



School of Pharmacy PhD Projects 2014

Project Title The role of dynamic conformational ensembles in substrate recognition, mechanism of inhibition and drug design against the malaria M1 aminopeptidase

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Description ***The Problem:*** Malaria is a serious tropical disease spread by mosquitoes and causes over 660,000 deaths per year worldwide, predominantly in children and pregnant women. The prevention and treatment of malaria is under threat due to the rise of drug-resistant parasites. As a result, there is a pressing need to identify and validate antimalarial targets.

Opportunity: Dalton laboratory has crystallised several structures of the *Plasmodium falciparum* M1 alanyl aminopeptidase (M1-AAP). The inhibition of M1-AAP prevents the supply of amino acids for parasite development within the blood cells and, therefore, is an attractive strategy for development of novel anti-malarial therapies. The Tikhonova laboratory offers a multi-scale modelling expertise to study the behaviour of proteins and its function at atomic level and, using the gained insights, to predict novel medical interventions. The structures of M1-AAP provide a first time opportunity for our teams to explore the molecular basis of substrate recognition and M1-AAP inhibition.

Strategy: This project involves computer simulations of the M1-AAP structure in wild type and mutant forms un/bounded to inhibitors. We will elucidate the process of inhibitor dissociation/association and define key amino acid residues in the substrate recognition and inhibition mechanism. We will also investigate the probability of M1-AAP allosteric regulations. Computer predictions will be validated using mutagenesis studies established in the Dalton laboratory and will provide the groundwork for novel anti-malarial drug design. The complex analysis and interpretation of simulations trajectories in this project will stimulate the development of novel multi-scale methodologies, which could be exploited in other area of anti-peptidase drug design. This project has direct relevance to the pharmaceutical industry in UK (> 1 million British visit malaria-endemic regions each year) and to sustainability in the developing world. The project facilitates skills development in the area of therapeutics research, which is applicable in academia and industry.

Start Date October 2014

Keywords Malaria, drug design, molecular modelling, molecular dynamics, mutagenesis, parasitology

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How to Apply

Postgraduate applications should be made using Queen's Online:

<http://go.qub.ac.uk/pgapply>

Please note that there are two application processes: one for admission to the university and another for postgraduate awards.

Further Information

Additional information for prospective postgraduate students can be found on the School of Pharmacy website:

<http://www.qub.ac.uk/pha>

and the Queen's Postgraduate website:

<http://www.qub.ac.uk/home/ProspectiveStudents/PostgraduateStudents/>