Rational Design of Novel Degraders for Targeted Protein Degradation

Project ID: 232

Supervisory team

Main supervisor: Dr Julien Licchesi (University of Bath)
Second supervisor: Prof Matthew Crump (University of Bristol)
Other supervisors: Dr Scott Lovell (University of Bath), Prof Christiane Berger-Schaffitzel (University of Bristol)

Collaborators: Dr Dr John Elkins (Nuffield Department of Medecine, University of Oxford), Dr Dr Christian Tiede (University of Leeds)

Host institution: University of Bath

Project description: Targeted Protein Degradation (TPD) has emerged as a transformative therapeutic strategy for the selective and on-demand removal of disease-associated proteins. Among the various TPD modalities, PROteolysis TArgeting Chimeras (PROTACs) have demonstrated clinical efficacy, particularly in the treatment of prostate and breast cancers. These heterobifunctional molecules simultaneously bind a protein of interest and recruit an E3 ubiquitin ligase, leading to ubiquitin-dependent proteasomal degradation of the target. Currently, only a handful of the ~600 human E3 ubiquitin ligases, primarily from the RING family, are utilised in PROTAC design. This leaves a vast, untapped pool of E3 ligases that could significantly expand the TPD toolkit.Despite their promise, PROTACs face several limitations, including poor oral bioavailability, limited cellular permeability, suboptimal pharmacokinetics, and high molecular weight. To address these challenges, aptamers, short, single-stranded DNA or RNA sequences that fold into three-dimensional structures, have emerged as a compelling alternative to bind protein targets. Aptamers mimic antibodies in their ability to bind target proteins with high specificity and affinity, while offering additional advantages such as low immunogenicity, enhanced tissue penetration, and improved stability. Our recent proof-of-concept work, alongside emerging literature has demonstrated that other E3 ubiquitin ligases can be harnessed for targeted degradation. However, the lack of known ligands to recruit these E3s remains a major bottleneck in their development as PROTAC components.This project aims to screen, identify, and optimize novel ligands for a new E3 ligase using a high-throughput aptamer-SELEX platform. A unique domain within the target E3 ligase has been identified to serve as bait for aptamer selection from a diverse library of ~10^{15} nucleic acid sequences. To further expand the TPD toolbox, we will also explore additional ligand discovery strategies including macrocyclic peptide binders via the RaPID (Random non-standard Peptides Integrated Discovery) system and affimers, through an established collaboration.Selected binders will be validated using biophysical methods and structural biology techniques such as NMR spectroscopy and Cryo-EM to elucidate binding modes and guide ligand optimization. Top-performing binders will be incorporated into next-generation BioPROTAC and PROTAC constructs, which will be evaluated in functional cellular assays including flow cytometry, western blotting, high-content microscopy, HiBiT-NanoLuc as well as in vitro biochemical assays. The project will benefit from ongoing collaborations with experts in chemical biology and structural biology further enhancing its scope and offering unique training potential to the student.

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.