Unlocking the therapeutic potential of E3 ubiquitin ligases through structure-function studies and Cryo-EM

This project is one of a number that are in competition for funding from the South West Biosciences Doctoral Training Partnership (SWBio DTP) which is a BBSRC-funded PhD training programme in the biosciences, delivered by a consortium comprising the Universities of Bath, Bristol, Cardiff and Exeter, along with the Rothamsted Research Institute. The partnership has a strong track record in advancing knowledge through high quality research and teaching, in collaboration with industry and government.

Studentships are available for entry in September/October 2019.

All SWBio DTP projects will be supervised by an interdisciplinary team of academic staff and follow a structured 4-year PhD model, combining traditional project-focussed studies with a taught first year which includes directed rotation projects.

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Co-supervisors: Prof Christiane Berger-Schaffitzel (University of Bristol), Prof Jean Van Den Elsen (University of Bath)

Project description

All cells within our body need to discard waste material such as damaged or no longer wanted proteins to ensure that cells remain healthy and functional. The small protein ubiquitin is essential in this process by functioning as an identification tag. Ubiquitin is the most versatile post-translational modification, it can exist as a single moiety on proteins, and this is important in protein trafficking and endocytosis, but also as a ubiquitin chain. It is only in the last decade that we have come to appreciate the complexity of the ubiquitin system. We now know for instance that ubiquitin can use any of its seven lysine residues, or its N-terminal Met, to assemble two ubiquitin chains together in order to form chains. Therefore, as many as eight linkage types have been found on proteins (i.e. Met1, K6, K11, K27, K29, K33, K48 and K63) in yeast and human cells.

E3 ubiquitin ligases plays a key role in protein ubiquitination, by mediating the transfer of ubiquitin onto protein substrates. Depending on the type of ubiquitin signals added, this can trigger recognition by the Ubiquitin-Proteasome System. Therefore, preventing the degradation of important proteins in age-related diseases could in theory be achieved through the targeted inhibition of the ligase activity of specific E3s, rather than the current and general/unspecific approach of inhibiting the proteasome. HECT E3 ubiquitin ligases are very good candidates for drug discovery given their Cys-based enzyme activity. However, the limited structural information and biochemical knowledge of these large enzymes has hindered their potential as therapeutic targets, despite mounting evidence for their importance in human health.

In this project, the student will undertake structure-function studies of HECT ligases. The student will be trained in protein expression and purification, ubiquitination assays, biophysical techniques, protein crystallography and state-of-the-art Cryo-EM. An important goal will be to also establish strategies for the expression and purification of full-length HECT E3 enzymes in eukaryotic systems, for Cryo-EM studies and future drug discovery projects.

This project will benefit from ongoing international collaboration with experts in proteomics and chemical biology as well as supportive and dynamic research environments at Bath and Bristol. Because of our combined expertise in protein ubiquitination, structure-function studies and Cryo-EM, the student will be in an ideal position to make an impact on the ubiquitin field.

Funding

Studentships provide funding for a stipend at the standard UKRI rate (currently £14,777 per annum, 2018/19 rate), research and training costs and UK/EU tuition fees 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 may be available to EU applicants who do not meet the residency requirement. Applicants who are classed as Overseas for tuition fee purposes are not eligible for funding.

Applications

Applicants must have obtained, or be about to obtain, a First or Upper Second Class UK Honours degree, or the equivalent qualifications gained outside the UK, in an appropriate area of science or technology such as Biochemistry. Further studies and laboratory experience gained for example through a Master Degree in Structural Biology/Biochemistry would be highly advantageous. We encourage interested applicants to get in touch with Dr Licchesi to discuss suitability for the project prior to submitting a formal application.

Applications should be submitted on the University of Bath's online application form for a PhD in Biosciences. Please ensure that you quote the supervisor's name and project title in the 'Your research interests' section. You may apply for more than one project if you wish but you should submit a separate personal statement relevant to each one.

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