Rational ligand design of inhibitors for *Plasmodium falciparum* glutathione-s-transferase

Marli Botha[1,2], Colin Kenyon[2], Fourie Joubert[1] and Abraham Louw[3]

[1] Bioinformatics and Computational Biology Unit, University of Pretoria, Pretoria, 0002, South Africa; [2]CSIR Bio/Chemtek, Modderfontein, 1645, South Africa; [3] Department of Biochemistry, University of Pretoria, Pretoria, 0002, South Africa

Given the rapid spread of drug resistance to malaria, the search for effective, safe and affordable drugs for *P. falciparum* malaria is one of the most pressing health priorities worldwide. In this study, the crystal structure of glutathione-s-transferase (GST) containing the ligand s-hexyl-glutathione (GTX) was employed as target for ligand discovery. The primary goal was to use rational design approaches to develop novel inhibitors to this enzyme, and to perform subsequent in vitro screening against the recombinant protein.

As a first step, the validation of different docking programs took place by removing GTX from the active site of the enzyme, and attempting to return it correclty by docking. Various docking programs were used for this, including AutoDock, FlexX, DOCK, Docking/Affininty, Ludi and Ligandfit. This was done to establish which docking programs can correctly reposition a known inhibitor to the target protein, thus indicating the program's ability to successfully dock novel compounds into the enzyme active site. Docking programs were rated according to the RMSD of the docked ligand vs. that of the ligand in the crystal structure. These results suggested that the AutoDock docking method can be exploited to predict the binding orientation of ligands to the G and H site of pfGST.

Additionally, pharmacophore descriptors were built using the Accelrys Catalyst Suite, and subsequently screened against the National Cancer Institute 3D and Maybridge 2004 databases. From this focused library, the most potential ligands were identified according to the binding energies produced by AutoDock. Screening and optimization of these compounds may lead to the design of novel lead drugs inhibiting pfGST.