The *Plasmodium falciparum* Glideosome – a Novel Drug Target.

by
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Abstract:
In the course of its life cycle, the malaria parasite *P. falciparum* invades various types of host cells. In the merozoite and sporozoite stages, an actin-myosin based motor complex (the glideosome) provides the driving force for successful invasion by enabling the zoite to glide on the host cell surface, until a suitable orientation for penetration is reached. Our goal is to reduce the parasite's ability for host cell invasion by attenuating the functional efficiency of the motor complex. We apply a novel structure-guided drug design approach, targeting protein-protein interaction kinetics between two key glideosome components, the glycolytic enzyme aldolase and its binding partner, TRAP, a Thrombospondin-related adhesion protein. A virtual ligand library of low molecular weight compounds was specifically designed to enforce the interactions between TRAP and aldolase, which acts as scaffolding protein in the context of the glideosome. During the gliding process, the aldolase-TRAP complex is believed to dissociate and re-form. By tightening the aldolase-TRAP interaction we propose to lower the dissociation rate of this key complex, yielding two effects: A) to limit the pool of aldolase molecules available for re-association with TRAP; and B) to reduce aldolase's catalytic activity in glycolysis, ultimately decreasing the available amount of energy necessary to drive gliding motility. These effects should decrease the parasite's invasive efficiency and potentially affect its overall metabolism.
In support of our hypothesis we will show a 2.4 Å ternary crystal structure of Aldolase-TRAP in the presence of a small molecule derived from our virtual screening efforts. In vivo experiments with Plasmodium sporozoites utilizing a gliding motility and a liver cell invasion assay indicate a reduction in infectivity by 95% while initial toxicity studies showed no signs of apoptosis of our small molecules in human liver cells.

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