Theodor Kocher Institute (TKI)

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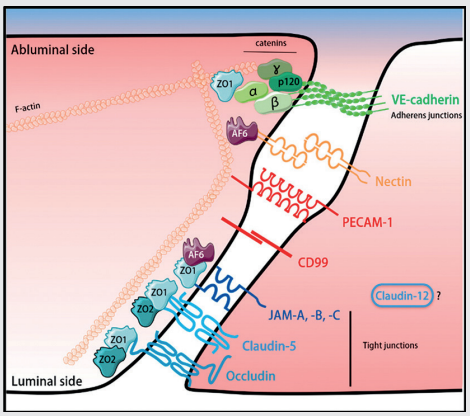
Profile

- Teaching bachelor and master students of the Medical, Science and Vetsuisse faculties in lectures and practical classes in immunology, vascular and cell biology. Educating graduate students of the Graduate School for Cellular and biomedical Sciences (GCB). Coordinating national PhD programs "Cell Migration" and "Cutting Edge Microscopy".
- The TKI hosts 5 research groups studying central nervous system immunity in health and disease with a focus on multiple sclerosis, stroke, Alzheimer's disease and brain metastasis of tumors by employing advanced in vitro and in vivo imaging aproaches.
- External partners: Prof. Thorsten Buch, University Zurich, Switzerland; Prof. Christer Betsholtz, Uppsala, Sweden, Dr. Yann Decker, University of the Saarland, Germany; Prof. Michael Detmar, ETH Zurich, Prof. Tobias Dick, University Heidelberg, Germany; Prof. Fabien Gosselet, University of Lens, France; Prof. Mikio Furuse, Kyoto University Faculty of Medicine, Japan; Prof. Jean-Charles Guery, INSERM, Toulouse, France; Prof. Jan Klohs, Neuroscience Center Zurich, Switzerland; Prof. Takashi Kanda, Yamaguchi University, Japan ; Prof. Martin Kerschensteiner, LMU Munich, Germany; Prof. Harm-Anton Klok, EPFL, Lausanne, Switzerland; Prof. Hans Lassmann, Vienna, Austria; Prof. Roland Liblau, INSERM Toulouse, France; Prof. Gianluca Matteoli, KU Leuven, Belgium; Prof. James McGrath, University of Rochester, NY, USA; Prof. Renaud du Pasquier, CHUV, Lausanne, Switzerland; Prof. Marco Prinz, University Hospital Freiburg, Germany, Prof. Federica Sallusto, ETH Zurich, Switzerland; Prof. Eric Shusta, Univesity of Madison-Wisconsin, USA

Grants

- Swiss National Science Foundation (grants 310030_189080, 31003A_170131, 310030_189226), EU Horizon 2020 MSCA-ITN 2015-675619 BtRAIN and MSCS-ITN-2018-813294 ENTRAIN; Fidelity Bermuda Foundation; ARSEP, Swiss MS Society; Bangerter-Rhyner Foundation; Scherbarth Foundation, Theodor Ott Fund, David and Betty Koetser Foundation; Swiss Heart Foundation, UniBE ID grant, Synapsis Foundation, Heidi Seiler Stiftung, UniBern Forschungsstiftung

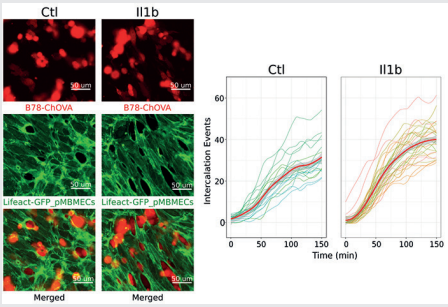
Highlights



Schematic representation of the molecular composition of BBB tight junctions

Molecular composition and function of blood-brain barrier tight junctions

Complex tight junctions (TJs) between brain microvascular endothelial cells forming the blood-brain barrier (BBB) block uncontrolled paracellular diffusion of molecules across the BBB. Our studies advanced understanding of the molecular composition of BBB tight junctions and identified a novel role for BBB cell-to-cell contacts in regulating T-cell trafficking across these cellular junctions of the BBB ensuring central nervous system immune surveillance.
Castro Dias et al., 2019, Sci Rep. 9(1):203); Castro Dias et al., 2019, FBCNS, 16(1):30; Castro Dias et al., Int J Mol Sci. 20(21), pii: E5372; Wimmer et al., 2019 Front Immunol, 5;10:711



