Targeted Protein Degradation as a Cutting-Edge Tool to Study Tyrosine Kinases in Platelet Signaling and Function

Project ID: 267

Supervisory team

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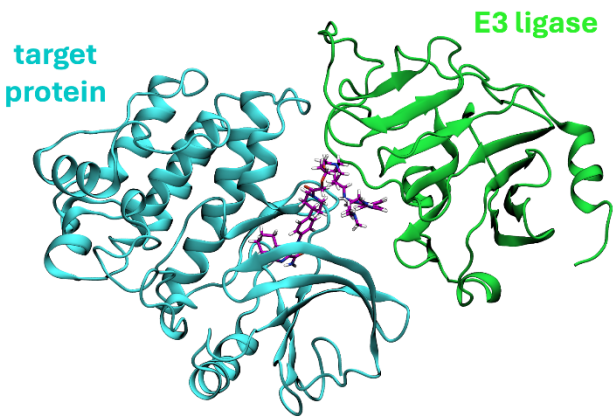

Project description: Proteolysis-targeting chimeras (PROTACs) and related chemical protein degraders are an exciting new tool in chemical biology. Unlike classical inhibitors, which transiently block catalytic activity, PROTACs use the cell's own ubiquitin–proteasome system to break down specific proteins. They work by simultaneously binding a target protein and an E3 ligase, thereby bringing them together so that the E3 ligase can tag the target with polyubiquitin, resulting in destruction by the cell's proteasome. This removes the protein, including both its enzymatic and non-enzymatic roles, and produces long-lasting effects. Protein degradation technologies also make it possible to study proteins that are difficult to target with traditional drugs. Mathematical molecular modelling is increasingly important in degrader design. It provides predictions about how PROTACs interact with both their protein target and an E3 ligase, guiding the selection and optimisation of compounds.Platelets offer a valuable biological system for applying these technologies. They are small blood cells without a nucleus that play a central role in haemostasis, the process that stops bleeding after injury. Platelets respond quickly to vascular damage, forming a first barrier against blood loss. Their activity is controlled by complex signalling networks inside the cell. Many of these networks depend on protein tyrosine kinases (PTKs), including members of the Src and Syk families. These enzymes link signals from platelet surface receptors to processes that drive activation and aggregation. Studying PTKs in platelets however is challenging because the cells cannot be genetically modified and many kinase inhibitors lack specificity.This project will apply PROTACs to selectively remove tyrosine kinases in human platelets. Existing degraders will be tested, while mathematical molecular modelling will guide the design of new ones. Candidate compounds will be synthesised through collaboration with specialist chemists and assessed in silico to predict their effectiveness. Laboratory experiments will then use biochemical, biophysical, and pharmacological approaches to measure how PROTACs bind to their targets, alter kinase levels, and affect platelet function.This project is an excellent opportunity for a PhD student to work in a highly interdisciplinary environment. It brings together chemical design and synthesis, computational modelling, and experimental platelet biology. Data from biochemical and pharmacological studies will be integrated with computational models to understand how tyrosine kinases control platelet signalling and responses. These combined approaches will generate new insights into platelet biology and provide a general framework for using targeted protein degradation to study complex signalling networks.

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.