

SWBIO Funded Studentship

Professor Matthew Crump and Dr John Crosby.

Project Description

The overall aim of this PhD studentship is to obtain further detailed knowledge of the structure and function of the enzymes (PC-4 and insulin degrading enzyme, IDE) involved in processing and clearance of the insulin growth factor-2 (IGF2) and its 'BIG' isoforms.

Insulin and Insulin-like growth factors (IGFs) are a family of proteins that share sequence and structural homology. Insulin is produced in the pancreas and is well known for its role in controlling blood glucose levels whereas IGF2's role lies principally in fetal growth and development and in adults is produced at a basal level in the liver and is thought to be important for regulating cell growth as well as metabolism. IGF2 has drawn considerable interest due to high circulating levels of this mitogenic peptide being associated with hypoglycaemia and is implicated in several cancers.

Mature IGF2 contains only 67 amino acids and is processed from a larger isoform, called Pro-IGF2, that contains 156 amino acids. Pro-protein convertases (PCs) including PC-4 sequentially process Pro-IGF2 to the mature form via intermediate 'BIG' IGF2 isoforms containing 104 and 87 amino acids. These BIG isoforms are of considerable interest as they are particularly bioactive and may not be cleared from tissues or sequestered in the blood stream in the same way as mature IGF2. The first of the two main aims of the project are to express, purify, characterise and determine first, the three-dimensional X-ray structure of the catalytic domain of PC-4 (which is currently unknown) and the full-length protein if possible and determine the structure-function of this enzyme and the mutations that might block its activity and thereby lead to generation of unwanted big-IGF2 isoforms.

Insulin degrading enzyme, or IDE, is thought to degrade IGF2 by sequentially clipping the protein into smaller fragments. The enzyme works by engulfing IGF2 in a large cavity and exposing it to the internal catalytic residues. Whereas there is some mechanistic work on how this occurs with mature IGF2, there is nothing known about how it might process big-IGF2 isoforms. IGF2 isoforms are expensive and very difficult to make in the laboratory but we have developed a folding protocol for these and we can produce active IDE.

This interdisciplinary project will combine the expertise and training from chemists, biochemists, mass spectrometrists, structural biologists, molecular modellers to elucidate how key components of the IGF2 processing pathway work to both produce and clear IGF2 isoforms.

Main supervisor: Prof Matthew Crump (Chemistry, University of Bristol)

Second supervisor: Dr John Crosby (Chemistry, University of Bristol)

Additional supervisory team: Dr Nick Harmer (Biosciences, University of Exeter)

Collaborators: Professor Bass Hassan (University of Oxford)

APPLICATION

Applicants must have obtained, or be about to obtain, a First or Upper Second Class UK first degree, or the equivalent qualifications gained outside the UK, in an appropriate area of science or technology.

Note this PhD is also listed under the projects page on the Bristol SWBIO website (<https://www.swbio.ac.uk>) and is part of the cohort also advertised on findaphd.com (<https://www.findaphd.com/search/phd.aspx?keywords=swbio>)

To apply - Follow the 'Start a new application' link on this page: <http://www.bristol.ac.uk/study/postgraduate/apply/>
Please ensure that you quote the supervisor's name and project title in the 'Your research interests' section.

The deadline for the receipt of applications is Monday 3 December 2018.

We encourage you to make a formal enquiry to Prof Matt Crump (matt.crump@bristol.ac.uk) if you have any queries or would like to discuss the project.

Funding Notes

A full studentship will cover UK/EU tuition fees, a training support fee and a stipend (£14,777 p.a. for 2018/19, updated each year) for 4 years. UK and EU applicants who have been residing in the UK since September 2016 will be eligible for a full award; a limited number of studentships will be available to EU applicants not meeting the residency requirement. Applicants who are classed as Overseas for tuition fee purposes are not eligible for funding.