Helmholtz Graduate School 'Molecular Cell Biology'
MDC Function and Dysfunction of the Nervous System and Affiliated Groups

NEURO GROUPS 2010

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The four major research areas of the MDC are: **Cancer, Cardiovascular and Metabolic Diseases, Function and Dysfunction of the Nervous System and Medical Systems Biology**.

This brochure presents our **Neuro research groups**. The MDC Neuro groups work in the fields Imaging of the Living Brain, Pathophysiological Mechanisms of Neurological and Psychiatric Disorder, and Signalling Pathways in the Nervous System.

Please see the last page of this brochure for contact details of the PhD Programme coordinators.

The Helmholtz Graduate School 'Molecular Cell Biology' (HGS-MCB)

The MDC established the Helmholtz Graduate School 'Molecular Cell Biology' (HGS-MCB) in 2007 to offer a unified interdisciplinary platform for structured PhD training at the MDC and its partners. We work in collaboration with our partners the Humboldt-Universität zu Berlin (HU), the Freie Universität Berlin (FU), and the Leibniz Institute for Molecular Pharmacology (FMP). There are currently about 200 international PhD students in the Helmholtz Graduate School selected on competitive basis. For more information please visit www.mdc-berlin.de/phd.

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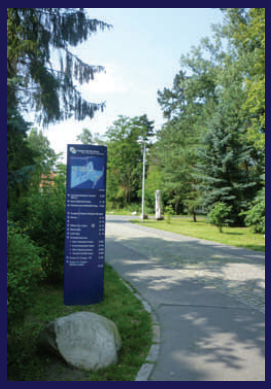

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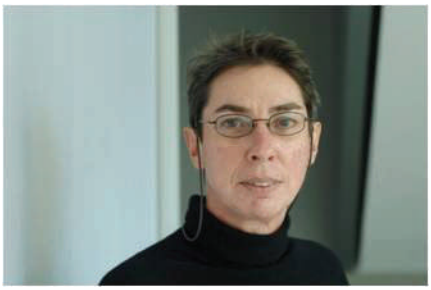
Signal Transduction/ Developmental Biology



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We analyze the functions of signaling molecules and of transcription factors in development of the nervous system and muscle. For this work, we use mice as a model organism. The molecular genetics of mice is well developed, and homologous recombination combined with embryonic stem cell technology can be used to introduce deletions or insertions into the genome. A further development of the technique, the Cre/LoxP technology, allows us now to introduce conditional mutations that are restricted to a particular cell lineage. We have used these technologies to analyze signals that maintain muscle progenitor cells and that allow the formation of satellite cells, the stem cells of the adult muscle. In addition, we identified the function of several transcription factors in development of the nervous system. Among these is a novel factor, Insm1,that we found unexpectedly to perform also important functions in development of pancreatic beta-cells, the insulin-producing endocrine cells.

Publications:

Sieber MA, Storm R, Martinez-de-la-Torre M, Muller T, Wende H, Reuter K, Vasyutina E, Birchmeier C. Lbx1 acts as a selector gene in the fate determination of somatosensory and viscerosensory relay neurons in the hindbrain. J Neurosci. 2007 May 2;27(18):4902-9.

Vasyutina E, Lenhard DC, Wende H, Erdmann B, Epstein JA, Birchmeier C. RBP-J (Rbpsuh) is essential to maintain muscle progenitor cells and to generate satellite cells. Proc Natl Acad Sci U S A. 2007 Mar 13;104(11):4443-8.

Willem M, Garratt AN, Novak B, Citron M, Kaufmann S, Rittger A, DeStrooper B, Saftig P, Birchmeier C, Haass C. Control of peripheral nerve myelination by the beta-secretase BACE1. Science. 2006 Oct 27;314(5799):664-6.

Gierl MS, Karoulias N, Wende H, Strehle M, Birchmeier C. The zinc-finger factor Insm1 (IA-1) is essential for the development of pancreatic beta cells and intestinal endocrine cells. Genes Dev. 2006 Sep 1;20(17):2465-78.

