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Characterisation of Proteins Along the Secretory Pathway in the Blood Stages of the Malaria Parasite *Plasmodium berghei*

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Academic dissertation

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Abstract
Malaria remains a major global health concern that threatens 40% of the world's population. Despite advancements in the development of antimalarial drugs and vector control strategies, the disease is yet to be eradicated. The emergence of drug resistance, the lack of a highly effective vaccine, and incomplete transmission control emphasize the relevance of continued research towards malaria eradication. A better understanding of the parasite's biology is crucial to developing interventions for malaria. Nearly half of the *Plasmodium* genome is predicted to be essential for parasite survival, yet much of it remains uncharacterized—highlighting a pool of potential targets for novel treatments and vaccines. In manuscript 1, we present a scalable CRISPR-based genome editing system for the ubiquitously used rodent malaria model parasite *Plasmodium berghei* called PbHiT. This platform enables efficient and high-throughput functional genetic screening of parasite genes, providing a novel tool for malaria research that can be tailored to study essential genes. Malaria pathogenesis is closely tied to the asexual blood stage where the parasite exports proteins to remodel the host red blood cells (RBCs) to support its survival. In manuscript 2, we identify a novel *P. berghei* protein, EMAP3, which localizes to the iRBC membrane and interacts with the exported protein EMAP1. The localization of EMAP3 makes it a potentially valuable scaffold for displaying *P. falciparum* proteins, enabling *in vivo* screening of cytoadherence inhibitors. Continuing the focus on parasite proteins that mediate interactions with the host, manuscript 3 investigates two previously uncharacterized rhoptry-associated proteins, MAP1 and RhoSH, shown to be implicated in parasite virulence. These proteins are localized to parasite secretory organelles called the rhoptries and are likely injected into the host cell upon infection where they function to form or maintain the protective vacuole the parasite creates upon infection. Notably, MAP1 contributes to adipose tissue sequestration and MAP1 knockout parasites fail to induce host leptin production, which is associated with severe disease. Together, these findings advance our understanding of parasite-host interactions during the blood stage and help identify new molecular targets for therapeutic intervention and malaria eradication strategies.

Keywords
Plasmodium berghei, surface protein, infected red blood cell, EMAP1, CRISPR, protein export, gene editing

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