seminars of the DFG ’Forschergruppe’ FOR 302/2-1

2003 - 2006

Andrzej Pilc, Beata Legutko, Krakow
Glutamate and depression

Dr. Madalina Stanciu, Pittsburgh
Mitogen-activated protein-kinases (MAPK) signaling in neuronal death

Neurobiology Seminars

2003-2005

Nikolaus J. Sucher, Hongkong University of Science and Technology
The NMDA receptor complex: A target for traditional chinese medicine

Valentin Stein, UC San Francisco
Cellular and molecular aspects of synaptic plasticity: PSD-95 mimics LTP

Dmitri Tkachev, The Babraham Institute, Cambridge, U.K.
Expression profiling in Schizophrenia: An integrative complementary approach
Kelly Rogers, Institut Louis Pasteur, Paris
Visualisation of local Ca2+ dynamics with genetically encoded bioluminescent reporters

Eckehard Freitag, Universität Leipzig
Laser-mediated analysis of cellular events - Netrin-1 overexpression studies on neural cells

Seminars Clinical Neurobiology

2003-2005

Rossella Conti, Laboratoire de Physiologie Cérébrale, Université de Paris, France
Two-photon imaging of Action Potential and ryanodine evoked Ca2+ transients in synaptic terminals of cerebellar interneurons

Sebastian Jungnickel, Howard Florey Institute for Experimental Physiology and Medicine, Melbourne, Australia
Role of neuropeptides in the motor/sensory function of the inferior olive-cerebellum: Galanin systems in the mouse

Elisabeth Foeller, Zoologisches Institut, Uni Frankfurt
A possible role of inhibition in whisker map plasticity in rat somatosensory cortex

Gernot Riedel, University of Aberdeen
Involvement of dentate gyrus in memory formation in mice

Tatiana Korotkova, Institut für Neurophysiologie, Universität Düsseldorf
Hypothalamic modulation of the midbrain dopaminergic system

Alexei Ponomarenko, Institut für Neurophysiologie, Universität Düsseldorf
The why, where and how of hippocampal ripple oscillations

Nail Burnashev, Dept. of Experimental Neurophysiology, Frije Universiteit Amsterdam
Smart mouse: NR2B or not NR2B?

Dr. K. V. Raghavan, National Centre for Biological Sciences, Bangalore, India
Muscle identity, fibre number, and the development of movement in Drosophila

Michael Reid, Rutgers University, New York
Spiral ganglion neurons; not so simple after all

Olivia Dumitrescu, MPI f. Hirnforschung, Frankfurt
Glutamate receptors of amacrine cells in the mouse retina

Hans-Rudolf Brenner, Biozentrum Basel
Neural control of synapse-specific gene expression at the neuromuscular junction

Roger Traub, Dept. of Physiology, Pharmacology and Neurology, State University New York/USA
Evidence for electrical coupling between the axons of pyramidal neurons, and the role of such coupling in generating oscillations

Samuel Lagier, Institut Pasteur, Paris
Gamma oscillations in the rodent olfactory bulb: generation mechanisms and function

Wolfgang Driever, University of Freiburg
Developmental neurogenetics in zebrafish: Cell specification in the dopaminergic and noradrenergic systems

Tatsuhiro Hisatsune, Dept. Integrated Biosciences, University of Tokyo
Theta oscillations activate adult hippocampal stem cells
IZN Retreat SFB 488 FOR 302 Symposium Kloster Schöntal, June 25-26, 2003

“Development & Circuit Formation”

Session 1:
Chair: Klaus Unsicker

Laure Bally-Cuif, Neuherberg
Dynamics of neurogenesis at the zebrafish midbrain-hindbrain boundary

Claudio Stern, London
Molecular dissection of neural induction in the chick embryo

Rüdiger Klein, Munich
Role of ephrins in neuronal networking and plasticity

Session 2:
Chair: Andreas Draguhn

Eric Frank, Boston
The beginning of a molecular basis for the formation of the simple stretch reflex

Javier de Felipe, Madrid
Cortical interneurons: From Cajal to 2003

Session 3:
Chair: Andreas Draguhn

Manfred Heckmann, Freiburg
Electrical events and exocytosis in mossy fiber

Henry Markram, Lausanne
Molecular basis of electrophysiological diversity

Session 4:
Chair: Hilmar Bading

Stephen P. Hunt, London
Substance P in depression and addiction

Christian Büchel, Hamburg
The importance of connectivity for brain function

Session 5:
Chair: Hannah Monyer

Herta Flor, Mannheim
Learning, neuroplasticity and psychopathology

IZN Retreat Kloster Schöntal, June 1-3, 2004

Introduction: Klaus Unsicker

Session 1:
Chair: Hannah Monyer

Erwin Neher
Modulation of short-term synaptic plasticity

Yehezkel Ben-Ari
GABA: a pioneer transmitter

Session 2:
Chair: Hilmar Bading

Andrew Lumsden
Forebrain patterning – a new perspective

Diethelm Richter
Serotonin receptors: guardians of stable breathing

Session 3:
Chair: Kerry Tucker

Mart Saarma
Structure and biology of GDNF family neurotrophic factor receptors

Carlos Ibanez
Trophic signaling in the nervous system

Christopher Henderson
Coordinated development of individual motor units

Session 3:
Chair: Andreas Draguhn

Round table:
Goals and strategies of European Neuroscience Centers
Thursday, June 3