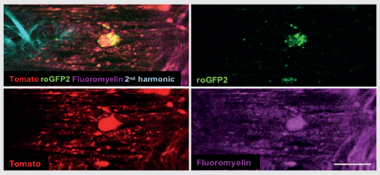
Inflamed condition of the in vitro BBB (pMBMECs, Il1b) led to significant stronger melanoma cell (B78chOVA) intercalation compared to control (Ctl).

Brain metastasis formation: Melanoma cells breach the blood-brain barrier

Prior to colonization of the brain, metastatic melanoma cells breach the BBB. We have developed a high-throughput live cell imaging setup combined with an automated evaluation pipeline to identify inhibitors of this process. Proof-of-concept experiments confirmed applicability: Inflammatory conditions of the BBB accompanied by impaired barrier properties significantly increased melanoma cell intercalation with the BBB when compared to control conditions of the BBB.

Oxidative pathology in mitochondria of oligodendrocytes

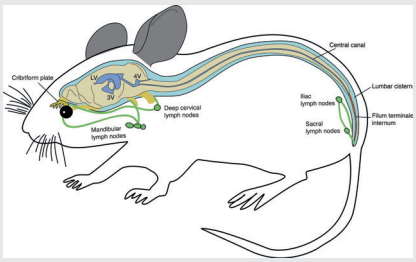
We have established a novel transgenic mouse model which allows imaging of oxidative pathology in oligodendrocyte mitochondria by 2-photon microscopy. By expressing a reporter protein sensitive to variations in oxidative agents (Orp1-roGFP2), specifically in mitochondria of myelin-producing oligodendrocytes, we can visualize - at a single organelle level - dynamic redox changes in the spinal cord of anesthetized animals. After establishing the surgical approach and data analysis, we now move toward dissecting the mechanisms of mitochondrial pathology during the development of anti-CNS inflammation.



Mitochondrial fluorescence from the cervical spinal cord of a MOG-mitoORP1-roGFP2 x Ai14 mouse image with 940 nm excitation by 2-photon microscopy. In cyan, collagen signal; in green, mitochondrial signal; in red, cytosolic ODC signal, in magenta, myelin sheaths. Scale bar, 20 um

Clearance of cerebrospinal fluid from the sacral spine through lymphatic vessels

We have recently shown with dynamic in vivo imaging that routes of outflow of CSF in mice occur along cranial nerves to extracranial lymphatic vessels rather than directly to venous blood as commonly assumed. In this project, we used near-infrared and magnetic resonance imaging to demonstrate a cranial-to-caudal flow of CSF tracers within the spinal column and revealed that the major spinal pathways for outflow occurred to lymphatic vessels at the sacral region. Outflow of CSF from the spine to lymphatic vessels may have significance for many conditions, including multiple sclerosis and spinal cord injury.
Ma Q et al., J Exp Med 2019 : 216 (11), 2492-2502



Overview of CSF efflux sites in mice

Successful finalization of the international PhD program BtRAIN

The EU Horizon 2020 funded ITN BtRAIN coordinated by Britta Engelhardt was successfully finished. BtRAIN has created novel knowledge on the vertebrate brain barrier signature genes and their specific role in regulating brain barriers function in development, health, ageing and disease. BtRAIN has educated 12 young brain barrier researchers in an interdisciplinary manner allowing them to obtain unique skills and thus making them highly desired researchers in the academic and non-academic sector in the brain barriers field.

The 12 BtRAIN students at the final BtRAIN meeting