universität innsbruck

CaVX PhD PROGRAM
Calcium channels in excitable cells

MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

Call for applications to the PhD program Ca_VX in Neuroscience

Students with a keen interest in neuroscience are invited to apply for vacant doctoral studentships within the PhD program ***Ca_VX – Calcium channels in excitable cells.***

In the PhD program, which is run by the Universities in Innsbruck, we are studying the roles of voltage-gated calcium channels (Ca_V) in health and disease. Students accepted into the program will be enrolled in the existing graduate program in Neuroscience and receive a specialized training in signaling processes of ion channels, membrane excitability, calcium signaling, and channelopathies.

Research topics: Roles of voltage-gated calcium channels in CNS neurons, skeletal muscle and pancreas, distinct brain disorders, retinal dysfunction, and diabetes.

Candidates must hold a master's degree or equivalent in the life sciences, medicine, pharmacy or physics. Excellent command of English is indispensable.

- Research projects
- General information

PhD candidates need to fill out the application form and submit the signed application form by E-mail to CavX@i-med.ac.at. Applications must be received by **January 6, 2020!**

FWF
Der Wissenschaftsfonds.

Research projects

1. **Regulation of the voltage-sensitivity of calcium channels (Flucher)**
2. **Calcium channels in congenital stationary night blindness (Koschak)**
3. **Calcium channels in intra-islet cell communication (Meyer)**
4. **Voltage-gated calcium channels and synaptic functions (Obermair)**
5. **Calcium channels in regulation of dendritic complexity (Di Biase)**

Project 1: Regulation of the voltage-sensitivity of calcium channels (Flucher)

In nerve and muscle cells voltage-activated calcium channels control activity-dependent cell functions like muscle contraction and neurotransmitter secretion. Recently we described a novel molecular mechanism important for the regulation of voltage-sensitivity of $Ca_V1.1$ by alternative splicing. Here we will combine state-of-the-art protein structure modeling and site-directed mutagenesis with whole-cell and single-channel patch-clamp analysis to unravel the molecular mechanism by which the voltage-sensing domains of calcium channels determine their specific gating properties.

Methods: Site-directed mutagenesis of recombinant $Ca_V1.1$ channels; expression in heterologous cell systems and functional reconstitution of null-mutant muscle cells; functional analysis with whole-cell and single-channel patch-clamp recordings and with microfluorometry analysis using fluorescent calcium indicators.

References: Tuluc et al., 2015, Structure, 24:261-271; Tuluc et al., 2016 J. Gen. Physiology, 147:437-449; Flucher and Tuluc 2017, J. Physiol., 595:1451-1463; Campiglio and Flucher, 2017, Sci. Rep., 7:41003; Campiglio et al., 2018, PNAS, 115:1367-1381. Costè de Bagneaux et al., Channels, 12,249-261, 2018.

Salary: According to the rates of the Austrian Science Fund (FWF) for PhD students plus travel funds for international scientific meetings.

Contact: Univ.-Prof. Dr. Bernhard E. Flucher. Medical University of Innsbruck, Division of Physiology, Schöpfstraße 41, A-6020 Innsbruck, Austria
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Project 2: Calcium channels in congenital stationary night blindness (Koschak)

Photoreceptors are morphologically and physiological highly specialized light sensing cells of the retina where sustained release of glutamate from ribbon synapses is calcium dependent and L-type calcium channels (LTCC) serve as the predominant source for Ca2+ entry. Mutations in the CACNA1F gene encoding Cav1.4 LTCCs were identified among patients diagnosed with congenital night blindness type 2 (OMIM: 30071). Ongoing work investigates the pharmaco-therapeutic potential of retinal Cav1.4 LTCCs.

Methods: Functional analyses in isolated retinal neurons, retinal whole-mounts and slices (patch-clamp, slice electrophysiology); cell culture; retinal AAV gene-therapy.