Session 5:
Chair: Joachim Kirsch

Anders Björklund
Induction of Parkinson-like neurodegeneration by overexpression of human alpha-synuclein in the nigrostriatal system
Symposia

Nils Brose
Short term synaptic plasticity: Molecules and mechanisms

Session 6:
Chair: Ulrich Misgeld

Olaf Pongs
On the episodic nature of channelopathies

Kai Kaila
GABA: an exciting inhibitory transmitter

Session 7:
Chair: Christoph Schuster

Thomas Gasser
Genetics of PD: Monogenic forms as models for the disease

Lars Olson
Genetic risk factors in Parkinson’s disease

SFB 488 Symposium / IZN Retreat
Kloster Schöntal, June 15-17, 2005
“Neural Development:
From Patterning to Network Formation”

Session 1:
Chair: H. Bading

Yoshiki Sasai
Molecular and cellular control of regional specification in the nervous system

Wieland Huttner
Cell biology of neurogenesis

Session 2:
Chair: K. Tucker

Guo-Ping Fan
Epi genetic gene regulation in neural development

Patrizia Casaccia-Bonnefil
Histone deacetylases in oligodendrocyte development

Session 3:
Chair: A. Draguhn

Wolfgang Wurst
Dissection of the genetic pathway controlling midbrain dopaminergic neuron induction and differentiation

Susan Ackerman
Genetic control of cerebellar development

Session 4:
Chair: G. E. Pollerberg

Mary Hatten
New directions in CNS migration

Elke Stein
Molecular mechanism of axon guidance in the developing vertebrate CNS

Esther Stoeckli
New tricks for an old dog: Sonic hedgehog is a guidance cue for postcommissural axons

Session 5:
Chair: H. Simon

Liliana Minichiello
TrkB regulates neocortex formation through the Shc/PLCg-mediated control of neuronal migration

Dennis O’Leary
Genetic specification of cortical areas and implications for behaviour

Session 6:
Chair: K. Unsicker

Tom Curran
The Shh pathway and pediatric brain tumors

Hermann Rohrer
Specification and differentiation of autonomic neurons

Session 7:
Chair: C. Schuster

Patrik Ernfors
The transcriptional control of nociceptive neuron subtype specification

Frances Lefcort
Imaging formation of the DRG and sympathetic ganglia
Symposia

Session 8:
Chair: U. Misgeld

Qiufu Ma
Molecular control of nociceptive/pain sensory neuron development

SFB 488 / FOR 302 Symposium / IZN Retreat
Kloster Schöntal, July 2-4, 2006

‘Development of Transmitter Systems’

Session 1:
Chair: H. Bading

Susanne Schoch, Bonn
Genetic ablation of alpha-RIMs: effect on synaptic functions

Jens Rettig, Homburg
The role of CAPS1 in LDCV secretion from adrenal chromaffin cells

Session 2:
Chair: K. Tucker

Nicholas Spitzer, La Jolla
Activity-dependent transmitter specification and receptor matching

Session 3:
Chair: G.E. Pollerberg

Tania Vitalis, Paris
Origin and fate determination of a subpopulation of telencephalic interneurons

Stewart Anderson, New York
Specification of cortical interneurons

Session 4:
Chair: A. Draguhn

Claudio Rivera, Helsinki
Role of the neuron specific K-Cl cotransporter KCC2 in synaptic transmission during development and trauma

Derek Sieburth, Boston
Systematic analysis of neurotransmission in C. elegans

Session 5:
Chair: U. Misgeld

Alexander Dityatev, Hamburg
Recognition and neurotransmission: impact of recognition molecules on development of glutamatergic and GABAergic systems in the hippocampus

Session 6:
Chair: H. Monyer

Josef Bischofberger, Freiburg
Associative synaptic plasticity in mature and newly generated hippocampal granule cells

Hans Van Hooft, Amsterdam
Serotonergic control of postnatal cortical development by 5-HT3 receptor

Session 7:
Chair: K. Unsicker

Chris Deppmann, Baltimore
Neurotrophin Signaling and the Development of the Sympathetic Nervous System

Marten Smidt, Utrecht
Development and subset specification of the mesodiencephalic dopaminergic system

Session 8:
Chair: C. Schuster

Roland Friedel, Munich
Role of Plexins and Semaphorins in cerebellar development

Amir Dori, Tel-Aviv
Acetylcholinesterase splice variants influence murine neocortical development through catalytic and non-catalytic mechanisms
IZN/SFB 488 Retreat
Kloster Schöntal, July 8-9, 2007
“Neuronal Networks: from Cell Biology to Cognition?”

