MALARIA BIFUNCTIONAL DHFR-TS ENZYME AS A TARGET FOR DRUG DISCOVERY AGAINST ASEXUAL STAGES OF *P. FALCIPARUM*

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Malaria is a deadly infectious disease which affects millions of people each year in tropical areas. The causative agent is a protozoan parasite that belongs to the genus *Plasmodium*. Resistance to current antimalarial treatments is alarming, being necessary to discover new drugs against the human pathogen displaying a novel mechanism of action able to bypass current resistances. With this aim, the Bill & Melinda Gates Foundation has granted several laboratories to identify new antimalarial targets using chemogenomic methods. A progression cascade from diverse libraries was established in GSK in order to select compounds with good potency and a presumable novel mode of action. Then, *P. falciparum in vitro* resistant mutants have been selected under drug exposure using standard methodologies .

In this work, an example of the successful chemogenomic approach is given using the compound MMV027634. After two weeks, a culture under continuous drug pressure at a dose of 10x IC50-fold rendered parasite growth. Selected mutants displayed a high level of resistance when compared to the wild type strain. Whole genome sequencing of resistant mutants to MMV027634 revealed mutations in the dihydrofolate reductase-thymidylate synthase (dhfr-ts) gene. Mutations mapped in aminoacids of the highly conserved TS domain.

The role of this enzyme in *Plasmodium* metabolism, mode of action studies including metabolic bypass, cross-resistance of derivatives as well as combinations with MMV027634 are discussed. Results of these studies highlight the importance of the DHFR-TS enzyme in parasite metabolism and open possibilities to explore thymidylate synthase as a target to discover promising novel drugs with therapeutic efficacy against asexual stages of *P. falciparum*.