References: Knoflach et al. (2015) Channels (Austin) 9(5):298-306; Seitter and Koschak (2018) Neuropharmacology 132:58-70. (Review); zur Nedden et al. (2018) J. Clin Invest; Pangrsic et al. (2018) Physiol Reviews (Review).

Salary: According to the rates of the Austrian Science Fund (FWF) for PhD students plus travel funds for international scientific meetings.

Contact: Ao. Univ. Prof. Alexandra Koschak, University of Innsbruck, Institute of Pharmacy, Pharmacology and Toxicology, Innrain 80/82, 6020 Innsbruck, Austria
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Project 3: Calcium channels in intra-islet cell communication (Meyer)

L-type calcium channels (LTCC) are crucial in controlling β-cell insulin synthesis and secretion, electrical activity, and β-cell mass. Recently, using zebrafish as a model to study diabetes risk factors, we showed that genetic loss of the α_{1C} subunit gene CACNA1C causes unsynchronized and glucose-independent β-cell excitation in combination with hyperglycemia. The goal of the PhD thesis project is to understand how altered channel function affects islet synchronized hormone release and paracrine modulation by combining genetic and in vivo calcium imaging approaches. For this project several calcium channel mutants and strains expressing different genetically encoded calcium indicators have already been generated.

Methods: Molecular genetics, CRISPR/CAS9 genome editing, high resolution in vivo and ex vivo calcium imaging, single cell and whole islet patch-clamp, histology, electron microscopy

References: Kimmel et al. (2015) **Sci. Rep.** 5, 14241; Freudenblum et al. (2018) Development 145, dev158477; Lorincz et al. (2018) Islets 10: 221-238; Kimmel and Meyer (2016) Meth Cell Biol. 134: 431-461 (Review)

Salary: According to the rates of the 'Kollektivvertrag' for PhD students plus travel funds for international scientific meetings.

Contact: Univ. Prof. Dr. Dirk Meyer, University of Innsbruck, Institute of Molecular Biology, Technikerstr. 25, A-6020 Innsbruck, Austria.
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Project 4: Voltage-gated calcium channels and synaptic functions (Obermair)

In the central nervous system voltage-activated calcium channels regulate calcium influx and mediate cell-cell signaling functions. Altered function of channel subunits α_1 or $\alpha_2\delta$ has been implicated in neuropsychiatric disorders such as autism and schizophrenia. Ongoing work in our laboratory provided novel insights into the role of specific subunits of pre- and postsynaptic calcium channels in synapse formation and glutamatergic and GABAergic synaptic transmission. The goal of the PhD thesis project is to understand how specific calcium channel subunit isoforms and splice variants regulate synaptic differentiation and how they contribute to aberrant synaptic functions and neuropsychiatric disorders.

Methods: Synapse structure/function analyses, experimental cell culture models, cell culture, high- and super-resolution fluorescent microscopy, histology, behavior, patch-clamp electrophysiology, electron microscopy.

References: Geisler et al. (2019), J Neurosci. 39:2581-2605; Wang et al. (2017), J Neurosci. 37:4679-4691; Fell et al. (2016) J Neurosci. 36:11024-11036; Stanika et al. (2016) Sci Rep. 6:34528; Stanika et al. (2015) Curr Mol Pharmacol. 8):95-101. (Review); Geisler et al. (2015) Gen Physiol Biophys. 34:105-118. (Review)

Salary: According to the rates of the Austrian Science Fund (FWF) for PhD students plus travel funds for international scientific meetings.

Contact: Assoz.-Prof. Mag. Dr. Gerald J. Obermair, Medical University of Innsbruck, Division of Physiology, Schöpfstraße 41, A-6020 Innsbruck, Austria
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Project 5: Calcium channels in regulation of dendritic complexity (Di Biase)

In the central nervous system L-type voltage gated calcium channels are prominently involved in regulation of dendritic complexity. However, the underlying signaling pathways and their regulation are surprisingly underexplored. An increasing body of evidence shows that calcium channels are involved in psychiatric disorders, intellectual disabilities, and ageing, all conditions characterized by the remodeling of the dendritic arbor. Ongoing results in our laboratory suggest that channel phosphorylation is intriguingly a key regulator of dendritic complexity. This project aims at understanding the channel phosphorylation dependent cellular biology underpinning dendritic complexity in hippocampal neurons.

