Abstract

Title: Targeting epigenetics for antimalarial development

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Rising artemisinin resistance necessitates the urgent discovery of antimalarials with novel mechanisms of action. Epigenetic regulation, essential for *Plasmodium falciparum* survival, stage-specific gene expression, and antigenic variation, presents a compelling therapeutic frontier.

Here, we investigated three epigenetic proteins: PfBDP6 (reader), PfSET3 (writer), and PfSET1 (reader/writer), alongside the established target PfBDP1. Using a loxP–DiCre conditional knockdown system, we revealed divergent essentiality profiles. While PfSET1 and PfBDP6 depletion caused slow-to-moderate growth defects, PfSET3 excision resulted in drastic parasite mortality, establishing it as a highly vulnerable target. To support these findings, functional domains were recombinantly expressed, enabling *in vitro* bromodomain and methyltransferase assays.

Complementing our genetic validation, a screen of small-molecule predicted epigenetic inhibitors identified chemical probes exhibiting potent sub-micromolar antiplasmodial activity. Crucially, repeated attempts to select resistant parasites failed, suggesting their targets possess a high barrier to resistance.

Currently, we are employing quantitative chemical proteomics to validate predicted compound-target engagement with PfSET3. Concurrently, a glmS-based knockdown strategy is being utilised to assess shifts in inhibitor sensitivity upon PfSET3 depletion. This integrated genetic, biochemical, and chemical biology approach robustly validates epigenetic modifiers, particularly PfSET3, as highly promising targets for next-generation antimalarial drug discovery.