



ERC-funded PhD position at the University Hospital Heidelberg

The newly created **Nephrogenetics unit** headed by **Matias Simons** is looking for a PhD student to join our research group at the Institute of Human Genetics of the University Hospital Heidelberg. The position will be funded by an **ERC Consolidator Grant**. The general interest of the lab is in the **molecular mechanisms underlying hereditary kidney and metabolic diseases**. Most of these diseases are caused by single-gene defects and thereby offer unique opportunities to decipher fundamental regulatory pathways of human physiology and to develop targeted diagnostic and therapeutic options. We are particularly interested in diseases affecting renal proximal tubules, a nephron segment specialized in protein and lipid endocytosis. Recent publications include Bedin et al, J Clin Invest 2020; Marchesin et al, Cell Rep 2019; Goncalves et al, PloS Genetics 2018; Simons, JASN 2018; Rujano et al, J Exp Med 2017; Trepiccione et al, JASN 2016; Gleixner et al, Cell Rep 2014. We combine human genetics with several experimental approaches, including fly and mouse genetics, cell culture, microscopy and biochemistry. More information can be found at www.simons-lab.de.

Project description: The rate of chronic kidney disease is on the rise worldwide. Many forms of chronic kidney disease are featured by the loss of albumin into the urine (albuminuria). When the cause of albuminuria lies within the glomerulus, such as in diabetic kidney disease, then the albumin overload in the tubular lumen may lead to damage of the downstream tubular cells, especially when albumin carries toxic fatty acid species. Particularly vulnerable are proximal tubular cells (PTCs), because these cells are specialized in protein reabsorption and have a high metabolic demand. Using a proximal tubular cell culture system that mimicks the albumin-lipid overload, we were able to show that albumin-bound saturated but not unsaturated fatty acids cause cytotoxicity. We could further show that the saturated fatty acid palmitic acid (PA) causes ER stress when incorporated into phospholipids, an effect that was reversed upon co-incubation with the unsaturated fatty acid oleic acid (OA). Using RNA-sequencing, we were able to identify a hitherto uncharacterized lipid-binding protein that is strongly downregulated by PA and upregulated by OA. In the proximal tubules of the kidney this protein seems to be highly expressed. Moreover, its gene locus associates with changes in serum LDL-cholesterol in genome-wide association studies (GWAS). Therefore, we speculate that this protein is a previously uncharacterized player in lipid metabolism with potential relevance for renal diseases such as diabetic kidney disease.

We now offer an exciting project aimed at the functional characterization of this protein. The PhD candidate will use a variety of cell and molecular biology techniques. As experimental systems, she/he will employ cell culture and potentially *Drosophila* and/or mouse. The projects will be carried out in a stimulating work environment with scientific collaborations within the institute, across the Heidelberg life science community (e.g. EMBL, DKFZ) and worldwide.

Qualifications: We invite applications from individuals with a solid background in molecular cell biology. The successful applicant will have good communication and organisational skills and a Master degree in a relevant area (or be in the final stages of completion). We also invite applications from research-oriented MDs. Candidates are expected to be highly motivated and to work independently with a strong work ethic.

Application will be via the Heidelberg Biosciences International Graduate School (HBIGS) website: <http://www.hbigs.uni-heidelberg.de>. The deadline is Dec 31st, 2020.

Keywords: kidney, lipotoxicity, lipid metabolism, mitochondria, endoplasmic reticulum, diabetic kidney disease, genome-wide association studies