Instituto de Medicina Molecular Lisboa

Master Project Proposal

Title: Inhibition of *Plasmodium* liver infection by *Trypanosoma* parasites

Synopsis:

Malaria and sleeping sickness are tropical diseases that share overlapping geographical distributions in sub-Saharan Africa. Malaria is caused by *Plasmodium* parasites, which are delivered to their mammalian hosts in the form of sporozoites, through the bite of an infected *Anopheles* mosquito. *Plasmodium* sporozoites undergo an obligatory stage of infection in their host's liver, where they invade and develop inside hepatocytes to form exoerythrocytic forms (EEFs). *Trypanosoma brucei* (Tb) parasites, responsible for causing sleeping sickness, are transmitted to their mammalian hosts by the bite of a Tsetse fly. They proliferate in the bloodstream and interstitial spaces of multiple organs.

Although *Plasmodium* and *Trypanosoma* overlap geographically in different areas of sub-Saharan Africa, co-infections by these two parasites remain largely understudied. In order to overcome this gap, we established a new rodent co-infection model. Our results showed that an ongoing infection by Tb leads to a marked inhibition of a subsequent liver infection by *Plasmodium berghei* (Pb). This observation is at the core of the proposed project, whose objective is to elucidate the molecular mechanisms underlying the impairment of Pb hepatic infection by Tb.

The exciting results obtained in our array of preliminary experiments constitute the scaffold of the present proposal. In order to pursue our goals, we will employ state-of-the-art methodologies to address the hypotheses outlined above from different, complementary strategies. Specifically, we will employ (1) immunofluorescence and intravital confocal microscopy to fully characterize Pb liver infection phenotype in co-infected mice; (2) our rodent model to carry out co-infection experiments aimed at identifying the Tb molecular components responsible for Pb infection impairment; and (3) transgenic mice to evaluate the role of selected host molecules and pathways on the inhibition of Pb liver infection. Ultimately, we expect this project to contribute to the fight against malaria, by identifying the molecules responsible for the inhibition of *Plasmodium* infection and by elucidating the mechanisms that mediate the observed inhibitory effect of Tb.

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