
Jan Erik Siemens, Ph.D. - Curriculum Vitae

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Education

- 2004 **Ph.D. in Neuroscience**
Graduate Program of the Friedrich Miescher Institute in Basel, Switzerland.
Honors: Summa Cum Laude
- 1999 **B.S. in Biochemistry (Diplom Biochemist)**
J. W. Goethe-Universität, Frankfurt am Main, Germany.
Grade: 1.0

Research Experience

- April 2013-
Present **Professor**, Department of Pharmacology, Heidelberg University
- Mai 2009-
March 2013 **Research Group Leader** at the Max Delbrueck Center in Berlin, Germany
- Jan. 2005-
April 2009 **Postdoctoral Fellow**
Departments of Physiology and Cellular & Molecular Pharmacology
University of California, San Francisco
Advisor: Dr. David Julius
- Identified tarantula toxins as activators of TRPV1
 - Characterized TRPM8 as the principal detector for environmental cold
 - Identified 4-HNE as an endogenous pro-inflammatory agonist for TRPA1
- 2000-2004 **Graduate student**
Friedrich-Miescher Institute (FMI) in Basel, Switzerland
(Lab relocated to Scripps Research Institute in San Diego, CA in 2003)
Advisor: Dr. U. Müller
- Thesis: „Functional Characterization of the Usher Syndrome Proteins Cadherin 23 and Harmonin in the Mouse Inner Ear”
- Identified Cadherin 23 as a core component of hair cell tip link in the vertebrate inner ear
 - Identified and characterized a physical complex formed by the Usher-Syndrome genes Cadherin 23 and Harmonin

- 1999- 2000 **Diploma Thesis**
Institute for Diabetes Research
Eberhard-Karls-Universität, Tübingen, Germany
Advisor: Dr. Reiner Lammers (Director: Dr. Ulrich Haering)
Diploma Thesis: „Proteolytical Processing of Protein Tyrosine Phosphatase PTP alpha”
- 2004 **Student Intern**
Psychiatric Unit
Novartis, Basel, Switzerland
Advisor: Dr. Johannes Mosbacher
Project: „Generation and electrophysiological characterization of GABA-A expressing cell-lines“
- 2000 **Summer student**
Developmental Biology Research Unit
European Molecular Biology Laboratory (EMBL), Heidelberg, Germany
Advisor: Dr. Dirk Bohmann
Project: „Identification of target genes for the transcription factor Jun in *Drosophila M.*”
- 1998 **Student Intern**
Department for Preclinical Pharma Research II
Merck, Darmstadt, Germany
Project: „Generation and characterization of cDNA libraries from colon carcinoma tissue”
- 1997 **Summer student**
Institute of Genetics
Research Center Karlsruhe, Germany
Advisor: Dr. A. Kato (Director: Prof. Dr. P. Herrlich)
Project: „Funtional characterization of the interaction of the androgen receptor with the family of 14-3-3 proteins“
- 1995 **Summer student**
Institute of Genetics
Research Center Karlsruhe, Germany
Advisor: Dr. M. Goettlicher (Director: Prof. Dr. P. Herrlich)
Project: „Introduction to the yeast two-hybrid system“

Teaching Experience

- 2009-now **Neuroscience Lectures**
MDC, Berlin
• Several Lectures as part of the curriculum of the Graduate School „Molecular Neuroscience“ of the Helmholtz Graduate School at the MDC
- 2007 **Postdoctoral Teaching Fellow**
University of California, San Francisco

- Instructed medical students during small-group problem solving sessions during fall of 2007. Topics: Pharmacology and Biochemistry

2005-2009

Research Mentor of several rotation students and graduate students*University of California, San Francisco*

- Arthur Millius (rotation student); Project: “Insect venom screen for TRP channel modulators”
- Beatrice Wang (rotation student); Project: “ Heterologous expression and purification of tarantula toxins activating TRPV1”
- Chris Bohlen (rotation student, now graduate student); Project: “Characterization of the TRPV1 binding site for vanillotoxins”

Fellowships and Awards

- 2011 ERC Starting Grant (European Research Council)
- 2009 Career Development Award (Human Frontier Science Program - HFSP)
- 2008 Sofja Kovalevskaja Award (Alexander von Humboldt Foundation - BMBF)
- 2008 K99/R00 Pathway to Independence Award (NIH)
(I declined the award due to my relocation to the MDC in Berlin, Germany in 2009)
- 2007 Sandler Postdoctoral Research Award
- 2006 Postdoctoral Fellowship, Human Frontier Science Program Organization (HFSP)
- 2005 Postdoctoral Fellowship, Swiss National Research Foundation and the Novartis Research Foundation
- 2004 Most outstanding Ph.D. Thesis-Award selected by the Faculty for Natural Sciences (Philosophisch - Naturwissenschaftliche Fakultät II), University of Basel, Switzerland
- 2001 Ph.D. fellowship from the Boehringer Ingelheim Fonds, Germany

Patents

- 2003 Patent: Compositions For Regulation of Mechanically Gated Ion Channels and Methods of Use Thereof.
Inventors: Ulrich Müller and Jan Siemens.