Wildner H, Muller T, Cho SH, Brohl D, Cepko CL, Guillemot F, Birchmeier C. dILA neurons in the dorsal spinal cord are the product of terminal and non-terminal asymmetric progenitor cell divisions, and require Mash1 for their development. Development. 2006 Jun;133(11):2105-13.

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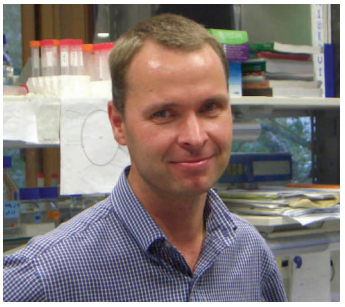
Membrane Biochemistry and Molecular Cell Biology



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Our group is active in the field of cellular and molecular neuroscience with the following major areas:

(1) Cellular and molecular mechanisms of synaptic vesicle recycling;

(2) Regulation of synaptic transmission and vesicle turnover by phosphoinositides;

(3) Molecular basis of the recognition of postsynaptic ion channels by endocytic adaptor;

(4) Proteins and cytoplasmic scaffolds and their role in synaptic plasticity;

(5) Ubiquitin-mediated modulation of synaptic morphogenesis and membrane turnover;

(6) Cellular and molecular mechanisms involved in the establishment and maintenance of;

(7) Neuronal polarity and its implications for axonal regeneration.

Publications:

Jung N, Wienisch M, Gu M, Rand JB, Müller SL, Krause G, Jorgensen EM, Klingauf J, Haucke V. (2007) Molecular basis of synaptic vesicle cargo recognition by the endocytic sorting adaptor stonin 2. J Cell Biol. Dec 31;179(7):1497-510.

Kastning K, Kukhtina V, Kittler JT, Chen G, Enders S, Lee SH, Sheng M, Yan Z, Haucke V (2007) Molecular determinants for the interaction between AMPA-type glutamate receptors and theclathrin adaptor complex AP-2. Proc Natl Acad Sci USA 104:2991-9

Diril MK, Wienisch M, Jung N, Klingauf J, Haucke V (2006) Stonin 2 is an AP-2-dependent endocytic sorting adaptor for synaptotagmin internalization. Dev Cell 10:233-44

Krauss M, Kukhtina V, Pechstein A, Haucke V (2006) Stimulation of PIPK type I-mediated phosphatidylinositol (4,5)-bisphosphate synthesis by endocytic AP-2mu adaptor cargo complexes.Proc Natl Acad Sci USA 103:11934-39

Jia JY, Lamer S, Schumann M, Krause E, Haucke V (2006) Quantitative proteomic analysis of detergent-resistant membranes from chemical synapses: evidence for cholesterol as spatial organizer of synaptic vesicle cycling. Mol Cell Proteomics 5:2060-71

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Targeting Ion Channel function

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Communication between populations of physically interconnected neurons defines a recognizable neuronal circuit. Contemporary genetic methods allow targeting specific cell types within complex neural circuits, but few methods are available to manipulate and observe neural circuits in action. For this purpose, we have recently developed a strategy that blocks ion channels with genetically expressed cell-membrane bound neurotoxins. This idea originated from our previous discovery of an endogenous prototoxin, lynx1, which modulates nicotinic receptors, nAChRs. By tethering venom neurotoxins to the cell membrane we can exploit their discriminative and high blocking capability but restrict their action to ion channels and receptors coexpressed in the same cell. The ongoing projects in our group are aimed at either silencing or manipulating specific ion channels in defined neuronal circuits in the mouse nervous system. The questions we are addressing are: how a particular class of ion channels in one cell population contributes to the function of a given neuronal circuit, and whether silencing one cell population has an impact in only that circuit and/or also affects the next circuit. Another question of interest is whether these functions can be restored upon reversibly inhibiting the expression of the toxin. To approach these questions, we are focusing on specific neuronal circuits in which manipulation of certain ion channels could help dissecting the cascade of events that leads to chronic pain, hearing impairment, and nicotine mediated effects. To target these circuits, we are using two complementary approaches: one employs BAC transgenesis to achieve cell-specific and stable expression, the second uses lentiviral vectors that are microinjected directly into specific brain areas in the mouse. These studies provide a new framework for in vivo manipulating ion channels and diseases of electrical excitability.

