Instituto de Medicina Molecular

Master Project Proposal

Title: Mechanisms of inhibition of *Plasmodium* liver infection by amino acid supplementation

Synopsis:

Malaria is caused by *Plasmodium* parasites that are transmitted to their mammalian hosts through the bite of infected female *Anopheles* mosquitoes. *Plasmodium* sporozoites are deposited under the skin of their mammalian host and are carried by the circulatory system to the liver, where they invade hepatocytes. There, each sporozoite develops into an exoerythrocytic form (EEF), containing thousands of newly formed merozoites that are eventually released into the bloodstream where they invade red blood cells, initiating the symptomatic, erythrocytic stage of the disease.

During the liver stage of infection, parasites scavenge host pathways to their own benefit. Previous work from the host laboratory identified arginine metabolism and, more specifically, the polyamine synthesis pathway as being crucial for *Plasmodium* intra-hepatic development. This work also showed that appropriate amino acid supplementation results in a striking decrease of hepatic parasite load.

In this context, we now propose to deepen our understanding of the cellular and molecular mechanisms that underlie the effect of nutritional supplementation in *Plasmodium* infection.

This goal will be pursued through the use of state-of-the-art methodologies, including immunofluorescence microscopy, quantitative real-time PCR (qRT-PCR) and flow cytometry. The work will employ in established *in vitro*, *in vivo* and *ex vivo* models of infection and rodent models of *Plasmodium* infection.

Ultimately, we expect that this project will not only enhance our current knowledge of fundamental aspects of malaria biology, but also contribute significantly to the development of a low-cost, high-quality targeted nutritional supplementation that can be safely administered to the highest risk groups, reducing malaria morbidity and mortality.

Supervisor: *Patrícia Meireles, Prudêncio Lab, pmeireles@medicina.ulisboa.pt*

Co-Supervisor: *Miguel Prudêncio, Prudêncio Lab, mprudencio@medicina.ulisboa.pt*

Bibliography (facultative):

Prudencio, M.; Rodriguez, A.; Mota, M. M., The silent path to thousands of merozoites: the Plasmodium liver stage. *Nat Rev Microbiol* **2006,** *4* (11), 849-56.

Prudencio, M.; Mota, M. M.; Mendes, A. M., A toolbox to study liver stage malaria. *Trends in parasitology* **2011,** *27* (12), 565-74.

Zhu, X., et al., Supplement of L-Arg improves protective immunity during early-stage Plasmodium yoelii 17XL infection. Parasite Immunol, **2012**, 34(8-9): p. 412-20.

Olszewski, K.L., et al., Host-parasite interactions revealed by Plasmodium falciparum metabolomics. Cell Host Microbe, **2009**, 5(2): p. 191-9

Balmer, P., et al., The effect of nitric oxide on the growth of Plasmodium falciparum, P. chabaudi and P. berghei in vitro. Parasite Immunol, **2000**, 22(2): p. 97-106.

Remunerated or volunteer training: This is a VOLUNTEER training offer.