Opening Lecture:
Stephan Frings
Olfactory receptor neurons - feeding a sensory network

Highlight Lecture:
Thomas Söllner
Molecular machinery involved in regulated exocytosis

Session 1:
Chair: K. Unsicker
Rohini Kuner
The cannabinoid system and pain: novel insights via molecular and genetic approaches
Ulrike Müller
The APP gene family: genetic models to dissect functional domains

Session 2:
Chair: C. Schuster
Hartwig Spors
Spatio-temporal patterns in the mammalian brain - in vivo imaging with voltage sensitive and calcium sensitive dyes
Christian Fiebach
Neural networks of verbal working memory: FMRI studies

Session 3:
Chair: S. Frings
Detlev Arendt
Evolution of the telencephalon: associative brain centres in a marine annelid, Platynereis dumerilii
Rainer Spanagel
Clock genes and their role in psychopathology
Thomas Kuner
Synaptic inhibition accelerates odor discrimination in mice

IZN/SFB 488 Retreat
Kloster Schöntal, July 20-21, 2008
“Technologies for the Neurosciences”

Session 1:
Chair: J. Wittbrodt
Johann Engelhardt, DKFZ
High resolution fluorescence microscopy beyond the diffraction limit
Ernst Stelzer, EMBL
Light sheet based fluorescence microscopes (LSFM, SPIM, DSLM) reduce phototoxic effects by several orders of magnitude

Special Lecture:
Chair: H. Bading
Angela Stevens, Applied Mathematics, Uni HD
Mathematical modeling and analysis in the life-sciences: Examples and perspectives

Session 2:
Chair: G. Schratt
Holger Erfle, EMBL/BioQuant
RNAi screening by automated microscopy
Joe Lewis, EMBL
The Chemical Biology Core Facility: finding needles in haystacks

Session 3:
Chair: A. Draguhn
Moritz Helmstädt, MPIMF
Reconstructing neural circuits using serial blockface Scanning Electron Microscopy and machine learning
Dirk-Peter Herten, BioQuant
Single-molecule spectroscopy in living cells

Session 4:
Chair: G. Köhr
Ulrich Schwarz, BIOMS
Modelling the stochastic dynamics of adhesion sites
Fred Hamprecht, IWR
Pattern recognition and image processing
SFB488 Symposium
Heidelberg, October 14-16, 2004

“Developmental Neurobiology: From Molecules to Neural Systems”

Session 1: Mechanisms of Neural Crest Development
Chair: Klaus Unsicker

Nicole Le Doarin
The neural crest in the development of the vertebrate head

Marianne Bronner-Fraser
Hierarchy of regulatory events in neural crest formation

Session 2: Wnt Signaling and Neural Crest Development
Chair: Jochen Wittbrodt

Chaya Kalcheim
Regulation of neural crest delamination by BMP-dependent Wnt signalling

Andy McMahon
Ligand export and feedback control in HH-mediated patterning of the mammalian neural tube

Lukas Sommer
Wnt signalling in early neural crest stem cells

Session 3: Neuronal Stem Cells
Chair: Hilmar Bading

Miriam Bibel
Differentiation of mouse embryonic stem cells in Drosophila

Magdalena Götz
Neurogenesis from glial cells: Pax6 as a master regulator?

Session 4: Neuron Survival and Shape
Chair: Joachim Kirsch

Christopher Cowan
Ephs and GEFs: Coupling receptor activation to endocytosis, axon guidance and synapse formation

Alex Kolodkin
Molecular mechanisms of neuronal growth cone guidance

Liqun Luo
Exploring neural circuits using genetic mosaic methods in flies and mice

Matthias Landgraf
Patterning of dendrites in the Drosophila CNS

Session 5: Synapse Formation
Chair: Andreas Draguhn

Peter Scheiffele
Control of CNS synapse formation by the Neuroligin-Neurexin adhesion system

Eckart Gundelfinger
Assembly and molecular organization of the active zone of neurotransmitter release

Pico Caroni
Mechanisms controlling synapse maintenance and remodelling in young adults

Patricia Salinas
Regulation of neuronal connectivity: a role for Wnt signalling

Session 6: Development of Neural Systems
Chair: Ulrich Misgeld

Peter Mombaerts
Olfaction targeted

Wenbiao Gan
Synaptic plasticity and pathology in vivo

Miles Whittington
The rise and fall of gamma rhythms: Oscillations in the developing and ageing brain

SFB 488 Symposium
Heidelberg, September 20-23, 2007

“TGF-βs: Signaling and Roles in Neural Development, Maintenance, and Disease”

