Severe malaria risks health and lives of mainly children in subtropical areas (WHO 2011) and is related to Plasmodium falciparum parasites invasion and asexual proliferation cycles in host erythrocytes. However, individuals with mutated hemoglobin such as sickle cell, thalassemia, and other hemoglobinopathies are protected from severe outcomes of malaria. Central to Plasmodium pathogenesis is the cytoadhesion of infected erythrocytes to the endothelium and intracapillary sequestration (Voss 2006). The blood stages parasites produce cyto-adhesins (PfEMP1) that are transported through the cytosol of host erythrocyte and presented on the surface. This poses a challenge for the parasite as the entire transport machinery must be assembled de novo.

Using cryo-electron tomography, we have viewed into whole, intact erythrocytes infected with P. falciparum (Cyrklaff 2011, Cyrklaff 2012) (Fig 1). The tomograms revealed that the parasitic assemblies in host erythrocyte, such as Maurer’s clefts, tubulo-vesicular networks and knobs are interconnected via elaborated networks of actin filaments (Fig 1A). The parasite majorly remodels the actin networks from what was seen in uninfected erythrocytes (Fig 1B) and used it to its own benefits. Numerous vesicles were attached to the networks and we proposed that the parasite uses the vesicular transport along actin filaments to facilitate presentation of the adhesins at the erythrocytic surface.

Markedly, the actin networks appeared incomplete in Plasmodium infected sickle cells (Fig 2). This presents a likely explanation for the protective mechanism of sickle erythrocytes, whereby the parasite was not capable of remodelling the host actin cytoskeleton. We attributed this to differences in actin polymerization dynamics in the presence of denatured hemoglobin, the process that we also verified in vitro (Cyrklaff 2011). The mechanism of interference in the transport of malicious adhesins to cell surface is similar for homo- and heterozygotic hemoglobinopathies. The latter are of particular medical interest, as the protection against malaria is not compromised by disorders associated with strong phenotypes such as sickle disease and thalassemia major.

What we have learned from natural protection we want to apply in practice. We try to replicate the protective role of sickle cells in normal erythrocytes by interfering with the parasitic export through host cytoplasm. This concept is worth pursuing as, when successful, it would eliminate the problem of resistance, similarly to the fact that there is no parasites resistant against the structural hemoglobinopathies.

Acknowledgement: This work is supported by the grant from the Bill and Melinda Gates Foundation (Grand Challenges Explorations; grant number OPP1069409)
Fig. 1: Sections through cryo-electron tomograms and surface rendered views of (A) P. falciparum-infected erythrocyte containing normal HbAA hemoglobin; (B) uninfected HBAA erythrocyte; PM, erythrocyte plasma membrane (dark blue); K, knobs (red); V, vesicles (cyan); MC, Maurer’s clefts (cyan); filaments (yellow)-arrowheads. Scale bars: 100 nm

Fig. 2: Section through cryo-electron tomogram and surface rendered view of P. falciparum-infected erythrocyte containing mutated HbCC hemoglobin; colours and marking as in Fig 1. Scale bar: 100 nm