

## **Molecular basis of the host-specificity of malaria merozoites (*Plasmodium*).**

Malaria is a disease caused by parasites called *Plasmodium* and transferred via female mosquito (*Anopheles*) bites. Only five genus of *Plasmodium* is able to infect humans. The most malignant of them – *Plasmodium falciparum* – belongs to subgenus *Laverania* and is more related to ape-infecting parasites, especially *P. reichenowi* infecting chimpanzees and *P. praefalciparum* infecting gorillas. Despite high genetic similarity, they are very host-specific. Main differences were observed in genes connected to erythrocyte invasion, the step believed as the most important for *Plasmodium* development.

One of proteins participating in erythrocyte invasion is EBA-140 ligand. Glycophorin C is its receptor on human erythrocytes and its homolog from *P. reichenowi* recognizes its truncated form, Glycophorin D on chimpanzee erythrocytes. EBA-140 binding is sialic acid-dependent. Sialic acid pattern on human and ape erythrocytes differ from each other and this factor was proposed as explanation for *Plasmodium* host-specificity.

The aim of this doctoral project was to examined if the theory proposing that the host-specificity of *Plasmodium* parasites is based on the difference in specificity of EBL ligands for SA compared to the EBA-140 ligand. In this research I used recombinant full ectodomain of EBA-140 homologs of three *Plasmodium* species (*P. falciparum*, *P. praefalciparum* and *P. reichenowi*) infecting humans and apes, respectively. Recombinant homologs were bound to Neu5Ac, main human SA, and Neu5Gc, that is dominant on ape erythrocytes. Specificity of recombinant full ectodomain EBA-140 homologs were examined with using surface plasmone resonance (SPR) and biolayer interferometry (BLI) methods. I confirmed that all three EBA-140 homologs recognized both SA and theirs binding level to Neu5Ac is weaker than to Neu5Gc, that is not expressed in human tissues.

Moreover, I generated *P. falciparum* transgenic lines in which I deactivated EBA 140 ligand or modified its binding region RII for binding region RII from EBA 140 *P. praefalciparum* homolog. I analysed changes in growth and invasion pattern to neuraminidase- and chymotrypsin-treated erythrocytes of those transgenic lines. I shown that RII modification for RII recognizing ape erythrocytes weakens the parasites bonding to human erythrocytes on similar level as EBA-140 knock-out. Nonetheless, EBA-140 ligand is not the main factor of erythrocyte invasion and its changes or dezactivation does not significantly change the level of invasion, what suggests that the invasion process is multifactorial and ligands can compensates for the lack of one of them.

Due to close evolutionary relationship between humans and apes, as well as *P. falciparum*, *P. praefalciparum* and *P. reichenowi* parasites knowing their invasion mechanisms brings us closer to understanding the basics of specificity and evolutionary processes that have taken place over the centuries and allowed *Plasmodium* to adapt to its new, human host.