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

MoSMed Molecular Sciences for Medicine

www.ccdc.cam.ac.uk

PROTACS: new computational methods, targets and experimental validation

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Project overview/context

In spite of great advances in understanding the molecular mechanisms of diseases such as cancer, the discovery of new drugs remains a huge challenge in academia and the pharmaceutical industries. Over the last decade, PROteolysis TArgeting Chimeras (PROTACs) drugs have gained significant traction as these compounds target proteins not by inhibition but by tagging them for protein degradation. PROTACs are bifunctional molecule where two ligands are connected by a flexible linker. This project is aimed at developing and testing new methods for the rational design of PROTACs in a close collaboration between the Cambridge Crystallographic Data Centre (CCDC), Newcastle University and Durham University.

Research Project

PROtealysis **TA**rgeting **C**himeras, also designated PROTACs, are bifunctional molecules composed of two protein ligands connected by a linker. The ligand on one side binds to the E3-ubiquitin ligase, which targets a protein for degradation, while the other ligand binds the unwanted proteins that needs to be removed from the cell. Since PROTACs had first been described in 2001, the technology has been applied to an increasing range of targets, with the first molecules now in clinical trials.

All PROTACs are based on known ligands for an E3-ligase on one side, in many cases, the Von Hippel-Lindau tumor suppressor (VHL) connected to a known or novel ligand for the target protein. However, only recently, it has become clear that the length and chemistry of the linker, in most cases composed of polyethylene glycols, or alkyls, alkynes or triazoles, plays a major role in the biological activity of the PROTAC compound. With a virtually unlimited number of potential linkers, new computational methods are needed to guide and support the development of new PROTACs.

In this project, the student will develop and validate new molecular modelling tools for linker design that use the structures of the VHL ligase and the target protein in combination with empirical rules derived from successful linkers. These tools will initially be tested and validated using one well-established PROTACs model system, VHL bound to the human bromodomain 4 (Brd4), a major target for cancer therapies, where crystals structures of the ternary VHL-PROTAC-Brd4 complex have been determined. New compounds will be synthesized by our collaborators at Durham University and Newcastle University and then validated using a wide range of biochemical and biophysical techniques. The validation includes the structure determination by X-ray crystallography and/or cryo Electron Microscopy in collaboration with MoSMed students involved in the project. After the proof-of principle experiments we will apply and further develop the methods on a number of proteins that are currently targeted in the research groups involved in this project.

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Training & Skills

The training program will encompass a wide range of computational and experimental aspects. Starting with basic programming skills in Python and Linux scripting, the the succesful candidate will be trained to be an expert user of the CCDC software in drug discovery including MOGUL and GOLD, as well as complementary molecular modelling programs such as GROMACS or NAMD/VMD.
In addition, the PhD candidate will obtain the key molecular biology training required for a drug-discovery campaign. These include recombinant protein expression, protein purification and characterisation by biochemical and biophysical methods for quality control. This will be followed by the standard biophysical techniques for measuring protein-ligand interactions including thermal shift assays (TSA), surface plasmon resonance (SPR) as well as the use of the state-of-the-art NanoTemper Dianthus® screening platform.
The ultimate goal, the structural characterisation of a ternary complex of a newly designed PROTAC molecules with its two target protein will be achieved in a close collaboration of all groups involved.

Further Information

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How to Apply

To apply for this project please visit the Durham University application portal to be found at: Home · Application Portal (microsoftcrmportals.com)

Please select the course 'PhD in Molecular Sciences for Medicine (EPSRC CDT)', which is registered in the Chemistry Department and indicate the reference **mos23_16 i**n the 'Field of Study' section of the application form. Please note that there is no need to submit a Research Proposal with your application, however we do require a Covering Letter, CV, academic transcripts, the contact details of two referees and proof of English language proficiency if relevant.

Within the MoSMed CDT we are committed to building a diverse community based on excellence and commitment. To that end in our recruitment of Doctoral Researchers we welcome applications from outstanding candidates of all backgrounds regardless of ethnicity, disability, gender identity, sexual orientation and will consider all applications equally based on merit.

Please note due to funding commitments this studentship is available to applicants who qualify for UK /Home tuition fees only.

Should you have any queries regarding the application process at Durham University please contact the Durham MoSMed CDT Manager, Emma Worden at: emma.worden@durham.ac.uk

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