Session 1:
Chair: Klaus Unsicker

Michael B. Sporn, Hanover
New triterpenoid drugs that enhance TGF-beta signaling and are neuroprotective
Symposia

Rik Derynck, San Francisco
  Non-Smad signaling pathways complement Smad-mediated signaling by TGF-β

Session 2:
  Chair: Michael B. Sporn

Carl-Henrik Heldin, Uppsala
  Signaling via the TGF-beta receptors: possible targets in tumor treatment

Peter ten Dijke, Leiden
  TGF-β signaling in vascular development and diseases

Session 3:
  Chair: Jochen Wittbrodt

Christof Niehrs, Heidelberg
  Regulation of BMP signalling

Edward de Robertis, Los Angeles
  A self-regulating system of TGFβ/BMP cell-cell signaling that integrates embryonic patterning

Session 4:
  Chair: Christof Niehrs

Petra Knaus, Berlin
  Regulation of BMP signaling by receptor endocytosis and receptor associated proteins

Joachim Wittbrodt, Heidelberg
  Factors and signals in eye development and morphogenesis

Chaya Kalcheim, Jerusalem
  A BMP-dependent molecular cascade that generates neural crest cell migration

Session 5:
  Chair: Chaya Kalcheim

Lukas Sommer, Zürich
  TGFbeta signaling regulating proliferation and fate decisions in neural stem cells

Danny Huylebroeck, Leuven
  Sip1/Zfhx1b in CNS and PNS development and Mowat-Wilson syndrome

Suzana Atanasoski, Basel
  The role of Ski in neural development

Session 6:
  Chair: Mart Saarma

Kristján R. Jessen, London
  The role of TGF beta in perinatal nerves

Vassilis Pachnis, London
  The Ret signaling pathway and its role in enteric nervous system development

Session 7:
  Chair: Kerstin Krieglstein

Thomas Holstein, Heidelberg
  BMP/Chordin signaling and Cnidarian neurogenesis

Mart Saarma, Helsinki
  GDNF interactions with old and new receptors

Session 8:
  Chair: Tony Wyss-Coray

Carlos Ibanez, Stockholm
  TGFB superfamily signaling in the nervous system

Kerstin Krieglstein, Göttingen
  Role of TGF-β in nervous system development

Stuart E. Dryer, Houston
  TGF-β signaling and the regulation of ion channel trafficking in developing neurons

Session 9:
  Chair: Michael Sendtner

Brian McCabe, New York
  Neuronal activity and retrograde BMP signaling at the synapse

Michael B. O’Connor, Minneapolis
  Role of BMP signaling in hippocampal mediated learning and memory in the mouse

Tony Wyss-Coray, Stanford
  Genetic mouse models for the study of TGF-beta signaling in the brain

Session 10:
  Chair: Thomas Holstein

Adriano Fontana, Zürich
  On the role of TGFbeta in infectious and autoimmune diseases of the nervous system
Ludwig Aigner, Regensburg
Regulation of neurogenesis in the healthy and diseased brain: a potential role of TGF-beta1

Session 11:
Chair: Adriano Fontana

Michael Weller, Tübingen
TGF-ß: a key mediator of the malignant phenotype of glioblastoma

Ulrich Bogdahn, Regensburg
TGF-ß based therapy of malignant glioma (from bench to bedside)

Patrick Mehlen, Lyon
The dependence Receptor notion: when apoptosis controls nervous system development and tumorigenesis

Session 12:
Chair: Ulrich Bogdahn

Michael Sendtner, Würzburg
Mouse models of motoneuron disease

Klaus Unsicker, Heidelberg
Functions of GDF-15 in the nervous system

SFB 488 “Christmas Symposia“ 2003

Session 1:
Chair: Klaus Unsicker

Christof Niehrs
The transmembrane protein FLRT3 is a novel regulator of FGF signalling

Jochen Wittbrodt
Control of proliferation and differentiation in the developing retina

Uwe Strähle
Regulation of the neural determination gene neurogenin1 in the zebrafish CNS

Andreas Draguhn
Function and plasticity of synaptic inhibition – the role of GABA-synthesis and GABA-uptake

Session 2:
Chair: Peter Seeburg

Joachim Kirsch
Targeting inhibitory synapses: How neurotransmitter receptors find their ways

William Wisden
GABA-A receptors in brain development

Dirk Feldmeyer
Early postnatal development in the Barrel Cortex

Session 3:
Chair: Hannah Monyer

Stefan Offermanns
Gq/11 and G12/13 functions in the nervous system

Rohini Kuner
Expression and functions of plexin- B family members in the developing rodent nervous system

Dusan Barsch
Conditional regulation of minibrain kinase expression

Peter Seeburg
Behavioural consequences in mice from GnRH promoter-directed changes in AMPA receptors

SFB 488 “Christmas Symposia“ 2004

Session 1:
Chair: Peter Seeburg

Christof Niehrs
Large scale microarray analysis provides a panoramic view of embryonic gene expression

Klaus Unsicker
The sympathoadrenal cell lineage: adrenal cortex is not required for chromaffin cell specification

Hans-Hermann Gerdes
Tunneling nanotubes: a new principle of intercellular communication for neuronal cells?

