

ORAL PRESENTATION

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Development of a novel drug for uncomplicated malaria targeting the mitochondrial NADH:quinone oxidoreductase

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From Parasite to Prevention: Advances in the understanding of malaria
Edinburgh, UK. 20-22 October 2010

NADH:quinone oxidoreductase (PfNDH2) represents a metabolic choke point in the respiratory chain of *Plasmodium falciparum* mitochondria and is the focus of a drug discovery programme. A miniaturised assay for recombinant PfNDH2 with robust assay performance measures was generated for the high throughput screening (HTS) of a focused library of 17,000 drug-like compounds. A quantitative structure-activity relationship has been developed around one of the chemical templates derived from the HTS hits. Lead molecules developed to date show selective inhibitory activity against PfNDH2 versus *P. falciparum* bc₁ or dihydroorotate dehydrogenase (DHODH). Potent enzyme inhibition is accompanied by *in vitro* parasite kill of multidrug-resistant strains in the low nM range and clearance of parasites from *in vivo* *P. berghei* models. Lead molecules also display excellent *in vitro* therapeutic indices against human cell lines and bovine *bc1*. Initial metabolic studies in human liver microsomes and hepatocytes indicate favourable pharmacology. These data support the further development of this new candidate drug targeting a novel parasite component.

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Published: 20 October 2010

doi:10.1186/1475-2875-9-S2-O4

Cite this article as: Biagini et al.: Development of a novel drug for uncomplicated malaria targeting the mitochondrial NADH:quinone oxidoreductase. *Malaria Journal* 2010 **9**(Suppl 2):O4.

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