Selected Presentations

- 2012 Conference Organizer (together with Gary Lewin, MDC) “Force Transduction and Emerging Ion Channels”, MDC, Berlin.
- 2010 Conference “TRP Ion channels in Health and Disease”, Alicante, Spain
Talk: “Spider Toxins: Pharmacological Tools to Study the Capsaicin Receptor TRPV1”
- 2008 Conference “Molecules and Mechanisms in Sensory Neurobiology”, Berlin Germany
Talk: “TRP ion channels in temperature sensation & inflammation”.
- 2007 Society for Neuroscience Meeting, San Diego, CA
Talk: “TRPM8 is the principal detector for environmental cold”
- 2003 Gordon Research Conference “Mechanosensory Transduction”, New London, CT
Poster: “Differential expression of two Cadherin 23 splice variants in the inner ear”
- 2001 Molecular Biology of Hearing and Deafness Conference, Bethesda, MD
Poster: “Identification of polarity genes in the vertebrate inner ear”

Peer Reviewed Publications

Proteolytic processing of the protein tyrosine phosphatase alpha extracellular domain is mediated by ADAM17/TACE

Katja Kapp*, **Jan Siemens***, Hans-Ulrich Häring, Reiner Lammers
2012, **Eur J Cell Biol**, 91, 687-693

**denotes equal contribution*

A Bivalent Tarantula Toxin Reveals a Unique Role for the Outer Pore Domain in TRP Channel Gating

Christopher J. Bohlen, Avi Priel, Sharleen Zhou, David King, **Jan Siemens***, and David Julius*
2010, **Cell**, 141, 834-845

** Corresponding Authors*

4-Hydroxynonenal, an Endogenous Aldehyde, causes Pain and Neurogenic Inflammation through Activation of the Irritant Receptor, TRPA1.

Marcello Trevisani*, **Jan Siemens***, Serena Materazzi, Diana M. Bautista, Romina Nassini, Barbara Campi, Noritaka Imamachi, Eunice Andrè, Riccardo Patacchini, Graeme S. Cottrell, Raffaele Gatti, Allan I. Basbaum, Nigel W. Bunnett, David Julius and Pierangelo Geppetti
2007, **PNAS**, 104, 13519-13524

**denotes equal contribution*

TRPA1 mediates Formalin Induced Pain.

Colleen R. McNamara, Josh Mandel-Brehm, Diana M. Bautista, **Jan Siemens**, Kari L. Deranian, Michael Zhao, Neil J. Hayward, Jayhong A. Chong, David Julius, Magdalene M. Moran, and Christopher M. Fanger
2007, **PNAS**, 104, 13525-13530

The Menthol Receptor TRPM8 is the Principal Detector of Environmental Cold.

Diana M. Bautista*, **Jan Siemens***, Josh Glazer*, Pamela R. Tsuruda, Allan I. Basbaum, Cheryl L. Stucky, Sven-Eric Jordt, and David Julius

2007, **Nature**, 448, 204-208

**denotes equal contribution*

Extracellular Domain Splice Variants of a Transforming Protein Tyrosine Phosphatase alpha mutant differentially activate Src-kinase dependent Focus Formation.

Katja Kapp*, **Jan Siemens***, Peter Weyrich, Jörg B. Schulz, Hans-Ulrich Häring, Reiner Lammers
2007, **Genes to Cells**, 12, 63-73

**denotes equal contribution*

Spider Toxins activate the Capsaicin Receptor to produce Inflammatory Pain.

Jan Siemens, Sharleen Zhou, Rebecca Piskorowski, Tetsuro Nikai, Ellen A. Lumpkin, Allan I. Basbaum, David King, David Julius

2006, **Nature**, 444, 208-212

Cadherin 23 is a Component of the Tip Link in Hair Cell Stereocilia.

Jan Siemens, Concepcion Lillo, Rachel A. Dumont, David Williams, Peter Gillespie, and Ulrich Müller

2004, **Nature**, 428, 950-955

Mutations in Cadherin 23 affect Tip Links in Zebrafish Sensory Hair Cells.

Christian Söllner, Gerd-Jörg Rauch, **Jan Siemens**, Robert Geisler, Stephan C. Schuster, the Tübingen 2000 Screen Consortium, Ulrich Müller, & Teresa Nicolson

2004, **Nature**, 428, 955-959

The Usher Syndrome Proteins Cadherin 23 and Harmonin form a Complex by means of PDZ Domain Interactions.