G. Elisabeth Pollerberg
Cell adhesion molecule DM-GRASP: Glue or cue?
Symposia

Session 2:
Chair: Andreas Draguhn

Ulrich Misgeld
Modulation of inhibition in substantia nigra by retrograde signals

Hannah Monyer
GAP junctions and their role in network synchrony

Veit Witzemann
Control of synapse formation in muscle

Session 3:
Chair: Klaus Unsicker

Günther Schütz
Analysis of glucocorticoid and mineralocorticoid receptor function by gene targeting

Hilmar Bading
Nuclear calcium signalling in plasticity and neuronal survival

Andreas Draguhn
GABA-metabolism and the plasticity of GABAergic synapses

Peter Seeburg
Tet-regulated Cre in hypothalamic GnRH neurons of the mouse

SFB 488 “Christmas Symposia“ 2005

Session 1:
Chair: Hilmar Bading

Gerhard Schratt
MicroRNAs in synapse development

Veit Witzemann
Formation of neuromuscular junctions: neurocentric versus myogenic view

Rainer Friedrich
Function and development of neuronal circuits in the zebrafish olfactory bulb

Peter Seeburg
Gene regulation in defined hypothalamic cell populations

Session 2:
Chair: Stefan Offermanns

Hannah Monyer
Neurogenesis of distinct GABAergic interneurons in the postnatal brain

Ulrich Misgeld
GABAergic control of retrograde signaling in substantia nigra

Session 3:
Chair: Klaus Unsicker

Thomas Holstein
Wnt-signalling and cnidarian neurogenesis

Christof Niehrs
The role of Kremen in Wnt modulation during neural crest specification

Rohini Kuner
Plexin-B2 modulates neural patterning in vivo

SFB 488 “Christmas Symposia“ 2006

Session 1:
Chair: Hilmar Bading

Gerhard Schratt
MicroRNAs in synapse development

Veit Witzemann
Formation of neuromuscular junctions: neurocentric versus myogenic view

Rainer Friedrich
Function and development of neuronal circuits in the zebrafish olfactory bulb

Peter Seeburg
Gene regulation in defined hypothalamic cell populations

Session 2:
Chair: Stefan Offermanns

Hannah Monyer
Neurogenesis of distinct GABAergic interneurons in the postnatal brain

Ulrich Misgeld
GABAergic control of retrograde signaling in substantia nigra
Joachim Kirsch  
Map4K4 – a novel regulator of glycine receptor clustering?

Session 3:  
Chair: Klaus Unsicker

Thomas Holstein  
Wnt-signalling and cnidarian neurogenesis

Christoph Niehrs  
The role of Kremen in Wnt modulation during neural crest specification

Rohini Kuner  
Plexin-B2 modulates neural patterning in vivo

SFB 488 “Christmas Symposia“ 2007

Session 1:  
Chair: Jochen Wittbrodt

Christof Niehrs  
DNA demethylation, DNA repair and pluripotency

Thomas Holstein  
Structure and function of an unusual neuronal cell type

Christoph Schuster  
Flies and Psychiatry?

Session 2:  
Chair: Klaus Unsicker

Thorsten Bus  
GnRH neuron specific gene manipulation

Joachim Kirsch  
Glycine receptors in spinal cord development

Andreas Draguhn  
Assembly formation and memory consolidation in the hippocampus

SFB 488 “Christmas Symposia“ 2008

Session 1:  
Chair: Jochen Wittbrodt

Thomas Holstein  
Comparative genomics and the origin of the nervous system

Detlev Arendt  
Evolution of the central nervous system in animals

Darren Gilmour  
Coordinating cell movement and shape within neurogenic placodes

Session 2:  
Chair: Stefan Offermanns

Rohini Kuner  
Role of Plexin-B proteins in laminar development of the cortex and spinal cord

Veit Witzemann  
AChR-mediated activity determines positioning of synapses and nerve growth

Ingrid Lohmann  
Transcriptional control of morphogenesis by Hox proteins

Laurence Ettwiller  
Highly conserved non-coding DNA elements in fish reveal enhancer function in neuronal structures

Session 3:  
Chair: Andreas Draguhn

Peter Seeburg  
Genetic manipulation of hypothalamic functions

Thomas Dresbach (Kirsch group)  
Role of Neuroligins in presynaptic maturation

Christoph Schuster  
Myosin-VIIa is required to maintain postsynaptic glutamate receptor function

“Recent advances and perspectives in developmental biology”  
Heidelberg, October 24-28, 2007

