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PhD Position in Biosciences

Heidelberg, February 2019

- Project Title:** The adhesion of malaria-infected red blood cells
- Project leader:** Prof. Dr. Michael Lanzer (Heidelberg University Hospital, Centre for Infectious Diseases, Parasitology Unit, INF 324, 69120 Heidelberg, Germany)
- Start of PhD project:** as early as April 2019
- Source of Funding:** German Research Council and the Sumaya Biotec Company

Project Description:

Cytoadhesion of red blood cells (RBCs) infected by *Plasmodium falciparum* (iRBCs) to the vascular endothelium avoids clearance by the spleen and is the main cause for the clinical symptoms of the disease malaria. Cytoadherence results from the remodelling of the wildtype RBC by the malaria parasite. After invasion, the parasite starts to export hundreds of effector proteins into the host cell that lead to profound changes in the iRBC's spectrin cytoskeleton underlying the plasma membrane. In particular, actin is mined from the network and used to build new transport pathways to the plasma membrane. In addition, the spectrin network increases its pore size and a system of adhesive knobs is established. While knob-associated histidine-rich protein (KAHRP) self-assembles into spiral-shaped platforms underneath the plasma membrane, *Plasmodium falciparum* erythrocyte membrane protein-1 (PfEMP1) inserts into these and forms the adhesive clusters that can bind endothelial factors such as CSA, CD36 or ICAM1.

The PhD project will focus on the molecular changes to the spectrin network that underlie these cell-level processes. The starting point will be the generation of parasite lines that feature mutations in KAHRP, the main constituent of the knobs. KAHRP contains several protein binding domains and is known to interact with both parasite and host factors to form knobs and the cytoadhesion complex. For instance, KAHRP interacts with several membrane skeletal proteins of the host erythrocyte, including spectrin, actin and ankyrin. KAHRP further self-aggregates and it can bind to the cytoplasmic domain of PfEMP1. We will ablate certain binding domains of KAHRP using CRISPR/CAS9 genome editing technology and will investigate the effect on cytoadherence and the spectrin membrane skeleton in *P. falciparum*-infected erythrocytes. To this end, we will image the corresponding changes to the spectrin network and the knobs using scanning electron microscopy (SEM), cryo-EM, atomic force microscopy (AFM) and super resolution microscopy (RESOLFT, STORM). The PhD project will be tightly linked to the group of Prof. Schwarz who are experts in multi-scale mathematical modeling of cell movement in shear flow. The Schwarz group will predict how such changes should translate into cytoadhesion, and the predictions will be tested experimentally in flow chamber experiments.

References:

1. Lansche C, Dasanna AK, Quadt K, Fröhlich B, Missirlis D, Tétard M, Gamain B, Buchholz B, Sanchez CP, Tanaka M, Schwarz US, Lanzer M. (2018) The sickle cell trait affects contact dynamics and endothelial cell activation in *Plasmodium falciparum*-infected erythrocytes. *Commun Biol.* 1:211.

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2. Dasanna AK, Lansche C, Lanzer M, Schwarz US (2017) Rolling adhesion of schizont stage malaria-infected red blood cells in shear flow. *Biophys J.* 112:1908-1919.
3. Cyrklaff M, Srismith S, Nyboer B, Burda K, Hoffmann A, Lasitschka F, Adjalley S, Bisseye C, Simpore J, Mueller AK, Sanchez CP, Frischknecht F, Lanzer M (2016) Oxidative insult can induce malaria-protective trait of sickle and fetal erythrocytes. *Nat Commun.* 7:13401.
4. Helms G, Dasanna AK, Schwarz US, Lanzer M (2016) Modeling cytoadhesion of Plasmodium falciparum-infected erythrocytes and leukocytes-common principles and distinctive features. *FEBS Lett.* 590:1955-71.
5. Cyrklaff M, Sanchez CP, Kilian N, Bisseye C, Simpore J, Frischknecht F, Lanzer M (2011) Hemoglobins S and C interfere with actin remodeling in Plasmodium falciparum-infected erythrocytes. *Science* 334:1283-6.

Methods that will be used:

super resolution microscopy; molecular cloning; cell culture; transfection of *P. falciparum*; CRISPR/CAS9-based genome editing; confocal microscopy; flow chamber experiments; scanning electron microscopy, electron microscopy; atomic force microscopy

Collaboration Partners:

This is a joint project with Prof. Ulrich Schwarz from the Department of Theoretical Physics; Heidelberg University.

Profile of candidate's qualification:

Qualified candidate should have a degree from an internationally accredited institution of higher education. Technical skills in molecular cloning, cell culture, super resolution microscopy are desirable. Interest in interdisciplinary collaborations is highly desirable.

Keywords:

Plasmodium; CRISPR/Cas9; malaria; high-resolution microscopy; cytoadhesion; cytoskeleton; spectrin; actin; biomechanics.

Payment will be according to the German TV-L, E13 (part-time: 65%). Applications are to be submitted via the online application tool of the local Graduate School HBIGS https://hbigssystem08.de/intern/reg_registration_for.php (project reference: Lanzer0119). Questions pertaining to the project may be addressed to jobs.para@med.uni-heidelberg.de.

Heidelberg University Hospital is strongly committed to promoting equality and diversity. People with disabilities are given priority with the same suitability. Appointment will always be made on merit.