Publications:

Miwa JM, Stevens TR, King SL, Caldarone BJ, Ibanez-Tallon I, Xiao C, Fitzsimonds RM, Pavlides C, Lester HA, Picciotto MR, Heintz N. The prototoxin lynx1 acts on nicotinic acetylcholine receptors to balance neuronal activity and survival in vivo. Neuron. 2006 Sep 7;51(5):587-600.

Ibañez-Tallon I, Wen H, Miwa JM, Xing J, Tekinay AB, Ono F, Brehm P, Heintz N. Tethering naturally occurring peptide toxins for cell-autonomous modulation of ion channels and receptors in vivo. Neuron. 2004 Aug 5;43(3):305-11.

Ibañez-Tallon I, Pagenstecher A, Fliegauf M, Olbrich H, Kispert A, Ketelsen UP, North A, Heintz N, Omran H Dysfunction of axonemal dynein heavy chain Mdnah5 inhibits ependymal flow and reveals a novel mechanism for hydrocephalus formation. Hum Mol Genet. 2004 Sep 15;13(18):2133-41.

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Physiology, Pathology and Cell Biology of Ion Transport

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Ion transport processes play crucial roles in neuronal excitability and intracellular signal transduction, transport of salt, water, and other substances across epithelia, and the homeostasis of extracellular, cytosolic, and vesicular compartments. We focus on three gene families, namely CLC chloride channels and transporter, KCNQ (Kv7) potassium channels, and KCC K-Cl-cotransporters. Our investigations stretch from structure-function studies and biophysical analysis to cell biological aspects like endocytosis and to the physiological and systemic role of particular transport proteins. We have identified several human genetic diseases that are due to mutations in ion channels and have generated various knock-out mouse models. Their phenotypes yield important insights into the normal role of particular ion transporters and indicate candidate genes for human diseases. In accord with the broad importance of ion transport, these disorders include epilepsy and neurodegeneration, deafness, kidney stones, urinary protein loss, hypertension, and thick bones (ostepetrosis), among others. Our work bridges the gap between molecular studies and systems biology.

Publications:

Novarino G., Weinert S., Rickheit G., Jentsch T.J. (2010). Endosomal chloride-proton exchange rather than chloride conductance is crucial for renal endocytosis. Science 328, 1398-1401.

Weinert S., Jabs S., Supanchart C., Schweizer M., Gimber N., Richter M., Rademann J., Stauber T., Kornak U., Jentsch T.J. (2010). Lysosomal pathology and osteopetrosis upon loss of H+-driven lysosomal Cl- accumulation. Science 328,1401-1403.

Rickheit G., Maier H., Strenzke N., Andreescu C.E., De Zeeuw C.I., Zdebik A.A., Jentsch T.J. (2008). Endocochlear potential depends on chloride channels: mechanism underlying deafness in Bartter syndrome IV. EMBO J. 27, 2907-2917.

Lange P.F., Wartosch L., Jentsch T.J., Fuhrmann J.C. (2006). ClC-7 requires Ostm1 as a β-subunit to support bone resorption and lysosomal function. Nature 440, 220-223

Kharkovets T., Dedek K., Maier H., Schweizer M., Khimich D., Nouvian R., Vardanyan V., Leuwer R., Moser T., Jentsch T.J. (2006). Mice with altered KCNQ4 K+ channels implicate sensory outer hair cells in human progressive deafness. EMBO J. 25, 642-652.

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Cellular Neuroscience

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Our goal is to understand the role of glial cells in physiology and pathology. We focus on questions as to how neuronal activity is sensed by astrocytes, how astrocytes communicate among each other, and how they feedback on neurons. A second focus addresses the expression of transmitter receptors in microglial cells and how activation of these receptors influences microglial function. This is of particular interest within the context of pathology and we are currently studying this question in stroke and gliomas. A third line of research addresses the question as to how glioma cells interact with the intrinsic brain cells, specifically microglia and stem cells. We are aiming to understand this interaction on a molecular level, in particular with the hope of identifying tools which impair glioma invasion.

