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

Development of multi-functional cyclic peptide probes

Newcastle University, Chemistry

Partner: NovoNordisk A/S

Supervisory Team	• **Prof. Akane Kawamura, Newcastle University (Lead)** • **Dr Martin Münzel, NovoNordisk A/S** • **Prof. Mike Waring, Newcastle University** • **Prof. Steven Cobbs, Durham University**

Project overview/context

Multi-functional molecules are chemical entities with two or more structural domains that have different biological functions. Many variations of such molecules are used in chemical biology, including those that bind to multiple protein targets, or inhibitors/binders linked to recruiting/affinity or labeling handles. These molecules have wide-ranging applications as research tools to study biological pathways and protein-protein interactions and hold promise as starting points for therapeutics discovery. The aim of this project is to develop methods to generate multi-functional cyclic peptide probes against targets of interest using chemical and display methodologies. These tools will be used to study and modulate therapeutic target functions.

Research Project

Multi-functional molecules have many important applications as chemical biology research tools to study and target multiple biological pathways or protein-protein interactions (PPIs) and hold promise as starting points for therapeutics discovery.[1] Multi-functional molecules often have two (or more) targeting ligands conjugated by a linker. While the target potency/affinity of each motifs are prerequisite, one of the major challenges in developing such molecules is to maintain the functions / target affinity of the individual motifs when combined. For example, heterobifunctional molecules, such as PROTAC that contain a target-binding motif and a ubiquitin-ligase binding motif, require extensive effort to rationally design and optimise the chemistry and length of the linker to maintain the ligand affinity for both targets. Thus, a rapid and robust way to generate high-affinity multi-functional chemical probes is needed.

Cyclic peptides (CPs) are gaining attention as an attractive class of molecules in drug discovery. Peptides offer diverse and complex 3D scaffolds covering immense chemical space distinct from traditional small molecule scaffolds. Cyclisation induces structural constraint, increased target affinity and, in some cases, improved cell permeability. There are now many examples of natural product / natural product-derived cyclic peptides used as drugs. Interestingly, cyclosporin, a natural product CP drug, is a bifunctional molecule that binds to cyclophilin and calcineurin. While such molecules have no linkers, they have evolved to efficiently bind to both protein targets. Rational design of chimeric, dual-targeting cyclic peptide antibiotics inspired by natural product CPs (with and without linkers) have shown great promise.[2,3] Thus, multi-targeting CPs provide new therapeutic opportunities in many diseases.

In this project, we will explore different chemical and display selection strategies to rapidly design and generate multi-functional CPs against targets of interest. We will utilize mRNA-display, a powerful screening technology, that enables the discovery of high affinity de novo peptide ligands.[4,5] The platform couples encoded library technology and cell-free *in vitro* translational system, allowing the generation of peptide libraries with immense chemical diversity (>10^{12}). The versatility of the cell-free system means that it is

compatible with genetic code reprogramming and post-translational chemical modifications, thus non-proteinogenic residues can be incorporated into the peptide libraries for diversification and functionalisation. Generated multi-functional cyclic peptide hits will then be validated using biophysical and cellular assays.

This project provides an exciting opportunity to develop new peptide-based targeting approaches for chemical biology and drug discovery.

References: [1]Nature Chem Biol (2020) 16 369-378. [2]Nature (2019) 576, 452–458. [3]Nature Chem (2019) 11, 254–263 (2019). [4]Nature Communications (2017) 8:14773. [5]Chemical Science (2018) 9, 4569 – 4578.

Training & Skills

The student will be based in the recently refurbished state-of-the-art chemical biology laboratories in the Bedson building at Newcastle University, and will work alongside a team of experienced chemists, chemical biologists and molecular/cell biologists. The student will receive extensive training in cutting-edge methods in chemical biology, including encoded library technologies, peptide chemistry / synthetic chemistry, biophysical and biochemical and cellular assays, and will be supported by academic and industrial supervisors. The student will work closely with NovoNordisk, a global pharmaceutical company specialising in diabetes care and peptide therapeutics discovery. The student will have the opportunity to visit NovoNordisk in Copenhagen, Denmark, for industrial placements during the course of their PhD.

Further Information

Professor Akane Kawamura, Newcastle University
akane.kawamura@ncl.ac.uk

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_01)** 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.

This project is co-funded by NovoNordisk A/S.