The *in vitro* pharmacodynamic response of antimalarial endoperoxides on *P. falciparum* gametocytes

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Plasmodium falciparum's sexual stages (gametocytes) are not associated with malarial pathogenesis or clinical symptoms, but they are responsible for the transmission of the disease from human hosts to mosquitos. As such, the development of gametocytocidal intervention that targets the transmission stage to break the disease's lifecycle forms the basis of efforts towards malaria elimination and eradication. However, despite the importance of this developmental stage, the biology and pharmacology of gametocytes are still very poorly understood.

Using a newly generated luciferase-reporting transgenic line, pharmacodynamic gametocyte studies are being performed to characterise the activity of selected antimalarial endoperoxide against the sexual stages. This novel assay reveals that the activity of endoperoxide is stage-specific. Early gametocytes (stages I–II) are killed by all selected compounds at relatively low concentrations (nano-molar), whereas it was only the active metabolite dihydroartemisinin (DHA) that displayed potency in late (IV–V) gametocytes (~70% inhibition).

Of all tested endoperoxide drugs, DHA is the most potent antimalarial across all gametocyte stages, and at clinically relevant levels (IC_{50}: 26nM). A time-killing dependent assay has been performed with different concentrations of DHA over discrete time intervals to determine the drug's kill rate. These parameters have been used to simulate the PK/PD relationship of the drug in order to estimate gametocyte clearance profiles during the treatment period.

We have also investigated the activity of new inhibitors in pre-clinical development as well as synthesised peroxide tetraoxane. These analyses are presented and discussed in the context of strategies that aim at the discovery and development of new transmission-reducing antimalarial drugs.