Cell Egress and Invasion Inhibitors and Their Use as Antiparasitical Agents

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Technology description

The emergence of drug resistance by P. falciparum, necessitates the development of novel antimalarials to stay one step ahead of the rapidly evolving parasite. We are working to identify compounds that can disrupt the parasites key pathways. In this project, we are targeting the parasites invasion and egress pathway to prevent proliferation. The parasite employs an actomyosin motor as part of a larger invasion machinery complex known as the glideosome to invade target cells. A key component of the invasion machinery is a tetrameric complex of Aldolase that connects the motor to the cytoplasmic domain of a transmembrane adhesive protein, TRAP (thrombospondin related anonymous protein). Aldolase interacts with the C-terminal tail of the TRAP proteins, which are specific to different stages of invasion, such as TRAP for sporozoite invasion of liver cells, MTRAP for merozoite invasion of red blood cells, and CTRAP for ookinete invasion of the mosquito midgut. We have screened the Medicines for Malaria Ventures box (Spangenberg 2013 PLoS One doi: 10.1371/journal.pone.0062906) to identify compounds that affect the TRAP-Aldolase interaction. Due to the high conservation of the Aldolase active site where TRAP tails bind, we cannot develop drugs that will disrupt the complex without interfering with the hosts Aldolase. Alternatively, we are working to promote the interaction based on the idea that as invasion progresses, that the TRAP-Aldolase complex must periodically dissociate for invasion to progress.

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