



## INDO SWISS JOINT RESEARCH PROGRAMME (ISJRP)

### JOINT RESEARCH PROJECT

#### **ABSTRACT**

**Grant No.: 138850**

#### **MOLECULAR MACHINERY FOR APICAL ORGANELLE RELEASE DURING HOST CELL INVASION IN MALARIA**

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Indian PI: Dr. Chitnis E. Chetan, International Centre for Genetic Engineering and  
Biotechnology ICGEB, New Delhi

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Project finish date: 30<sup>th</sup> June 2014

#### **PROJECT ABSTRACT**

Malaria remains the most important parasitic disease worldwide and one of the outstanding challenge for global human health. About 40% of the world's population is currently at risk, 300-500 million cases of clinical malaria and more than 2 million deaths each year primarily children. To fight against this disease it is imperative to identify and validate novel drug and vaccine targets. Egress of merozoites from mature Plasmodium falciparum schizonts and reinvasion of erythrocytes are critical steps in the erythrocytic cycle of the malaria parasites. Here, we propose to study the signaling events and pathways that mediate these processes.

Parasite ligands that interact with host receptors to mediate erythrocyte invasion are localized in apical organelles that are referred to as micronemes and rhoptries. The timely release of these secretory proteins is critical for parasite egress and successful invasion. We have previously demonstrated that low potassium environment as found in blood plasma serves as an external signal for intracellular calcium surge that triggers the discharge of micronemes in P. falciparum merozoites during erythrocyte invasion. However, the mechanism by which these signals are relayed has not been explained. Here, we propose to determine the role of a calcium dependent phosphatase (calcineurin) and candidate factors implicated in organellar release of microneme proteins. These candidates are related to ferlins/synaptotagmins, which that are known to trigger exocytosis by acting in membrane fusion events, in different types of eukaryotic cells, such as exocytosis of the extensively studied synaptic vesicles. We propose to combine the expertise of Chetan's lab on calcium signaling in malaria with the experience of Soldati's lab in developing and applying novel reverse genetic methods in malaria parasites to study signal transduction pathways for microneme discharge and to identify novel parasite proteins involved in this process.

These studies will characterize and shed light on the function of calcium dependent proteins that are likely connected to the discharge of highly specialized organelles in the malaria parasites. As such, they will be part of the signaling cascade involved in release of microneme proteins in response to



external signals. In addition, this project has the potential to identify novel targets for the design of inhibitors that block translocation of apical organelle proteins and inhibit red cell invasion by malaria parasites. These studies will not only improve our understanding of the biology of blood stage malaria parasites but will also provide valuable leads to take forward in a translational drug development program with the hope to identify new targets for the development of novel interventions against malaria.