Publications:

Färber, K., Markworth, S., Pannasch, U., Prinz, V., Kronenberg, G., Gertz, K., Endres, M., Enjyoji, K., Robson, S. C. and Kettenmann H. (2008) The ectonucleotidase cd39/ENTPDase1 modulates purinergic-mediated microglial migration, Glia, 56:331-341.

Schipke C. G., Haas B. and Kettenmann H. (2008), Astrocytes Discriminate and Selectively Respond to the Activity of a Subpopulation of Neurons within the Barrel Cortex Cereb Cortex, published on March 4, 2008; doi: doi:10.1093/cercor/bhn009

Waelzlein JH, Synowitz M., Engels B., Markovic D. S., Gabrusiewicz K., Nikolaev E. Yoshikawa K., Kaminska B., Kempermann G., Uckert W.,Kaczmarek L., Kettenmann H., and Glass R. (2008), The anti-tumorigenic response of neural precursors depends on subventricular proliferation and age. Stem Cells Express, published online August 28, 2008; doi:10.1634/stemcells.2008-0307

Hanisch, UK and Kettenmann, H. (2007) Microglia – active sensor and versatile effector cells in the normal and pathologic brain, Nat. Neurosci. 10:1387 – 1394.

Pocock, J. M. and Kettenmann H. (2007) Neurotransmitter receptors on microglia, Trends Neurosci., 30:527-535

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Molecular Physiology of Somatic Sensation

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We focus of the molecular mechanisms of somatic sensation. Somatic sensation includes all those sensations that we are consciously aware of after stimulation of the body, e.g. touch, warmth, cooling, or even limb movement. We experience these sensations as a direct result of the activation of sensory neurons that are located in the dorsal root ganglia (DRG). Sensory neurons can, for example, detect changes in temperature of the skin in non-noxious (not painful) as well as the noxious range (painful heat, or cold). They can also detect gentle movement of the skin as well as intense mechanical stimulation of the skin that is normally harmful. One of our main interests is to identify the ion channels, expressed by sensory neurons, that transduce relevant stimuli. The molecular nature of the transduction molecules involved together with the developmental events that lead to specification of the appropriate sensory neuron sub-types are actively investigated the lab.

Publications:

Wetzel, C., Hu, J., Riethmacher, D., Benckendorff, A., Harder, L., Eilers, A., Moshourab, R., Kozlenkov, A., Labuz, D., Caspani, O, Erdmann, B., Machelska, H., Heppenstall P.A., Lewin, G.R. (2007). A stomatin-domain protein essential for touch sensation in the mouse. Nature 445, 206-209

Hu, J., Lewin, G.R. (2006). Mechanosensitive currents in the neurites of cultured mouse sensory neurones. J Physiol. 577, 815-828

Shin JB, Martinez-Salgado C, Heppenstall PA, Lewin GR (2003) A T-type calcium channel required for normal function of a mammalian mechanoreceptor. Nature Neuroscience 6:724-730.

Stucky CL, Shin JB, Lewin GR (2002) Neurotrophin-4: a survival factor for adult sensory neurons. Curr Biol 12:1401-1404.

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RNA Editing and Hyperexcitability Disorders

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In a healthy organism, a balance is maintained between the excitation and inhibition of electrical impulses generated by neurons in the brain. Deregulation of this balance results in nervous system disorders. A core aspect of our work concerns the study of the brain at the molecular level, by investigating a post-transcriptional enzymatic process known in research as "RNA editing". Thereby, after the DNA text of the genes has been transcribed into RNA, individual letters are replaced with others by enzymatic processing. As a result, the original genetic text no longer corresponds exactly to the resulting protein text. By this means, the cell succeeds in disregarding the information coded in the genome, and through specific alterations can give its own genetic text a completely different meaning. RNA editing is evolutionarily very old. Nevertheless, in humans only a few editing sites were identified so far. We search for such sites in the nervous system in order to find out what role they play in nervous system disorders, such as temporal lobe epilepsy. Within this context, we are more closely scrutinizing the glycine receptor - one of the neuronal receptors that inhibit electrical impulses in the brain.