A trilateral meeting organized by the Hebrew University, Jerusalem, and its partners, the Universities of Göttingen and Heidelberg

Keynote Lecture  
Chair: Klaus Unsicker

Chaya Kalcheim  
Lineage segregation in the somitic mesoderm
Session 2: Stem cells, neurogenesis
Chair: Chaya Kalcheim

Andreas Wodarz
Molecular control of cell polarity and asymmetric cell division in Drosophila

Victor Tarabykin
Transcriptional control of cerebral cortex development

Session 3: Gastrulation and signalling pathways
Chair: Kerry Tucker

Zeev Paroush
Groucho-mediated transcriptional repression in Drosophila development

Christof Niehrs
New aspects of neural crest development

Session 4: Cell migration, Axon guidance I
Chair: Zeev Paroush

Joel Yisraeli
The role of VICKZ proteins in cell migration and metastasis

Kerry Tucker
ENU screen for axonal pathfinding errors

Avihu Klar
Molecular mechanisms for increasing complexity of axonal guidance cues

Session 5: Axon guidance II, Synaptogenesis
Chair: Avihu Klar

Gudrun Rappold
Cell motility and mental retardation

Achim Kirsch
Glycine receptor development

Session 6: Neuron survival and death I
Chair: Kerstin Krieglstein

Oded Behar
Semaphorins and neurotrophins in axon guidance and cell death

Session 6: Neuron survival and death II
Chair: Kerstin Krieglstein

Offer Gerlitz
S149 is a new Dpp target gene that acts as a co-repressor with Brinker to promote cell death

Francesca Ciccolini
Regulation of stem cell proliferation in the postnatal subventricular zone

Session 7: Neuron survival and death II
Chair: Jochen Wittbrodt

Günther Schütz
Regulation of dopaminergic neuron survival

Kerstin Krieglstein
In vivo cooperativity of GDNF and TGFβ in the regulation of neuron survival

Session 8: Development of epi- and endodermal derivatives
Chair: Christof Niehrs

Uri Gat
The Runx family: from hair development in mice to the sea-anemone Nematostella

Tomas Pieler
Pancreas development in Xenopus laevis

Annette Borchers
The function of PTK7 in neural crest migration

Thomas Holstein
Patterning of an ancient nervous system

Session 9:
..and back to very early phylogensis and ontogenesis.
Chair: Klaus Unsicker

Herbert Steinbeisser
Gastrulation in Xenopus

Jochen Wittbrodt
Morphogenesis of the optic cup
Joint Symposium on Neurocomputing  
June 16-17, 2003

Center for Molecular Biology, ZMBH

Scientific Session I: New Microscopy Methods  
Chair: K. Unsicker

Jörg Langowski  
Fluorescence fluctuation microscopy as a tool for understanding molecular motion in cells

Christoph Cremer  
New microscopy methods to study cell nuclear structure and its relation to gene regulation

Winfried Denk  
Direction selectivity in the retina

Scientific Session II: Modeling  
Chair: A. Lewis

Tali Tishby  
Quantitative principles of biological information processing

Idan Segev  
Cooperative synaptic plasticity in cortical dendrites

Rainer Dalhaus  
On the identification of synaptic connections in neural networks by graphical models

Andre Rupp  
Cortical processing of auditory information

Israel Nelken  
Transformations of stimulus representation in the ascending auditory system

Scientific Session III: Cortical Dynamics  
Chair: I. Segev

Aaron Lewis  
Functional imaging of neurons and neural networks

Michael Brecht  
Sensorimotor representations and their cellular codes in the rat neocortex

Rony Paz (Lab E. Vaadia)  
Improvement of movements representation in the motor cortex of a monkey during learning

Yosef Yarom  
Oscillating without gap junctions

David Hanse  
Electrical synapses and synchrony: The role of intrinsic currents

Hannah Monyer  
The oscillating brain approached by mouse mutants

1. Bioquant Symposium  
December 9, 2004

Opening Remarks: The Bioquant concept  
Jochen Tröger, Willi Jäger, Bernd Bukau, Angret Joester

Session 1: Modeling in the life sciences  
Chair: Roland Eils

Joachim Spatz, MPI für Metallforschung - Stuttgart und Biophysikalische Chemie, Universität Heidelberg  
Models for studying chemomechanical coupling in cell adhesion and development

Matthias Weiß, MEMPHYS - Center for biomembrane physics, Odense, Denmark und BIOMS, Heidelberg  
Structure formation of active biomembranes

Ulrich Schwarz, MPI für Kolloid- und Grenzflächenforschung, Potsdam und BIOMS, Heidelberg  
Towards a quantitative understanding of cell adhesion

Gabriel Wittum, Interdisziplinäres Zentrum für Wissenschaftliches Rechnen, Heidelberg  
Towards Simulation of Neuronal Signal Processing

