Discovery and Characterization of Potent, Efficacious and Orally Available Antimalarial Plasmepsin X Inhibitors

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Malaria is a serious mosquito-borne disease with an estimated 247 million cases and 619 thousand deaths worldwide in 2021, predominantly in small children in Africa.[1] There is a constant need for novel antimalarial medicines to complement existing artemisinin-dependent therapies, which are under pressure from resistance conferring mutations. Plasmepsin X (PMX), an essential aspartyl protease of malaria parasite was recently identified as new potential multistage drug target to fight against malaria. PMX controls malaria parasite egress and invasion of erythrocytes, development of functional liver merozoites (prophylactic activity) and blocking transmission to mosquitoes.[2] In this talk, we will present the discovery of potent, orally available, PMX inhibitors and the efforts to overcome the challenges associated with the constraints of an antimalarial (single to three doses and the need for low dose). We will describe the *in vitro* and *in vivo* characterization of our lead molecules, confirmation of the transmission-blocking potential associated with PMX inhibition, efficacy data in a SCID mouse model of *Plasmodium* falciparum malaria and in a prophylactic liver mouse model for rodent *Plasmodium berghei* malaria. In addition, we will present the pre-clinical safety data including 7-day rat toxicology studies and the human dose prediction for these molecules.[3]

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