Publications:

Eichler SA, Kirischuk S, Jüttner R, Legendre P, Lehmann TN, Gloveli T, Grantyn R, Meier JC. (2008) Glycinergic Tonic Inhibition of Hippocampal Neurons with Depolarising GABAergic Transmission Elicits Histopathological Signs of Temporal Lobe Epilepsy. J Cell Mol Med in press. .

Eichler SA and Meier JC. (2008) E-I Balance and human diseases – From molecules to networking. Front. Mol. Neurosci., in press.

Singh B, Henneberger C, Betances D, Arevalo MA, Rodriguez-Tebar A, Meier JC, Grantyn R. (2006) Altered balance of glutamatergic/GABAergic synaptic input and associated changes in dendrite morphology after BDNF expression in BDNF-deficient hippocampal neurons. J. Neurosci. 26:7189-7200.

Meier JC, Henneberger C, Melnick I, Racca C, Harvey RJ, Heinemann U, Schmieden V, Grantyn R. (2005) RNA editing produces glycine receptor alpha3(P185L), resulting in high agonist potency. Nat. Neurosci. 8:736-44.

Meier JC and Grantyn R. (2004) A gephyrin-related mechanism restraining glycine receptor anchoring at GABAergic synapses. J. Neurosci. 24:1398-1405.

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Neural Circuits and Behaviour

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Our lab is broadly interested in how neural circuits control behaviour. We study the mouse as it is a mammalian, genetic model system where neurons can be recorded and their activity manipulated during quantified behaviour. We combine electrophysiological techniques (especially whole-cell patch clamp) with 2-photon microscopy, genetic manipulations, novel optical techniques for manipulating neural activity, anatomical reconstruction of stained neurons and behavioural training.

Publications:

Poulet and Petersen (2008). Internal brain state regulates membrane potential synchrony in barrel cortex of behaving mice. Nature. 454:881-885.

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Developmental Neurobiology

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A neuron establishes thousand of synapses which are the fabric of communication within the nervous system. The number, strength as well as specificity of synapses and the balance between inhibitory and excitatory neurons determine brain function. A long-standing goal of neuroscientist therefore is to understand how the enormous degree of connectivity of neurons is established during embryonic and early postnatal development and how this connectivity becomes modulated by experience-dependent processes. The research of our group focuses currently on two molecular aspects of neuronal connectivity: formation of axonal branches and regulation of synapse formation.

Publications:

Schmidt H, Stonkute A, Jüttner R, Schäffer S, Buttgereit J, Feil R, Hofmann F, Rathjen FG. (2007) The receptor guanylyl cyclase Npr2 is essential for sensory axon bifurcation within the spinal cord. J Cell Biol. 2007 Oct 22;179(2):331-40

Jüttner R, Moré MI, Das D, Babich A, Meier J, Henning M, Erdmann B, Müller EC, Otto A, Grantyn R, Rathjen FG. (2005) Impaired synapse function during postnatal development in the absence of CALEB, an EGF-like protein processed by neuronal activity.Neuron. Apr 21;46(2):233-45.

Jüttner, R. and Rathjen, FG. (2005) Molecular analysis of axonal target specificity and synapse formation. Cellular and Molecular Life Sciences, 62, 2811-2827.

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Animal Behaviour

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Do special "human" genes provide the biological substrate for uniquely human traits, such as language? Genetic aberrations of the human FoxP2 gene impair speech production and comprehension, yet the relative contributions of FoxP2 to brain development and function are unknown. Songbirds are a useful model to address this because, like human youngsters, they learn to vocalize by imitating the sounds of their elders. Previously, we found that when young zebra finches learn to sing or when adult canaries change their song seasonally, FoxP2 is up-regulated in Area X, a brain region important for song plasticity. We recently reduced FoxP2 levels in Area X before zebra finches started to learn their song, using virus-mediated RNA interference for the first time in songbird brains. Birds with experimentally lowered levels of FoxP2 imitated their tutor's song imprecisely and sang more variably than controls. FoxP2 thus appears to be critical for proper song development. These results suggest that humans and birds may employ similar molecular substrates for vocal learning, which can now be further analyzed in an experimental animal system. We are currently functionally characterizing FoxP2 on the molecular level in vitro and in the living animal using the lentiviral expression.

