EPSRC Centre for Doctoral Training (CDT) in Molecular Sciences for Medicine (MoSMed)

Novel approaches to targeted protein degradation

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Project overview/context

The cellular recyling of proteins by the proteasome by the E3 ligase-ubiquitin pathway has been exploited for targeted protein degradation, a possible therapuetic strategy. Linking a ligand for a target protein with a ligand for an E3-ligase gives a degrader molecule for the target protein.
Some proteins are inherently unstable (e.g. estrogen receptor), so when a ligand binds, they are degraded by the proteasome.
We will design, synthesise and explore the cellular activity of novel molecules bearing a ligand for an inherently unstable protein and a target protein. These molecules will reveal a novel route to targeted degradation of both proteins.

Research Project

Hypothesis: We propose to employ inherently unstable proteins as the signal for the proteasome in a bifunctional degron. In this system, the bifunctional degrader carries the ligand for the unstable protein and a POI.
Background: Since the disclosure of bifunctional degrons (PROTACS) based on an E3-ligase ligand, a linker, and a target protein (POI), there has been intense effort applying this method to numerous disease related protein targets. However, the approach suffers from its complexity. The degrons are required to attract the POI to the E3-ligase allowing the ligase reaction to occur with an available lysine residue. To date, this cannot be approached in a rational way (Figure 1).

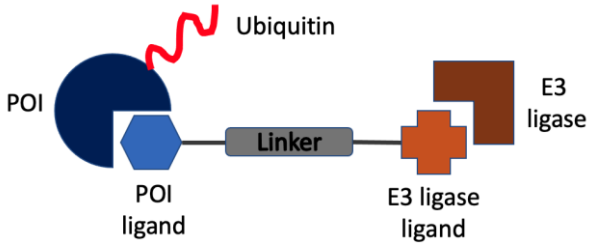

Figure 1: PROTAC degron binding E3-ligase and POI to transfer ubiquitin resulting in degradation of the complex

Proposed approach: In the case of a bifunctional degrader carrying the ligand for an unstable protein and a POI, the dual-binding event is not required to have any specific orientation in space, or specific linker chemistry, and so a significant degree of complexity should be removed (Figure 2). A chemically simpler system should require fewer iterations to optimization.

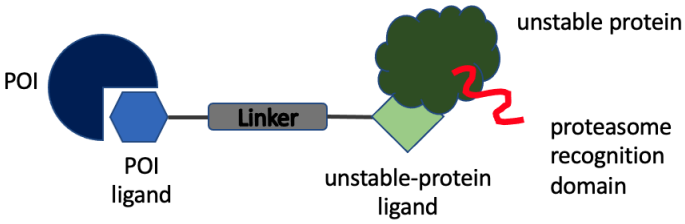

Figure 2: Bifunctional degron comprising POI ligand and ligand for an unstable protein. Binding of ligand signals the unstable protein (and complex) for degradation by the proteasome.

Specific protein degraders are used clinically to treat breast and prostate cancer, e.g. the specific estrogen receptor degrader (SERD). We will use these ligands to design prototype degrons based on known degrading ligands for the estrogen receptor (ER) with appropriate linkers to ligands for the chosen POI. The ability of the degrons to effect degradation of the POI will be measured in appropriate cell lines. The therapeutic

relevance of ER degradation is well established; however, resistance is a frequent problem. Dual degraders offer the opportunity of targeting hormone responsive tumours with the specific knockdown of another relevant therapeutic target.
In addition to studies with SERDs, we will investigate other unstable proteins that are found to be overexpressed in cancer. Large pharmaceutical investment has been made identifying potent small molecule inhibitors of many oncoproteins that were subsequently taken into clinical trials. However, despite elevated levels of these proteins, limited clinical responses to their inhibition and degradation have been seen. These ligands offer the opportunity for oncogene targeted degradation.
We will design oncoprotein targeted degrons linked to ligands for proteins (POI) that are either essential for cell survival and progression, or where degradation may trigger apoptosis. The cellular activity of of these molecules in oncoprotein expressing cell lines will be explored.
Targeted-protein degradation is a 'hot-topic' in drug discovery chemistry and biology. This project offers a novel approach to protein degradation and will give an excellent training.

Training & Skills

The project will provide invaluable training in the fields of organic synthesis, cell and molecular biology and molecular biophysics, which will be highly desirable for a future career in medicinal chemistry or related areas.
Medicinal chemistry: structure-based drug design, synthesis and chemical analysis.
Cell and molecular biology: cell culture, Western blotting, cell-growth inhibition studies. **Cell biophysics and chemical biology**: protein binding affinity and kinetics by surface-plasmon resonance (SPR); and protein-folding by circular dichroism (CD) spectroscopy
You will join a vibrant and thriving research group centred on the application of chemistry to biological and medical problems. This will provide an inspiring and supportive environment for your PhD studies.

Further Information

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How to Apply

You must apply through the University's online postgraduate application system

You will need to:

- Insert the **programme code 8207F** in the programme of study section
- Select '**PhD in Molecular Sciences'** as the programme of study
- Input (only) the **studentship reference code (e.g. 21_04)** that you are applying for in the studentship/partnership reference field when prompted (all codes are outlined in the individual project adverts found on the MoSMed website: https://research.ncl.ac.uk/mosmed/phdstudentships/)
- Attach all documents that are requested including a CV and cover letter. The cover letter must **clearly** state the project reference code, the full title of the studentship and set out how your interests and experience relate to the project
- Attach degree transcripts and certificates and, if English is not your first language, a copy of your English language qualifications
- Email: mosmed.cdt@ncl.ac.uk once you have submitted your application to confirm the project you have applied for. Please include the studentship reference code and full project title.

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