Title: PfGCN5 bromodomain, a novel drug target

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The emergence of resistance to existing drugs has highlighted the need for new antimalarials. Bromodomain-containing proteins (BDPs) bind to acetylated lysine residues in histones and regulate transcription involved in the pathogenesis of a variety of diseases. BDPs have been exploited as drug targets in various diseases for new therapeutic development. *Plasmodium falciparum* General Control Non-repressed 5 protein (GCN5) has been shown to play a role in invasion and virulence. Here, we show that conditional knockout of the PfGCN5 bromodomain is essential for parasite survival in the blood stage. Next, we investigated the activity of small molecule inhibitor L45 and the possibility of exploiting PfGCN5 bromodomain as a potential drug target. The protein structure of the PfGCN5 bromodomain in complex with the inhibitor has been previously resolved. L45 is active against the blood and liver stage of *P. falciparum* and *P. berghei,* respectively. In vitro selection of drug-resistant parasites identified point mutations in the mitochondrial carrier protein (PfMCP1). Interestingly, L45-resistant parasites were hypersensitive to other mitochondrial drugs including atovaquone, DSM1, and myxothiazol. Furthermore, metabolomics studies showed the upregulation dUMP and peptides on L45 treatment. This suggests a link between PfGCN5 bromodomain inhibition and mitochondrial function. Our data indicate that L45 has a novel mode of inhibiting *Plasmodium*, and that PfGCN5 bromodomain inhibition may be a promising starting point for rational drug design.