Molecular mechanisms of the ubiquitin system

Supervisory team:
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Project description:

How does ubiquitin achieve specificity in regulating virtually all aspects of eukaryotic homeostasis? A key point is the action of E3 ubiquitin ligases (E3Ls), the most diversified class of enzymes in the ubiquitin system. The pharmaceutical industry is actively developing new drugs including PROTAC to recruit E3Ls for the on-demand proteasomal degradation of disease-causing proteins. At least 600 E3Ls are encoded in the human genome, yet only a handful have been exploited so far. To exploit these enzymes therapeutically, it is essential to obtain structural and mechanistic insights of how E3Ls work and are regulated. Here, we will use protein biochemistry, cell biology and cryo-EM to study (i) the structure of E3 ligases UPF1 and HECTD1; (ii) how their activity/specificity is regulated, and the cross-talk of the ubiquitin system with other post-translational modifications, e.g. phosphorylation; (iii) the potential for these E3Ls as new modalities for targeted protein degradation.

The nonsense-mediated mRNA decay (NMD) factor UPF1 comprises a CH-domain with two Ring-modules, characteristic of Ring domain E3 ubiquitin ligases but UPF1's E3L activity has to be demonstrated yet. Human UPF1 is involved in downregulation of MYOD, a key regulator of myogenesis, and we now will investigate whether UPF1 is the E3L regulating MYOD levels. We further aim to identify and validate potential other substrates of the UPF1 E3L using cell biology and proteomics. We are particularly interested to see if there is a link between UPF1 E3L activity and associated protein degradation or ubiquitin signalling and the NMD pathway that degrades faulty mRNAs.

The HECT E3 ubiquitin ligase HECTD1 has multiple roles including in cell migration, Wnt signalling and cell division as we have shown recently. Currently, HECTD1 is the only E3L which can assemble, on its own, branched polyubiquitin chains which is a potent degradative signal. To understand how these complex ubiquitin signals are made and how HECTD1 ligase activity is regulated, we will characterise HECTD1 biochemically, biophysically and structurally using cryo-EM and/or crystallography.

The student will be trained in eukaryotic protein expression and purification, ubiquitination assays, biophysical techniques, protein crystallography and state-of-the-art cryo-EM. An important goal will be to establish the expression and purification of full-length E3 enzymes for activity assays, biophysical and structural characterisation. The student will benefit from ongoing international collaborations, supportive dynamic research environments and our combined expertise in the Bristol and Bath teams.

Our aim as the SWBio DTP is to support students from a range of backgrounds and circumstances. Where needed, we will work with you to take into consideration reasonable project adaptations (for example to support caring responsibilities, disabilities, other significant personal circumstances) as well as flexible working and part-time study requests, to enable greater access to a PhD. All our supervisors support us with this aim, so please feel comfortable in discussing further with the listed PhD project supervisor to see what is feasible.