Methods: Primary culture of hippocampal neurons, calcium imaging and fluorescent microscopy of synapses and dendritic development, immunofluorescence, whole cell electrophysiology, calcium signaling analysis via pharmacological treatments and transient transfection of dominant negative or constitutively active kinases.

References: Folci et al. (2018), J Biol Chem 293:1040-1053; Etemad et al (2014) J Neurosci 34:1446-61; Di Biase et al. (2011) J Neurosci 31:13682-94; Di Biase et al. (2008) J Neurosci. 28:13845-55

Salary: According to the rates of the Austrian Science Fund (FWF) for PhD students plus travel funds for international scientific meetings.

Contact: Dr. Valentina Di Biase, Medical University of Innsbruck, Institute of Molecular and Cellular Pharmacology, Peter-Mayr Strasse 1, Innsbruck, Austria.

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More information and application: The successful candidate will be part of the Neuroscience PhD program ***CavX-Calcium channels in excitable cells***:

- https://phd-school.i-med.ac.at/phd-programs/doctoralprogram/neuroscience/
- https://phd-school.i-med.ac.at/events/

General information

1. Program description

Voltage-gated calcium channels (Cav) are critical regulators of vitally important cellular functions ranging from muscle contraction to brain functions such as learning and memory. Given their manifold roles it is not surprising that calcium channels are linked to a growing number of human diseases. Hence understanding the structural complexity, composition, and molecular interactions of calcium channels is key for elucidating their roles in physiological functions and ultimately in disease.

In the CavX PhD program we combine the worldwide unique research focus on Cavs in Innsbruck with an excellent doctoral training in Neuroscience. To this end CavX builds on the excellent scientific and methodological expertise of the steadily growing Cav faculty in Innsbruck, which consist of a lively mixture of experienced and newly established research groups. Thus, CavX combines a strong scientific focus on calcium signaling in excitable cells in general and the role of Cavs in physiology and human disease in particular with a sound education in neuroscience. Scientifically CavX comprises projects on the structure-function relationships, specialized functions in vision and in hormone secretion, synaptic modulation and connectivity in brain disorders, as well as skeletal muscle function. These research topics are highly relevant for the pathophysiology and treatment of a variety of diseases including brain disorders (e.g. autism, anxiety), diabetes, night blindness, and myopathies.

CavX utilizes state-of-the-art methodologies including newly developed cell culture models, unique genetically modified mice, super-resolution microscopy, electrophysiology and mouse behavior, zebrafish technology, and molecular modeling and dynamics. All faculty members have a strong history of collaboration and PhD student training. This is evidenced by many joint publications, meetings, and joint research grants. The program also achieves high international visibility, e.g. by organizing the European Calcium Channel Conferences every three years, which brings the world leaders of the field to Innsbruck.

CavX students will be offered a variety of networking opportunities and thereby connect with the other students. CavX faculty will contribute expertise and novel state-of-the-art methodology to the entire Neuroscience program. These intensified interactions will fill an important niche, namely the education of cellular and molecular neuroscientists with a particular focus on cellular physiology. This focus is of increasing international importance, particular for the identification of new drug targets for the future treatment of diseases for which current therapeutic approaches are insufficient (e.g. autism).

2. Requirements

Candidates must hold a master's degree or equivalent in the life sciences, medicine, pharmacy or physics. Excellent command of English is indispensable. Accepted PhD students will be hosted at the PIs institutions at the Medical University of Innsbruck or at the University of Innsbruck. The PhD student salary is according to the rates of the Austrian Science Fund (FWF) for PhD students plus travel funds for international scientific meetings (link). Applications must be received by **January 6, 2020!**

Speaker of the program: Assoz.-Prof. (PD) Mag. Dr. Gerald J. Obermair