3D hepatic cell models of Plasmodium infection

Research Plan

The screening of drugs that act on the hepatic stage of *Plasmodium* infection currently relies on the use of 2D cultures of hepatic cell lines. These, however, differ greatly from human liver hepatocytes in what concerns cell polarity, cell-cell interaction, metabolism and gene expression. As a result, many of the compounds identified in such assays as having a strong activity against the liver stage of infection don't hold when tested *in vivo*. 3D cell culture systems more closely resemble *in vivo* conditions, which makes them a better predictor of *in vivo* drug efficacy and toxicity. Therefore, our project aims at developing a 3D culture-based drug screening platform for the discovery of new anti-plasmodial drugs that can overcome these drawbacks.

In this project, funded by Merck, iBET (Instituto de Biologia Experimental e Tecnológica) will provide their expertise in 3D cell culture models while iMM (Instituto de Medicina Molecular) will provide the expertise concerning the hepatic stage of *Plasmodium* infection, in a collaborative effort to implement *Plasmodium* infection of 3D hepatic cell models. Initially, *Plasmodium berghei* will be used as a surrogate model of infection but the end goal will be the use of *Plasmodium falciparum*. The initial stages of optimization of infection of 3D hepatic cell models by *P. falciparum* will employ luciferase- and GFP-expressing *P. falciparum* sporozoites obtained from the dissection of infected mosquitoes purchased from RUMC (Nijmegen). Once optimized, this system will be validated for its capability to feed medium to high throughput drug discovery campaigns.