**Targeting a novel allosteric site on Trypanosoma cruzi trans-sialidase for future Chagas' disease therapy**

Theme: Infection, Immunity & Repair
Reference: MRC19IIRBa Crennell

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Chagas' Disease (CD), the cause of 10,000 deaths a year in Latin America, is a WHO 'Neglected Tropical Disease', since after an acute phase with non-specific symptoms, there is no effective treatment. CD is caused by *Trypanosoma cruzi*, infection usually arising from a bite from an infected insect. One of the virulence factors produced by *T. cruzi* in human hosts is the surface protein trans-sialidase (TcTS) which transfers terminal sugars (sialic acids) from host cells to the trypanosome, helping it to evade the immune system. In the two decades since the determination of the TcTS structure, intensive structure-based drug design programmes have failed to discover effective inhibitors. Recently we have discovered a novel inhibitory site on TcTS, binding amino-phosphonate compounds. The best of these has an IC50 of 15μM, comparable to the best published inhibitors. The discovery of this site opens a significant new line of anti-trypanosome research but poses many questions for instance: what is the inhibition mechanism, does this site have a role in substrate recognition or enzyme function, can targeting this site permit stronger inhibition?

This project seeks to evaluate the potential of this new TcTS allosteric site to provide novel therapeutics against CD. Following analysis of the new TcTS site to design compounds binding more tightly and specifically, these will be synthesised and their effectiveness tested against TcTS in vitro. Initial toxicity testing can be carried out in an invertebrate model (*Manduca sexta* caterpillars). Leading compounds will be sent to our collaborator in Argentina for in vivo testing in mammalian *T. cruzi* models. Inhibitor binding will be analysed by crystallography using X-ray data collected in-house and at the Diamond synchrotron. The mechanism of inhibition distant from the catalytic centre is unclear so computational analysis of the structure in the presence and absence of inhibitor using molecular dynamics will suggest hypotheses that can be tested through mutagenesis. An understanding of mechanism will inform the design of better inhibitors.

Through this research project the student will gain experience in a wide range of techniques across different disciplines and Universities, including protein production, enzyme characterisation, X-ray crystallography and toxicity (*M.sexta*) studies (Bath Biology & Biochemistry), inhibitor design, synthesis and evaluation (Bath Pharmacy & Pharmacology) and computational analysis, particularly molecular dynamics simulation (Bristol). Results will be communicated in research publications, and at conferences. Outcomes from the project will have immediate impact on the many academic and commercial groups working on CD therapies. Strong IP protection for allosteric regulation of TcTS will be necessary and we intend to file composition of matter patent applications on any lead compounds once structure-activity relationships have been established.

IMPORTANT: In order to apply for this project, you should apply using the DTP's online application form: https://cardiff.onlinesurveys.ac.uk/gw4-biomed-mrc-dtp-student-2019

More information on the application process may be found here:
http://www.gw4biomed.ac.uk/doctoral-students/

APPLICATIONS OPEN ON 24 SEPTEMBER AND CLOSE ON 23 NOVEMBER 2018.

You do NOT need to apply to the University of Bath at this stage – only those applicants who are successful in obtaining an offer of funding form the DTP will be required to submit an application to study at Bath.