

DrESS: A Biocatalytic Approach for Targeted Degradation of Oncogenic Transcription Factors

Supervisory team:

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Host institution: Cardiff University

Project description:

Here, the PhD candidate will develop a novel inhibition mechanism for “undruggable” oncogene through adapting advanced enzyme engineering and protein labelling technologies.

Targeted degradation of disease-causing proteins is an emerging strategy in molecular biology research and disease therapy. Existing methods rely on designing small-molecule binders, which can trigger addition of a molecular marker to the harmful proteins, signalling for their degradation. This approach has been used to reveal physiological functions of the target proteins and also stop them from causing diseases. However, small-molecule binders mainly target proteins with a binding pocket (e.g. enzyme active site). Nevertheless, many key drug targets lack this binding pocket rendering them “undruggable.”

Transcription factors (TFs) are a notable group of “undruggable” proteins. Acting as cellular switches, TFs control when genes should be active or silent. When these molecular switches malfunction, they can lead to severe diseases including cancers. Currently, small-molecule binders targeting these faulty switches are not always precise or effective, due to a lack of binding pocket, thus requiring a large dosage.

The aim of this project is to train a PhD candidate into an enzyme designer to enable a novel, and potentially more effective, TF degradation mechanism. They will develop a specialised biocatalyst called “DrESS.” Engineered to recognise a specific faulty switch (a disease-causing TF), DrESS can catalyse the addition of a degradation marker. Notably, DrESS is designed to recognise a broad surface area of TF, bypassing the need of a binding pocket. Once refined, DrESS will operate efficiently at a low dosage, similar to naturally occurring enzymes.

The PhD programme comprises three phases. Firstly, the PhD candidates will stitch TF peptide binders with enzymes by molecular cloning, creating precursors of DrESS. Subsequently, the molecular fitting of these precursors will be fine-tuned through mechanistic analysis and high-throughput screening, testing different versions of DrESS for improved activity. Finally, the optimised DrESS will be showcased on the stages of molecular biology and medicinal chemistry. With microscopy inspection and cell-culturing assays as experimental evidence, DrESS will be highlighted as a precise and effective tool for targeted protein degradation.

In sum, the journey of creating a DrESS will offer interdisciplinary training in the areas of enzymology, molecular biology and high-throughput screening, of which the project team have relevant expertise. Coupled with the opportunities to present in conferences, practice in scientific writing and participate in career-development workshops, this work nurtures a highly employable workforce from the GW4 network.

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.