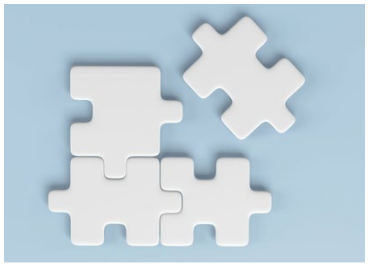

Sinergia grant with participation of the Theodor Kocher Institute approved.

As the prevalence of Alzheimer's disease and Multiple Sclerosis continues to increase, so does the pressure to find suitable treatment options – and with it the need to decipher the physiologic underpinnings of these pathologies. This includes the metabolite clearance and immune surveillance functions of the cerebrospinal fluid (CSF), as well as immune privilege established by the brain barriers, which are disturbed during neuroinflammation. In this Sinergia project funded by the Swiss National Science Foundation, we will investigate how CSF dynamics and brain barriers change with age, neuroinflammation, and neurodegeneration.

There is currently no consensus on the production mechanisms, exit locations, driving forces, and flow routes of central nervous system (CNS) fluids. To comprehend CNS diseases with cerebrospinal fluid (CSF) involvement, we must thus first establish the fundamental physiologic mechanisms of CSF dynamics. To this end, we will combine in vivo synchrotron radiation-based micro computed tomography, magnetic resonance imaging, near-infrared and two-photon fluorescence imaging of CSF pathways and CNS barriers in recently developed reporter mice. We will employ computational modeling to consolidate the acquired data. Our aims are to 1) establish a comprehensive overview of the physiologic basis of CSF dynamics, associated transport processes, and corresponding CNS barriers in mouse models, 2) analyze changes due to aging, neuroinflammation, and neurodegeneration, and 3) provide to the scientific community unrestricted access to hardware designs, experimental protocols, software, and data. Our work will not only contribute to the understanding of the involvement of CNS fluids and barriers in establishing CNS homeostasis and immune privilege, but also in neuroinflammatory and neurodegenerative pathologies including multiple sclerosis and Alzheimer's disease. It will further serve as a steppingstone for the scientific community towards the identification of targets for drugs as well as non-pharmacological interventions.
The project consortium includes the teams of Britta Engelhardt and Steven Proulx (Theodor Kocher Institute, University of Bern), Bert Müller (Biomaterials Science Center, University of Basel), and of Vartan Kurtcuoglu (Institute of Physiology, University of Zurich). Vartan Kurtcuoglu is specialized in the study of mammalian fluid physiology, with emphasis on the CNS, using image-based computational methods. Bert Müller investigates the application of physics to medically relevant challenges, with one of his foci being hard X-ray-based imaging down to the molecular level. Steven Proulx has developed innovative in vivo imaging techniques to visualize the function of lymphatic vessels and the flow of CSF in mouse models. He focuses on elucidating the mechanisms of CSF outflow to lymphatics and how this process plays a role in neurological disorders. Britta Engelhardt is specialized in CNS barriers research. She uses advanced in vivo and in vitro imaging technologies to elucidate the role of the CNS barriers in regulating immune cell trafficking into the CNS, and thus CNS immune privilege and neuroinflammation. https://data.snf.ch/grants/grant/213535