Publications:

Haesler S, Rochefort C, Georgi B, Licznerski P, Osten P, Scharff C. (2007) Incomplete and inaccurate vocal imitation after knockdown of FoxP2 in songbird basal ganglia nucleus Area X. PLoS Biol. Dec;5(12):e321

Rochefort C, He X, Scotto-Lomassese S, Scharff C. (2007) Recruitment of FoxP2-expressing neurons to area X varies during song development. Dev Neurobiol. May;67(6):809-17

Scotto-Lomassese S, Rochefort C, Nshdejan A, Scharff C. (2007) HVC interneurons are not renewed in adult male zebra finches. Eur J Neurosci. Mar;25(6):1663-8.

Haesler S, Wada K, Nshdejan A, Morrisey EE, Lints T, Jarvis ED, Scharff C.(2004) FoxP2 expression in avian vocal learners and non-learners. J Neurosci. Mar 31;24(13):3164-75

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Signaling and Transport Processes

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The last time you smelled a cookie and saliva was released into your mouth TMEM16A, a calcium activated chloride channel (CaCC), which was discovered recently, was involved. Its sequence is not related to any other ion channel or transporter and it is the founding member of a new protein family.

Calcium activated chloride currents have first been described in salamander photoreceptors in 1982, but the molecular identity remained an open problem until 2008. CaCCs are not only important for membrane potential stabilization in photoreceptors of the retina and the secretion of fluids in glands and airway epithelia They have also been implicated in a wide range of other physiological functions including the high-gain, low-noise amplification in olfactory transduction, taste adaptation, control of action potential waveform in neurons and positive feedback regulation of smooth muscle contraction induced by G protein-coupled receptors that is important to control vascular tone or uterus contraction.

Research in our laboratory focuses on the TMEM16 family of transmembrane proteins. The TMEM16 family has 10 members in mammals, 5 in fly and 1 in yeast. Beside the function of TMEM16A as CaCC little is known about this family. Mice containing a deletion in the TMEM16A gene die few weeks after birth and suffer from tracheomalacia, a development phenotype of the lung. Gnathodiaphyseal dysplasia, a rare disease characterized by bone fragility, sclerosis of tubular bones and lesions of the jawbone, is caused by mutations in the human TMEM16E gene. But the role of TMEM16E in healthy bone and how its disruption leads to the phenotype remain elusive. TMEM16J shows a very strong regulation by the tumor suppressor p53 and some TMEM16 proteins are highly amplified in specific forms of cancer.

Publications:

Schroeder BC, Cheng T, Jan Y, Jan LY, (2008). Expression cloning of TMEM16A as a calciumactivated chloride channel subunit. Cell, 134, 1019-1029.

Estévez R*, Schroeder BC*, Accardi A, Jentsch TJ, Pusch M., (2003). Conservation of chloride channel structure revealed by an inhibitor binding site in ClC-1. Neuron, 38, 47-59.

Schroeder BC*, Waldegger S*, Fehr S, Bleich M, Warth R, Greger R, Jentsch TJ., (2000). A constitutively open potassium channel formed by KCNQ1 and KCNE3. Nature, 403, 196-9.

Kubisch C*, Schroeder BC*, Friedrich T, Lutjohann B, El-Amraoui A, Marlin S, Petit C, Jentsch TJ., (1999). KCNQ4, a novel potassium channel expressed in sensory outer hair cells, is mutated in dominant deafness. Cell, 96, 437-46.