Session 2: Technologies for systems biology  
Chair: Christoph Cremer

Irmgard Sinning, Biochemiezentrum, Heidelberg  
Quantitative analysis of SRP receptor-membrane interaction

Stefan Hell, MPI für biophysikalische Chemie, Göttingen und DKFZ, Heidelberg  
Fluorescence nanoscopy: Concepts, experiments and instruments
Keynote lecture  
Chair: Willi Jäger  

Hans Westerhoff, Vrije Universiteit, Amsterdam  
Integrative systems biology: Bringing genomes to life  
Friday, December 10

Session 3:  
Challenges for systems biology in plant science and medicine  
Chair: Klaus Unsicker

Rüdiger Hell, Heidelberger Institut für Pflanzenwissenschaften, Heidelberg  
Functional characterization of sulfur metabolite-based regulatory networks in plants

Benedikt Kost, Heidelberger Institut für Pflanzenwissenschaften, Heidelberg  
Characterization of the actomyosin system mediating organelle motility in pollen tubes

Pascal Tomakidi, Poliklinik für Kieferorthopädie, Heidelberg  
Organotypic co-cultures: Tools to study morphogenesis of periodontal tissues in vitro

Christiane Schönbein (AG Mahlknecht), Medizinische Klinik und Poliklinik V, Heidelberg  
Analysis of epigenetical effects on the differentiation of hematopoietic stem cells

Session 4: Modeling of signal transduction  
Chair: Thomas Rausch

Victor Sourjik, ZMBH, Heidelberg  
Signal processing in bacterial chemotaxis

Stephan Frings, Zoologie, Heidelberg  
Olfactory sensory cilia – from cartoon to function

Ursula Klingmüller, DKFZ, Heidelberg  
Dynamic modelling of the JAK-STAT signaling pathway

Rainer Friedrich, MPI für medizinische Forschung, Heidelberg  
Neuronal circuits in the olfactory system: neurophysiology and computation

Peter Bengtson, Interdisziplinäres Zentrum für Neurowissenschaften, Heidelberg  
Transcription-dependent plasticity: Input/output function of nuclear calcium signaling in hippocampal neurons

Strategic discussion (group leaders only)  
Chairs: Winfried Denk, Roland Eils

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GK 791 Retreat  
Odenwald, October 24-25, 2003

Session I

Julia Mack (Dr. Rainer Friedrich, MPI, Heidelberg)  
Functional optical analysis of inhibitory interneurons in the developing olfactory bulb of zebrafish

Christine Hassler (Dr. Christoph Niehrs, DKFZ, Heidelberg)  
The mechanism of axis formation in the developing embryo

Caroline Schmitz (Dr. Harald Hutter, MPI, Heidelberg)  
Screens for genes controlling axon guidance in C. elegans

Session II

Bettina Maier (Prof. Dr. Elisabeth Pollerberg, Institute of Zoology, Dept. of Developmental Neurobiology, Heidelberg)  
Functional analysis of axonal cell adhesion molecules (CAMs) manipulated in their expression levels in the developing visual system

Suhua Deng (Prof. Dr. Stefan Offermanns, Institute of Pharmacology, Heidelberg)  
Generation and analysis of mice lacking the plexin-B family members plexin-B1 and plexin-B2

Session III

Gitta Erdmann (Prof. Dr. Günther Schütz, DKFZ, Heidelberg)  
Analysis of glucocorticoid receptor

Claus Beck (Prof. Dr. Dusan Bartsch, Zentralinstitut für seelische Gesundheit – Mannheim)  
Down syndrome and cognitive processes: The Minibrain Kinase

Nidhi Gakhar (Dr. Francesca Ciccolini, Prof. Dr. Hilmar Bading, Neurobiology-Heidelberg)  
The role of Calcium in embryonic striatal neural precursors

Markus Uhrig (Dr. Tobias Hartmann, DKFZ, Heidelberg)  
Gene expression profiling of human neuroblastoma cells exposed to Aβ42 and neural differentiation of human adult stem cells in vitro and in vivo

Session IV

Ayla Arslan (Dr. William Wisden, Clinical Neurobiology Heidelberg)  
A receptors segregation of different subunits in the membrane and modulation of benzodiazepine pharmacology for studying specific neuronal circuits
Oliver Schlicker (PD Dr. Hans-Hermann Gerdes, Neurobiology Heidelberg)  
GABA receptors in dendritic membrane traffic

Beril Doganci (Prof. Dr. Hannah Monyer, Clinical Neurobiology Heidelberg)  
NR2B conditional knock-out

Session V

Aleksandar Zivkovic (Dr. Andrei Rozov, Clinical Neurobiology Heidelberg)  
Characterization of excitatory synaptic transmission in GluR-D knock-out mice

Dragos Inta (Prof. Dr. Hannah Monyer, Clinical Neurobiology Heidelberg)  
Generation of transgenic mice expressing enhanced green fluorescent protein (EGFP) in 5-HT3 receptor positive neurons

