Project title: Development of chemical biology tools to study mammalian O-mannosylation pathways  
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Project Description:

The field of chemical biology aims to design and synthesize chemical tools (such as inhibitors, substrate mimics, or enzyme probes) to answer fundamental questions in biology. In this project, we are focusing on creating tools to study some of the key enzymes responsible for synthesizing specific carbohydrate structures in cells.

Proteins on the surface of cells are often modified with diverse, complex carbohydrate structures. These carbohydrates, named glycans, play roles in a range of cellular processes including cell-cell and host-pathogen interactions. Glycans are synthesized by networks of multistep enzymatic pathways. This project focuses on enzymes that are involved in the biosynthesis of O-mannosyl glycans, a type of glycan in which a mannose sugar is first linked to a protein and then further elongated into complex carbohydrate structures. The best studied O-mannosylated protein is α-dystroglycan (αDG), which plays essential roles in muscle tissue and the nervous system by linking the cytoskeleton with the extracellular matrix. Interest in this specific glycoprotein stems from the fact that defects in O-mannosylation cause a variety of congenital muscular dystrophies. In addition to αDG, another family of O-mannosylated proteins is that of the cadherins, proteins that control cell-cell adhesion and have been shown to play a role in pathogenic infections and cancers. Recent findings (2016/2017) revealed that the O-mannosyl glycans on these proteins are installed by a pathway separate from that dedicated to αDG, and that the initial mannose residue is not further elongated. However, it is unclear which enzymes are involved in this new pathway, and how cells decide which protein to target to which of the O-mannosylation pathways.

In this project, we aim to generate a new set of tools to enhance our understanding of the various cellular O-mannosylation pathways, by focusing on key enzymes that are responsible for synthesis of the mannose glycan. This research will be of interest not only to other researchers working in the field, but will also have a significant impact on clinical research by helping us better understand how specific clinical mutations in these enzymes contribute to disease.

In order to reach these goals, we will use an interdisciplinary approach that combines organic synthesis with biochemistry, basic cell biology and structural biology. The project consists of three parts:

1. Chemical synthesis of substrates for the target enzymes
2. Development of an assay to detect enzyme activity
3. The use of the developed tools to analyse enzyme function in vitro and in cells
Training:

All research students follow our innovative Doctoral Training in Chemistry (iDTC): cohort-based training to support the development of scientific, transferable and employability skills. All research students take the core training package which provides both a grounding in the skills required for their research, and transferable skills to enhance employability opportunities following graduation. Core training is progressive and takes place at appropriate points throughout a student’s higher degree programme, with the majority of training taking place in Year 1. In conjunction with the Core training, students, in consultation with their supervisor(s), select training related to the area of their research.

The training program will be of a multidisciplinary nature, combining synthetic chemistry with biochemistry and molecular biology techniques. Specifically, the student will receive training in organic synthesis (including carbohydrate synthesis and solid phase peptide synthesis), HPLC purification, and various analytical techniques including LCMS and NMR characterization; and will also develop skills in SDS-PAGE and immunoblotting, affinity purification, cloning, cell culture, protein expression in both bacterial and mammalian systems, enzyme activity assays, and mass spectrometry analysis. Furthermore, the student will have the opportunity to participate in crystallography studies in the laboratory of Prof Davies.

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:

This project has guaranteed funding, providing a suitable candidate can be found.

Value: Studentships are fully funded either by the EPSRC or a Department of Chemistry Teaching Studentship, and cover: (i) a tax-free annual stipend at the standard Research Council rate (£14,553 for 2017-18), (ii) tuition fees at the UK/EU rate.

Eligibility: EPSRC 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. Chemistry Teaching Studentships are available to any student who is eligible to pay tuition fees at the home rate. 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 Chemistry by 17:00 on Wednesday 28 February 2018
- Supervisors will interview their preferred candidates either by email, telephone, web-chat or in person
- Supervisors may nominate up to two candidates to the assessment panel
- Nominated candidates will be invited to a panel interview at the University of York in mid March (date TBC)
- The Chemistry Graduate Awards Panel 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/