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Temperature Detection and Thermoregulation

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Temperature detection and regulation is of vital importance to any homeothermic organism. This sensory process is not only needed to control and maintain internal temperature homeostasis but also serves as a warning system to inform us when our environment is too hot or too cold in order to prevent tissue damage. Therefore our sensory system consciously perceives our environment and influences regulatory mechanism to guarantee proper body function and homeostasis. Sensors for painful thermal stimuli include TRP channel family members TRPV1 (hot and Chilli), and TRPM8. TRPM8 is activated by menthol, a product of the mint plant used in chewing gum and toothpaste to evoke a cooling sensation. Low temperatures activate TRPM8 in vitro, further suggesting that TRPM8 is a cold receptor. To test this hypothesis in vivo, we generated TRPM8 deficient mice and examined their response to cold stimuli. We found that these mice were not able to discriminate between cold and warm temperatures in behavior assays and displayed dramatically reduced responses to cold stimuli at the cellular level. These findings validate the hypothesis that TRP channels are the principal sensors of thermal stimuli in the peripheral nervous system. But do these receptors play a role in core body temperature regulation?

Key centers for core body temperature control are situated in the preoptic area of the brain and the anterior portion of the hypothalamus. A small subset of cells in these regions not only detect changes in core body temperature (CBT), but are also receiving input from ascending somatosensory pathways carrying information from peripheral temperature sensors. One aspect of our current research focuses on elucidating the impact of peripheral temperature sensation on core body temperature. By using implanted sensors and radio telemetry to measure CBT, we ask whether TRPM8-deficient mice are able to maintain constant core temperature when challenged with different (cold) environmental temperatures. It is currently unknown whether peripheral or central temperature sensors dominate CBT regulation or if both contribute equally..

Publications:

Jan Siemens, Sharleen Zhou, Rebecca Piskorowski, Tetsuro Nikai, Ellen A. Lumpkin, Allan I. Basbaum, David King, David Julius: Spider Toxins activate the Capsaicin Receptor to produce Inflammatory Pain. 2006, Nature, 444, 208-212

Diana M. Bautista*, Jan Siemens*, Josh Glazer*, Pamela R. Tsuruda, Allan I. Basbaum, Cheryl L. Stucky, Sven-Eric Jordt, and David Julius The Menthol Receptor TRPM8 is the Principal Detector of Environmental Cold. 2007, Nature, 448, 204-208, *denotes equal contribution

Genetics

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At synaptic contacts between neurons, the presynaptic active zone organizes Ca2+-mediated release of neurotransmitter to activate neurotransmitter receptors localized at the postsynaptic specialization. How these synaptic compartments assemble and control their function is under intense investigation.

Genetic analysis in the fruit fly Drosophila allowed us to identify a master organizer of presynaptic active zones, a protein we called Bruchpilot. At synapses lacking Bruchpilot, clustering of presynaptic Ca2+-channels is defective, and efficiency of neurotransmitter release is dramatically reduced. Thus, this protein might well organize changes of synaptic performance in vivo. We now address the architecture of active zones systematically analyzing synapses in two models, flies and mice. To this end, genetic and biochemical analysis is combined with a recent advance of light microscopy, stimulated emission microscopy (STED). STED drastically increases resolution of fluorescence microscopy, uncovering so far unseen substructures in the molecular architecture of synapses. Our results are relevant in the context of learning and memory as well as degenerative diseases of the nervous system.

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Neuroproteomics

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Cells are made of macromolecules and metabolites that interact to form highly complex networks. Protein-protein, RNA-protein and DNA-protein interactions are critical for the formation of molecular machines, and contribute to global transcriptional networks, positive and negative circuits and other regulatory mechanisms. Macromolecular networks appear to govern all fundamental cellular processes, and perturbations of these networks obviously underlie many human diseases.

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The group works on immune regulation, neural cell damage and neuronal protection mechanisms in the context of inflammatory pathologies of the nervous system such as multiple sclerosis. Methodology ranges from murine and human lymphocyte and brain slice culture to models of neuroinflammation, in vivo multi-photon-microscopy and magnetic resonance imaging. The overall goal is to translate resulting knowledge into proof–of-concept clinical trials. The work is mainly performed within two collaborative research centers SFB TRR 43 and SFB 650, the NeuroCure Cluster of Excellence, and Berlin Center of Regenerative Therapies.

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