

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

**Cyclic peptide discovery for intracellular protein targets**

**Newcastle University, Chemistry/School of Natural & Environmental Sciences & Faculty of Medicine in collaboration with AstraZeneca**

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| **Supervisory Team** | * [**Prof. Akane Kawamura**](https://www.ncl.ac.uk/nes/people/profile/akanekawamura.html)**, Newcastle University (Lead)**
* [**Prof. Mike Waring**](https://www.ncl.ac.uk/nes/people/profile/mikewaring.html)**, Newcastle University**
* [**Prof. Ian Hickson**](https://www.ncl.ac.uk/medical-sciences/people/profile/ianhickson.html)**, Newcastle University**
* [**AstraZeneca**](https://www.astrazeneca.co.uk/)
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**Project overview/context**

Peptides hold enormous promise as chemical tools for selective intervention in biology. They can target chemical space distinct from that of small molecules and their chemical diversity provides high specificity and affinity or target binding. Advances in development of target-based screening technologies and complex peptide library synthesis techniques have enabled efficient peptide identification / development against numerous targets, including ‘difficult’ protein-protein interactions. One of the major hurdles, however, is reliable cell delivery of peptides. This PhD project aims to investigate different strategies to address this challenge.

**Research Project**

One of the major challenges in peptide discovery for intracellular targets lies in achieving reliable cell penetration. Unlike Lipinski’s 'rule of five' (Ro5), which can guide small molecule drug design, there is currently no defined set of rules for developing peptide drugs. However, several natural peptides, such as cyclosporin, exhibit intracellular activity. These peptides are often cyclic, providing structural constraints and enhanced resistance to proteolytic degradation. Many also feature reduced hydrogen-bond donors (e.g., backbone N-methylation), non-canonical amino acids (ncAA), and predominantly hydrophobic side chains. Such clues from nature have inspired the development of cyclic peptide platforms for target-based screening in drug discovery. These platforms (both biologically-/ chemically- generated) have enabled efficient generation of cyclic peptides against targets, including for ‘difficult’ protein-protein interactions. In particular, mRNA display platform has recently gained attention as a powerful technology that allows the incorporation of ncAAs and the screening of genetically encoded libraries of >trillion diversity. Such platforms can rapidly identify potent and tight-binding CPs against proteins of interest. However, in most cases, hit CPs from display technologies exhibit very limited or no cell activity, and engineering permeability is often a time-consuming and synthetically challenging endeavor.

The overall aim of this project is to establish general rules for peptide cell permeability, with the view to designing libraries for intra-cellular targets. We will explore synergistic and parallel strategies for determining the optimal peptide size, amino acid composition, ncAA incorporation and peptide elaboration. Our work will support future design of de novo CPs against intracellular protein targets of interest.

We are looking for a highly motivated, creative and enthusiastic candidate, with a strong background in chemistry/biochemistry or closely related subjects, who is passionate about working at the interface of chemistry, biology and medicine, and have interest in therapeutics discovery.

**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, bioinformatics, biophysical/biochemical and cellular assays, and will be supported by academic supervisors and industrial supervisors from AstraZeneca. The student will have opportunities to visit AstraZeneca for placements during the course of their PhD to gain industrial work experience.

The student will benefit from bespoke research and life skills training programme through alignment with the Newcastle-Durham MosMed EPSRC Centre for Doctoral Training.

**Further Information**

**For further information, please contact the lead supervisor**

Akane Kawamura

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Kawamura Group webpage: <https://kawamuraresearchgroup.com>

**How to Apply**

You must apply through the University’s [**Apply to Newcastle Portal**](https://applyto.newcastle.ac.uk/)

Once registered select **‘Create a Postgraduate Application’.**

**Use ‘Course Search’ to identify your programme of study:**

* search for the ‘Course Title’ using the programme code: **8100F**
* Research Area: Chemistry
* Select ‘PhD Chemistry (full time)’ or ‘PhD Chemistry (part time)’ as the programme of study, depending on your preference.

**You will then need to provide the following information in the ‘Further Details’ section:**

* a ‘Personal Statement’ (this is a mandatory field) - upload a document or write a statement directly in to the application form. Please include the full title of the studentship, the studentship code **(mos2\_02)**, and how your interests/experience relate to the project.
	+ the relevant studentship code **(mos2\_02)** in the ‘Studentship/Partnership Reference’ field. **You must include the relevant code for your application to be considered.**
	+ when prompted for how you are providing your research proposal - select ‘Write Proposal’. You should then type in the title of this project. You do not need to upload a research proposal.

**In the ‘Supporting Documentation’ section please upload:**

* An up to date CV.

Please upload all documents in PDF format.

**You must submit one application per studentship, you cannot apply for multiple studentships on one application.**

**Equality, Diversity and Inclusion (EDI)**

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.

Should you have any queries regarding the MoSMed application process to Newcastle University please contact Craig Hinds, the MoSMed CDT Manager: **mosmed.cdt@newcastle.ac.uk**