# Dissecting M5717 Killing of Malaria Parasites

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Malaria remains a major global health burden affecting roughly half of the world's population. Plasmodium falciparum, the causative agent of most human malaria cases resulting in mortality, is an apicomplexan parasite which traverses between a human host and an Anopheline mosquito vector. P. falciparum has developed resistance against all front- line therapies used against it, creating a need for efficient antimalarial treatments that have broad spectrum profile, relatively high resistance barrier and novel modes of action. One such promising chemoprotective agent is M5717 (DDD107498) which shows significant activity across the parasite's life cycle and is currently under clinical development.

Recrudescent parasites under drug pressure have shown that M5717 targets translation elongation factor 2 (PfeEF2) in the parasite, an essential elongation factor in eukaryotic protein synthesis. However, the role of M5717 binding to PfeEF2 as well as the specific effect of arrested protein synthesis in parasite clearance remains poorly understood. To tackle this, we used in situ cryo electron tomography (cryoET), proteomics and polysome profiling to better understand the role of M5717 inhibition of PfeEF2 in P. falciparum over time. From in vitro techniques, we observed prompt arrest in parasite development and delayed parasite death. Proteomics and polysome profiling coupled with cryoET show the varied translational states and protein turnover that result in the ultrastructural changes from M5717 inhibition of PfeEF2.

The insights from this study give us a better understanding of the mechanism of action of M5717 and the molecular basis of M5717 mediated delayed death of P. falciparum. With this, we can also better identify ideal partner-drugs which will aid in mitigating antimalarial drug resistance and gain a better understanding of the pathogenesis of malaria. Moreover, this work highlights the promise of coupling advances in cryoET with in vitro and genetic tools to address biological questions in situ.