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

Supervisory team:
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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 signal 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. E3 HECT 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 E3 HECT ubiquitin 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.