Project title: Bromodomain Proteins as Targets for anti-Leishmanial Drug Discovery

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Project Description:

The Leishmanias, caused by species of the kinetoplastid parasite *Leishmania*, are diseases associated with immune dysfunction, with millions of people at risk in the poorest countries of the world. Clinical symptoms range from the disfiguring skin lesions of cutaneous leishmaniasis, to the often fatal visceral leishmaniasis. The principal drugs used to treat visceral leishmaniasis suffer from serious drawbacks. The development of new therapies for treating leishmaniasis is an international priority.

Reversible histone acetylation by lysine acetyl transferases and histone deacetylases is an important mechanism of epigenetic control in eukaryotes. Following histone acetylation, nucleosomes, which hitherto form tightly packed chromatin, adopt a more open conformation that allows access to the transcription machinery. Transcription is often further regulated by the binding of bromodomain (BRD)-containing proteins. BRDs have as their core a four-helix bundle from which two prominent loops protrude to form an acetyl lysine binding site (Figure 1). BRDs bind to specific acetylated lysines on histones and can subsequently mediate the recruitment of transcriptional enhancers.

*Figure 1* Two molecules of the second bromodomain from *Leishmania* donovani LdBPK.091320 complexed with the inhibitor bromosporine (PDB Entry 5TCK; Lin et al to be published).

Parasites such as *Leishmania* spp. have complex life-cycles involving different developmental stages in more than one host. They are known to use epigenetic mechanisms, including lysine acetylation, to fine tune gene expression as they adapt to different hosts or conditions. The presence of multiple bromodomain containing proteins in the genome of the parasites suggests these proteins play a role in ‘reading’ lysine acetylation signals. In collaborative work with the pharmaceutical company GSK, the group of JCM has systematically knocked out/down genes encoding BRD-containing proteins. The results indicate that a subset of these proteins are essential for parasite proliferation and therefore represent targets for anti-leishmanial drug discovery.

Here, the student will use combinations of techniques of Structural Biology. This will include DNA manipulation and cloning to generate bacterial and/or insect cell lines over-producing recombinant proteins. These will be purified using advanced chromatographic techniques and the purified proteins used to support inhibitor-binding experiments using biophysical techniques including isothermal titration calorimetry, surface plasmon resonance and NMR spectroscopy. A key goal will be protein crystallisation and protein structure determination. We are well set up for protein crystallography with robotics devices for crystallisation and for crystal testing. We have monthly access to the synchrotron radiation source at DIAMOND for 3D data collection.

The student will be involved in a collaborative project and work closely with the molecular cell biologists performing the gene knock-outs in the parasites. There will be opportunities to interact with partners in the extended collaborative network including researchers in Brazil and industry.
Training:
This prestigious BBSRC funded Doctoral Training Partnership (DTP) brings together the very best molecular, chemical and cellular bioscience research across the White Rose Consortium of Universities (Leeds, Sheffield and York), which maps on to the research themes of the BBSRC. Students will benefit from a regional PhD training programme that has interdisciplinary collaboration at its core. The aim is to enable students to develop a range of research skills in biological and biochemical areas as well as equip them with core mathematical, data analysis and generic professional skills that are necessary for bioscience research in the coming decades. At York, the White Rose Partnership brings together researchers from the Departments of Biology and Chemistry. Additionally, all Chemistry research students have access to our innovative Doctoral Training in Chemistry (iDTC): cohort-based training to support the development of scientific, transferable and employability skills. The student will be centred in the Structural Biology Laboratory which is well set up for recombinant DNA work, large scale protein purification and crystallisation and structure solution using X-ray data collected in house or at the DIAMOND synchrotron. Many of the programmes used worldwide in crystallography were written or co-written at York, with YBSL an important node in CCP4 which is supported by BBSRC. Thus the student will be surrounded by capable researchers in a problem-solving environment. The student will interact closely with researchers in the Mottram laboratory which has leading facilities and expertise in parasitology and an active programme of gene knock-out studies using CRISPR-Cas9 systems. This context is extended through the network of collaborations JCM has with groups in Brazil and in industry (GSK Tres Cantos) and by the EU Drug Discovery ITN in which YBSL (Hubbard) is a node. The project will have a substantial ligand binding component to it and the student will have access to STD NMR or Microscale Thermophoresis. The student may also make use of the Molecular Interactions Laboratory in the Technology Facility to access Isothermal Titration Calorimetry, Fluorescence Spectroscopy and Microscale Thermophoresis, according to need.

Equality and Diversity:
The Department of Chemistry holds an Athena SWAN Gold Award and is committed to supporting equality and diversity for all staff and students. The Department strives to provide a working environment which allows all staff and students to contribute fully, to flourish, and to excel. Chemistry at York was the first academic department in the UK to receive the Athena SWAN Gold award, first attained in 2007 and then renewed in October 2010 and in April 2015. This PhD project is available to study full-time or part-time (50%).

Funding:
Value: Studentships are fully funded by BBSRC and cover: (i) a tax-free annual stipend at the standard Research Council rate (£14,296 for 2016-2017, to be confirmed for 2017-2018 but typically increases annually in line with inflation), (ii) research costs, and (iii) tuition fees at the UK/EU rate.

Eligibility: The studentships are available to UK and EU students who meet the UK residency requirements. Students from EU countries who do not meet the residency requirements may still be eligible for a fees-only award. Further information about eligibility for Research Council UK funding can be found at the following website: http://www.bbsrc.ac.uk/documents/studentship-eligibility-pdf/

Candidate selection process:
- Applicants should submit an application for a PhD in Biological Chemistry by midnight on Sunday 7 January 2018
- Supervisors will contact their preferred candidates either by email, telephone, web-chat or in person
- Supervisors may nominate up to two candidates to the assessment panel
- The assessment panel will shortlist candidates for interview from all those nominated
- Shortlisted candidates will be invited to a panel interview at the University of York on Tuesday 6 February 2018
- The York BBSRC White Rose DTP awarding committee will award studentships following the panel interviews
- Candidates will be notified of the outcome of the panel’s decision by email

For more information contact chemgrad@york.ac.uk or see our web page: http://www.york.ac.uk/chemistry/postgraduate/