Summary

Malaria is a major public health problem in the tropical world. Annually human malaria accounts for about 500 million clinical cases and 1-2 million deaths worldwide. Five Plasmodium species are reported to infect humans, of which *Plasmodium falciparum* causes the most severe form of malaria. Almost all the malaria related deaths are attributed to *P. falciparum* infections, mostly in young children. *P. falciparum* infected erythrocytes (IEs) exhibit cytoadherence phenotypes that are among its virulence mechanisms. These cytoadherence phenotypes include adhesion to vascular endothelium, platelet-mediated clumping and rosetting. Adhesion involves binding of mature stage *P. falciparum* IEs to host vascular endothelium. Platelet-mediated clumping involves formation of clumps of IEs bridged by platelets. Rosetting involves binding of IEs to uninfected erythrocytes (UEs) to form rosettes. Cytoadherence causes sequestration of IEs, clumps and rosettes in the host vasculature. Sequestration in host vasculature may lead to obstruction in vascular blood flow, endothelial cell activation and release of proinflammatory cytokines. Sequestration in certain organs such as brain and placenta is implicated in the pathology of severe malaria.

*P. falciparum* adhesion phenotypes are mediated by specific receptor-ligand interactions. Host molecules involved in adhesion are termed as 'receptors', whereas parasite counterparts are called 'ligands'. Receptors for adhesion to host vascular endothelium include thrombospondin (TSP), CD36, intercellular adhesion molecule 1 (ICAM1), CD31 and chondroitin sulfate A (CSA). Two receptors CD36 and P-selectin have been identified for platelet-mediated clumping. Parasite ligands that mediate adhesion belong to the *P. falciparum* erythrocyte membrane proteins-1 (PfEMP1) family, which are encoded by var genes. About 60 var genes exist in a *P. falciparum* genome. Switching of var gene expression attributes new adhesive phenotypes to the parasite and is a mechanism for the parasite to evade host immune responses.

This study reports the identification of gClqR, a 32 kD protein as a novel receptor for *P. falciparum* adhesion and platelet-mediated clumping. gClqR is expressed on variety of host cells such as human brain microvascular endothelial cells (HBMEC), primary human brain microvascular endothelial cells (PBMEC), human umbilical vein endothelial cells (HUVEC) as well as resting and activated platelets. *P.
Summary

*Plasmodium falciparum* IEs can use gC1qR as a receptor to adhere to HBMEC and PBMEC as well as for platelet-mediated clumping. Potential *P. falciparum* ligand that mediates adhesion to gC1qR is identified as a PfEMP1 encoded by var gene PFD1015c. To test the role of *P. falciparum* cytoadherence phenotypes in severe malaria, we carried out an age and gender matched case control study in a malaria endemic region of southern Mozambique. For the study, we recruited children presenting with severe and mild malaria at Manhica Health Research Center, Manhica Mozambique. In this study we find evidences that platelet mediated clumping is associated with severe malaria, severe anaemia and prostration, suggesting that platelet-mediated clumping is an important virulence factor of *P. falciparum*. Moreover, we observed that adhesion to gC1qR is associated with multiple seizures. Association of adhesion to gC1qR with multiple seizures, a severe malaria symptom involving central nervous system complications suggests that adhesion of IEs to brain endothelium using gC1qR may be a pathological event. Moreover we observed a correlation between adhesion to gC1qR and adhesion to ICAM1, suggesting that *P. falciparum* uses similar mechanisms for adhesion to gC1qR and ICAM1. ICAM1 which is implicated in cerebral malaria is expressed on HBMEC and PBMEC like gC1qR. gC1qR may have an important role in pathophysiology of cerebral malaria, however, this could not be determined in this study because there were only 3 cerebral malaria patients. Studies with larger sample size are needed to evaluate the role of gC1qR in cerebral malaria.