Jan Siemens, Piotr Kazmierczak, Anna Reynolds, Melanie Sticker, Amanda Littlewood-Evans, and Ulrich Mueller

2002, **PNAS**, 99, 14946-14951

Review Publications

Sensory transduction, the gateway to perception: mechanisms and pathology

Stefan G. Lechner, **Jan Siemens**

2011, **Embo Reports**, 12, 292-295

Genes, Deafness, and Balance Disorders

Jan Siemens, Amanda Littlewood-Evans, Mathias Senften, and Ulrich Mueller

2001, **Gene Function & Disease**, 2, 76-82

The Sound of Silence - Diseases that cause Deafness and Disequilibrium

Jan Siemens, Amanda Littlewood-Evans, and Ulrich Mueller

2001, **B.I.F. Futura**, 16, 222-228

Research Interests - Temperature Detection and Thermoregulation

Summary

Temperature affects all aspects of life, down to every enzymatic reaction. Thus, internal temperature homeostasis is of critical importance to our health as deviation from a normal, tightly controlled level (37 °Celsius) can cause fatal organ failures. Moreover, clinically controlled reduction of core body temperature under pathological conditions such as stroke, trauma, and certain surgical procedures has the potential to reduce tissue damage and to improve recovery. We are interested to understand central and peripheral mechanisms of Core body temperature regulation.

My team and I are using a multi-disciplinary approach to analyze peripheral and central temperature sensors on the cellular and molecular level. In this context we are studying members of the TRP family of receptor ion channels that are not only exquisitely sensitive to temperature changes but also respond to inflammatory and painful stimuli.

We also seek to identify and characterize neuroendocrine signals involved in thermoregulation in order to shed light on the interconnection between thermoregulatory and metabolic pathways.

Background

Humans have the ability to adapt to a broad range of environmental temperatures. Behavioral adjustments and autonomic mechanisms allow us to maintain a core body temperature (CBT) within a few tenths of a degree Celsius even at highly diverse ambient temperatures. The main neuronal circuitry involved in core temperature homeostasis is located in the hypothalamus, a brain area that is also engaged in the control and maintenance of other autonomic functions such as the sleep/wake cycle and energy balance/metabolism.

Within the hypothalamus, the preoptic area (PO) and the anterior hypothalamus (AH) play an important role in body temperature regulation. Local PO/AH warming and cooling experiments as well as studies introducing hypothalamic lesions have shown that neurons in these regions detect local brain temperature changes necessary for core temperature control. According to current models, which have evolved from Hammel's theory of "set-point" thermoregulation, warm-sensitive neurons in the PO/AH change their activity (the rate of action potential firing) when the core temperature deviates from the "set-point" of 37°C. In the case of temperature elevation from the "set-point", warm-sensitive neurons increase their activity and signal to effector neurons that in turn stimulate heat loss mechanisms (e.g. sweating, shallow and more rapid breathing, vasodilatation). Conversely, a body temperature decrease relative to the "set point" initiates heat production or heat conservation mechanisms (e.g. shivering, non-shivering thermogenesis in brown adipose tissue, vasoconstriction). While some progress has been made in uncovering the hypothalamic circuitry involved in thermoregulation, mechanisms underlying central temperature detection by hypothalamic neurons are unknown.

Hypothalamic neurons not only detect local brain temperature but receive and integrate information from peripheral temperature sensors located in the skin, spinal cord and viscera. It has been found that sensory nerve fibers of dorsal root ganglia (DRG) and trigeminal (TG) neurons detect temperature changes by direct activation of thermosensitive excitatory ion channels. Among these, the family of transient receptor potential (TRP) ion channels has gained considerable attention. TRP ion channels have been found to constitute important components in a number of different sensory systems. The founding member, *Drosophila* TRP, resides in a protein complex (termed "signalplex") that is essential for fly vision. In vertebrates, TRP family members TRPV1 (capsaicin receptor), TRPM8 (menthol receptor) and TRPA1 (mustard oil receptor) play prominent roles within the somatosensory system in the detection, transduction and modulation of thermal (and inflammatory) stimuli ranging from cool/cold to hot ambient temperatures. How these receptors mediate their temperature sensitivity

and how they are regulated/modulated on the molecular level is largely unknown. Additionally, the impact of peripheral TRP-mediated temperature information on central temperature regulation is largely unknown.

Research Aims

My scientific interest is centered on three interconnected research topics: The first line of research is geared towards a deeper understanding of TRP receptor function in the context of the somatosensory system and the detection of temperature and painful stimuli. Next, we have started to establish a human ES-cell based system to recapitulate sensory neuron development *in vitro*, with the goal to provide a cellular model system for biochemical and functional analysis of sensory transduction processes. The third line of research is geared towards understanding cellular and molecular mechanisms of central core body temperature detection and regulation as well as the connection between thermoregulatory and metabolic pathways.

