

***Plasmodium falciparum* GTP cyclohydrolase I (PfGCHI): Optimisation of purification and activity, structure determination and inhibition studies.**

The objectives of this project are to purify high yields of functional PfGCHI for the characterisation of the enzyme activity and to facilitate determining the structure of the enzyme. The ultimate purpose is to screen novel inhibitors for *in vitro* PfGCHI inhibition and *P. falciparum* growth.

Biomedical and Biotechnology Research Unit (BioBRU) – Rhodes University

This group is under the directorship of Prof Greg Blatch and a focus area is malarial research. In 2009 and 2010, the SAMI has funded research on two putative malarial drug targets, 1-deoxy-D-xylulose 5-phosphate and GTP cyclohydrolase I. Malarial proteins are frequently hampered by low yields of soluble protein by heterologous expression in *Escherichia coli* host cells. The researchers in this group have examined different strategies to improve the production of folded, functional protein. The successful approaches are co-expression of the target protein with particular molecular chaperones, harmonisation of the coding region and co-expression with overexpressed *lac* repressor. These co-expression systems should be applicable to other malarial proteins recalcitrant to soluble expression in heterologous systems. Homology modelling of these drug target proteins has been undertaken and the models can be used to develop an efficient approach to screen for potential tool compounds, *in silico*, for use in the rational design of novel inhibitors.

Publications

Goble, J.L.; Adendorff, M.R.; de Beer, T.A.P.; Stephens, L.L.; Blatch G.L. (2010) The malarial drug target *Plasmodium falciparum* 1-deoxy-D-xylulose 5-phosphate reductoisomerase (PfDXR): development of a 3-D model for identification of novel, structural and functional features and for inhibitor screening. *Protein and Peptide Letters* 17(1):109-120

Pesce, E-R.; Cockburn, I.L.; Goble, J.L.; Stephens, L.L.; Blatch G.L. (2010) Malaria Heat Shock Proteins: Drug Targets that Chaperone other Drug Targets. *Infectious Disorders – Drug Targets* 10(3):147-157