IN VIVO IMAGING OF *PLASMODIUM* PRE-ERYTHROCYTIC PHASE. VESSEL INVASION AND THE TROJAN HEPATOCYTE.

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The initial phase of *Plasmodium* infection in mammals is called pre-erythrocytic phase (PEP), which begins when a small number of sporozoites are injected by the mosquito into the dermis. These parasite reach the liver and develop in thousands of merozoites inside hepatocytes. The PEP ends with the release of merozoites into the blood. Using 4D intravital fluorescence microscopy, we imaged the PEP of fluorescent *P. berghei* in rodents, focused on how parasites get access to the blood circulation. After natural trasmission, the dermal sporozoites were highly motile and three distinct fates were observed: they invaded blood vessels and eventually reached the liver, invaded lymphatic vessels and accumulated in the draining lymph node, but also remained in the dermis, where a small proportion differentiated into merozoites. In the liver, we observed that infected hepatocytes generated buds filled with merozoites, which we called "merosomes". These merosomes crossed the endothelial barrier and protruded towards the lumen of sinusoids where they detached from the host cell and became individualized structures. The parasite also inhibited the translocation of phosphatidylserine to host cell/merosome membrane, avoiding being phagocytosed. In conclusion, sporozoite reaches the blood circulation by invading capillaries in the skin. Once in the liver parenchyma, the parasite manipulates the host cell to assure a safe release in the blood circulation, inside of a merosome.

Keywords: Malaria, Life Cycle, Host-cell interaction.