Srinivasa Subramaniam (Prof. Dr. Klaus Unsicker, Neuroanatomy Heidelberg)  
ERK activation promotes degeneration of cerebellar granule neurons independent of caspase-3

Ioana Potrovita (PD Dr. Markus Schwaninger, Neurology Heidelberg)  
TWEAK a new protein of the TNF family and its role in cerebral ischemia

Session VI

Corina Popovici (Prof. Dr. Klaus Unsicker, Neuroanatomy Heidelberg)  

Sabine Chourbaji (Prof. Dr. Fritz A. Henn, Zentralinstitut für seelische Gesundheit, Mannheim)  
Behavioural aspects of animal models for depressive disorders

GK 791 Retreat  
March 18-19, 2005

Session I

Gitta Erdmann, DKFZ, Prof. Günther Schütz  
Generating a mouse with a mutated glucocorticoid receptor allele leading to an impaired nuclear import

Markus Uhrig, ZMBH, Dr. Tobias Hartmann  
Gene expression profiling of human neuroblastoma cells overexpressing A peptides in the context of Alzheimer’s disease

Sabine Chourbaji, Central Institute of Mental Health (CIMH), Mannheim, PD Dr. Peter Gass/ Prof. Dr. Fritz Henn  
The significance of multiple stressors in prehistory for the specificity in the learned helplessness model of depression in mice

Claus Beck, Central Institute for Mental Health Mannheim, Prof. Dr. Dusan Bartsch  
Minimal Animal model for cognitive deficits in Down Syndrome

Session II

Caroline Schmitz, MPI für medizinische Forschung, Dr. H. Hutter  
Identification of genes controlling axon guidance in C. elegans by a large scale RNAi screen

Bettina Maier, Institute of Zoology, Dept. of Developmental Neurobiology, Prof. G.E. Pollerberg  
Functional analysis of axonal cell adhesion molecules (CAMs) manipulated in their expression levels in the developing visual system

Suhua Deng, Institute of Pharmacology, University of Heidelberg, Professor Stefan Offermanns  
Generation and analysis of mice lacking the plexin-B family members plexin-B1 and plexin-B2

Julia Mack, MPI für medizinische Forschung, Dr. Rainer Friedrich  
Early development of functional spatial maps in the zebrafish olfactory bulb

Session III

Dragos Inta, Clinical Neurobiology, Professor Dr. Hannah Monyer  
Expression profile of 5-HT3-positive neurons in a transgenic mouse model

Ioana Inta, Neurology, AG. PD. Dr. Markus Schwaninger  
TWEAK and NF-κB in cerebral ischemia

Nidhi Gakhar, Neurobiology, Prof. Dr. Hilmar Bading  
Calcium signalling in neural precursors

Session IV

Aleksandar Zikovic, Clinical Neurobiology, Dr. Andrei Rozov  
Role of Homer 1a in termination of LTP
Ali Cetin, MPI, Department of Molecular Neurobiology, Prof. Dr. Peter Seeburg
   Lentiviral based approach to study activity dependent development of cortical networks in the rat barrel cortex

Oliver Schlicker, Dept. of Neurobiology, Prof. Dr. Hans-Hermann Gerdes
   GABAA-receptors in dendritic membrane traffic

Beril Doganci, Clinical Neurobiology, Prof. Dr. Hannah Monyer
   Functional analysis of NR2B subunit
Campus „Im Neuenheimer Feld“
Location of IZN Groups

For the most part, the research groups of the IZN Investigators are accommodated in different buildings on the university campus “Im Neuenheimer Feld” (see map, buildings in black). Other IZN groups are located in Heidelberg’s old town, the EMBL, and in Mannheim (Central Institute for Mental Health/ZI, and University Clinics Mannheim).

INF 220/221  Von Deimling group

INF 230  Frings group
Holstein group
Wittbrodt group

INF 232  Pollerberg group

INF 280  Wiestler group

INF 282  Kins group

INF 307  Ernsberger group
Kirsch group
Kuner T. group
Simon group
Tucker group
Unsicker group

INF 326  Draguhn group

INF 345  Schratt group
Schuster group
Söllner group

INF 364  Bading group
Ciccolini group
Monyer group
Müller group

INF 366  Kuner R. group
Rappold group
Schwaninger group

INF 368  Wittum group

INF 400  Rupp group
Wick group

INF 581  Niehrs group
Schütz group

MPIMF  Denk group
Euler group
Köhr group
Seeburg group
Spors group
Sprengel group
Witzemann group

Groups outside the campus

Department of Psychology
Fiebach group
Pauen group

EMBL  Arendt group
Gilmour group

Department of Anesthesiology Mannheim
Schmelz group

ZI Mannheim Bartsch group
Bohus group
Flor group
Gass group
Meyer-Lindenberg group
Spanagel group

CBTM Mannheim  Mense group