Aim 1: The thermosensory TRP channel proteom

The TRP superfamily of non-selective cationic channels includes approximately 30 related molecules that respond to a remarkable variety of chemical and physical stimuli. While physiological roles for many TRP channels remain unknown, several family members have now been proposed to function as molecular sensors of environmental stimuli in organisms ranging from yeast to humans. A subset of these receptors, the so-called “ThermoTRPs”, detect a broad range of temperatures. Most prominent among these are the capsaicin receptor TRPV1, the menthol receptor TRPM8, and the mustard oil receptor TRPA1. Next to their function as molecular temperature detectors, they participate in the detection of a wide range of noxious stimuli and TRPV1 as well as TRPA1 have emerged as prototypical molecular nociceptors. While biophysical properties of these non-selective cation channels have been studied in some detail, little is known about the regulation and modulation of TRP channels by endogenous molecules under physiological and pathophysiological conditions. It is unclear how these receptors are able to respond to and integrate such a variety of different thermal and chemosensory stimuli to affect downstream signaling. It is unlikely that the receptors full-fill this function as individual detached molecular entities, but rather in the context of a larger signaling complex consisting of the ion channel along with a number of accessory proteins, which direct their trafficking and modulate their function. Although several lines of evidence support the conclusion that TRP ion channels reside in protein complexes to foster context-dependent function, their identity is unknown. We are using a genetic biochemical strategy to isolate and identify components of somatosensory TRP channel protein complexes from native sensory ganglia of transgenic mice. We express affinity-tagged TRP receptors in place of the endogenous wild-type receptors to enable specific isolation and purification of the receptor complexes from sensory neurons by affinity chromatography. Subsequently, we detect complex components by mass spectrometry. We have identified first targets and are now underway to characterize their impact on TRP channel function.

A variety of live-cell imaging and electrophysiological assays will be utilized to assess a target protein’s involvement in TRP channel gating, agonist selectivity, ion selectivity, channel kinetics, gating thresholds for agonists or thermal manipulation and other parameters. The *in vivo* model systems will not only allow us to study TRP protein complex composition under physiological (steady state) conditions but also investigate how compositions are altered under chronic inflammatory conditions.

Aim 2: Differentiation of human embryonic stem cells into sensory neurons

Our objective is to use human embryonic stem cells (hESCs) to generate sensory-like neurons of the peripheral nervous system. The long-term perspective is to obtain a homogenous population of sensory neurons for downstream biochemical and electrophysiological experimentation. As the isolation of specific neuronal subtypes residing in distinct areas of the central or peripheral nervous system is a great challenge and almost always affords the pooling of heterogenous tissue, the differentiation of homogenous populations of sensory neurons from human ES cells would be of great benefit to study aspects of sensory neurobiology in vitro. Additionally, sensory material from human tissues is very hard to obtain and a cellular system based on the differentiation of human embryonic stem cells would be a big advantage in the field.

Thus far, we have established a protocol to generate mechanoreceptors, one of the several highly specialized sensory neuronal subtypes found in the dorsal root ganglia (DRGs) of the peripheral nervous system, detecting and mediating mechanical stimuli from the outside world. We are now underway to characterize this population in great detail using electrophysiological means as well as transcriptional profiling. In the future we are aiming to derive additional sensory subtypes, in particular those involved in transducing painful stimuli.

Aim 3: Central temperature detection and thermoregulation

While much progress has been made in elucidating peripheral temperature detectors, mechanisms governing central temperature detection and regulation have remained a mystery. Two of the main reasons for this discrepancy are: 1.) Thermo-sensitive detector cells reside deep inside hypothalamic structures of the brain and are thus difficult to access; 2.) Detector cells are also scarce and intermingled with large numbers of neurons involved in other functions, which have complicated their analysis in the past.

In order to overcome these limitations, we are using Calcium-imaging to monitor the activity of temperature-stimulated hypothalamic neurons on a large scale in order to identify temperature-sensitive neuronal subpopulations. We are using hypothalamic slice preparations and dispersed cultures of primary hypothalamic neurons for these experiments, focusing on the preoptic area of the hypothalamus. Using this calcium-imaging approach, we can differentiate different categories of warming-activated neurons, cooling-activated neurons, and neurons activated by cooling and warming. We hypothesize that the temperature-sensitive neurons (or a subfraction of them) make up the cellular thermostat required for temperature homeostasis. We have begun to characterize these cellular processes in detail with the goal to elucidate the molecular basis of their temperature sensitivity and to understand their role in thermoregulatory processes.