Open PhD position at the Institute of Cell Biology, Medical University of Innsbruck, Austria.

We offer 1 fully funded PhD position with immediate effect located at the Institute of Cell Biology, Biocenter, Medical University of Innsbruck and supervised by **Ass.-Prof. Georg-Friedrich Vogel** (Cell Biology, Paediatrics I). The project is embedded within the PhD program Molecular and Cellular Basis of Diseases (MCBD) at the Medical University of Innsbruck, Austria. This interdisciplinary PhD program addresses the molecular control of metabolism & inflammation and connect basic life science and computational biology with medicine.

To read more about the program and the requirements, please use the following link: https://phd-cbdiseases.i-med.ac.at/

Project: Delineating hepatocytic apical trafficking defects in cholestatic liver disease
In enterocytes, myo5b dependent apical trafficking has been precisely characterised in several studies, including our own. Myo5b interacts with the Rab small GTPases rab8a and rab11a in order to transport cargo vesicles to the apical plasma membrane. There, interaction with the exocyst subunit sec15 allows tethering of the vesicle and subsequent vesicle-plasma membrane fusion is mediated via a SNARE complex formed by vamp8, slp4a, STXBP2 and syntaxin3. The resulting cargo-mislocalisation gives rise to MVIDs enteropathy. Recently, our genetic analysis further identified mutations in *STX3* and *STXBP2* genes causative for microvillus inclusion disease (MVID).

In hepatocytes however, cargo trafficking to the apical bile canaliculus is understood to a far lesser degree. A study could show that both myo5B and rab11 are required for the formation of bile canaliculi. Defects in the establishment of proper hepatocyte polarity can result in liver disease. Further evidence was published recently showing that only missense, presumably via a dominant-negative effect, rather than nonsense mutations or loss of *MYO5B* cause MVID associated cholestatic liver disease (CLD). This implies that loss of myo5b does not affect apical trafficking. Furthermore, the apical SNARE protein syntaxin3 seems not be expressed in hepatocytes. How vesicles are shuttled towards the apical plasma membrane, hence the patho-mechanism of myo5b related CLD remains to be elucidated.

We hypothesize that apical cargo trafficking in hepatocytes is orchestrated by a protein machinery of different composition as compared to enterocytes. In order to better understand and develop potential disease modifying compounds, we plan to study the subcellular pathophysiology in detail. This project aims to characterize the several essential constituents of apical cargo transport in hepatocytes:

(i) Which motor protein is responsible for transport of vesicles leaving the Golgi/trans-Golgi compartments? (ii) Which are the vesicle-motor-adaptors involved (e.g. Rab small GTPases)? (iii) What is the composition of the trans-SNARE-complex at the apical face of the hepatocytes (that form the bile canaliculus)? (iv) How does experimental cholestasis match the clinical, serological and histopathological presentation of CLD patients?

The proposed research project will be carried out in the human hepatocyte cell line HepG2 which grows polarised and forms proper bile canaliculi between the cells, and will comprise protein localization and interaction studies, as well as functional assays on proper hepatocyte polarity formation and apical cargo transport.

Contact:
georg.vogel@i-med.ac.at

Job Category: PhD