CSC-RUB PhD Project Proposal

Title: Targeting glycosome biogenesis by small molecules to provide novel therapeutic routes to treat parasite diseases

Sector of research: Biochemistry, Molecular Cell Biology, peroxisomal protein transport

Degree awarded: PhD/Dr. rer. nat in Biochemistry or Biology

Keywords: glycosomes, protein import, parasite diseases, drug screening

Supervisor of PhD project:

Prof. Dr. Ralf Erdmann, Medical Faculty, Dept. of Biochemistry and Pathobiochemistry, Ruhr University Bochum

Email: ralf.erdmann@rub.de

Research focus of supervisor:

Research focus is on the function and biogenesis of peroxisomes or glycosomes as they are named in certain parasites. These organelles have the ability to import folded or even oligomeric proteins into their matrix. For this, peroxisomes harbour a complex matrix protein import machinery consisting of several so-called peroxins, including cycling receptors, a docking complex, an ubiquitination machinery and an export machinery which extracts the ubiquitinated receptor protein for deubiquitination in the cytosol and subsequently another round of import. In our group, we investigate the underlying mechanisms of the peroxisomal protein import, the peroxisomal biogenesis, as well as the effect of peroxisomal dysfunction on our three model organisms (*Saccharomyces cerevisiae*, *Homo sapiens*, and *Trypanosoma brucei spp.*). The group hast established disruption of glycosome biogenesis as a novel target for drug development against trypanosomal diseases. For our research, we utilize a broad spectrum of methods including fluorescence microscopy, molecular biological methods (e.g. SDS-PAGE, Western blotting), cell fractionation, and plate-based assays. Utilizing these methods, as well as cooperations with experts in electron microscopy, crystallography, electro physiology, and mass spectrometry, our group strongly contributed to the understanding of peroxisomal biogenesis and protein import, as well as the identification and characterization of the 37 known peroxins. Major contributions of the group to the field were the discovery of the AAA-family of ATPases, the discovery of the first peroxin, the identification and functional characterization of the identification of the peroxisomal protein translocation pores, and the identification of glycosomal protein import as drug rated against parasite diseases.
Publications:


H-index of the last 5 years: 8 number of publications in the last 5 years: 28

Second Supervisor of PhD project

Prof. Dr. Raphael Stoll (Biochemistry), Prof. Dr. Thomas Günther-Pomorski (Biochemistry), or Prof. Dr. Stefan Herlitze (Biology)
Summary of research plan

**Background:** Trypanosoma are parasitic protists, which cause deadly diseases (trypanosimases), such as sleeping sickness, Chagas disease, and Leishmaniasis. There is an urgent medical need especially for novel drugs against Chagas disease and Leishmaniasis, devastating diseases that affect about 18 million people worldwide.

**Study objective:** Glycosomes require protein import to maintain their function. Peroxins (PEX-proteins) are responsible for recognition and transport of glycosomal proteins to the organelle. We could show that the disruption of this transport is suitable as a novel target for drug development against trypanosomal diseases (Davidowski et al, 2017). The aim of the PhD-project is the identification of new protein-protein interfaces of peroxins as possible drug targets and their application for inhibitor screening.

**Expected Results:** Identification and characterization of novel protein-protein interfaces as drug targets of the glycosomal protein import machinery. The suitability of the new binding interfaces as drug targets will validated and small molecule inhibitors will be identified that exhibit potent and selective trypanocidal activity in vitro and in vivo. These findings will establish a novel concept for effective drug development against trypanosomiasises and beyond.

**Methods:** Purification of recombinant proteins via established affinity and ion exchange chromatography. Study of protein-protein interactions by well-established assays, including two-hybrid analysis, affinity chromatography, co-precipitation and pull-down studies. Alpha-screen based interaction studies, screening of compound libraries, cytotoxicity assays with parasite and human tissue cultures, fluorescence microscopy, computational biology.

**Candidate Requirements:** Candidates should have a master’s degree in biology, biochemistry, microbiology or a related discipline. Experience with molecular biological methods and working with recombinant proteins is highly advantageous. Experience working with microorganisms (E. coli, S. cerevisiae, Trypanosoma) is helpful. Good English language skills are required.

**Motivation for CSC application:** The successful applicant will receive stringent and in-depth training in the broad variety of techniques required for the project stated above. PhD candidates will be supported by a team of highly skilled technicians as well as senior scientists. The Department of Biochemistry and Pathobiochemistry hosts scientists from all over the world with varied scientific backgrounds. The PhD project will be closely supervised by Prof. Dr. Ralf Erdmann, who is an internationally recognized researcher in the peroxisome field. State of the
art infrastructure and expertise is available for all elements of the projects. PhD candidates will be integrated into either the International Graduate School of Biology (IGB) or the Graduate School of Chemistry and Biochemistry (GSCB).