Developing New Tools for the Chemical Diversification of Peptide Scaffolds

Overview

Peptides are useful leads for the development of new drugs against a wide range of diseases. They occupy the chemical space between small molecules and antibodies and as such they can reach or selectively inhibit drug targets that these other molecules cannot. Within the peptide field developing efficient routes for the chemical diversification of peptide scaffolds is of considerable interest as this allows challenges like in vivo stability to be overcome. This project will develop new synthetic chemistry that can be used to chemically diversify peptide scaffolds. The chemistry will be exemplified and assessed in a biological context through collaborations between the Cobb, Waring and Kawamura research groups.

Research Project

Novel amino acid synthesis and late-stage peptide functionalisation are two areas that are attracting much attention in academia and industry where there is a desire to develop efficient methods for chemical diversification of complex organic (or bioorganic) scaffolds. This project will develop synthetic approaches to chemically modify “natural” peptides with the aim of improving their biological and physical properties. Two approaches will be developed (WP1 and WP2).

WP1: Preparation of Perfluorinated Amino Acids

As part of a long-established program designed to develop new approaches to accessing novel amino acids we recently exploited perfluoroheteroaromatics, such as pentafluoropyridine, as reagents to access a range of novel fluorinated amino acids [e.g. Cobb Org. Biomol. Chem 2019, Org. Biomol. Chem 2017]. These amino acids can be exploited as 19F NMR probes, as reactive handles for the selective chemical modification of peptides or to access novel cyclic peptide scaffolds. In this WP we will design a new generation of perfluorinated amino acids with the aim of: 1) selectively modifying peptide scaffolds; and 2) establishing new strategies for the bio-conjugation of peptides to other biomolecules via SN2 or SNAr reactions.

WP2: The Application of Electrochemistry in Peptide Science

Researchers such as Phil Baran [Chem. Rev. 2017] have utilised electrochemistry extensively in the small molecule arena. However, the use of electrochemical organic synthetic techniques to functionalise amino acids or large complex bio-
molecules such as peptides is yet to be explored. We will use electrochemistry to modify and functionalise both single amino acids and full peptides. Our aims will be to: 1) gain access to new amino acid building blocks for the preparation of novel peptides; and 2) develop a new route of the late-stage functionalisation of peptide scaffolds (linear and cyclic).

WP3: Assessing the Effect of Perfluorinated Amino Acids in a Biological Context [Collaboration with Professors Kawamura and Waring]

The Kawamura group has identified biologically active peptides against a wide range of biomedically important proteins (e.g. histone demethylases, Kawamura Nat. Comm, 2017). In this WP, we will incorporate novel (WP2) and perfluorinated amino acids (WP1) into selected hit peptide sequences and assess the effect on target affinity, cellular permeability and activity using established assays in the group. Aims are: to see if the incorporation of novel/ perfluorinated amino acids can improve: 1) target engagement; 2) proteolytic stability and 3) cellular permeability / activity.

In addition the within the Newcastle Cancer Drug Discovery Group a range of thus far intractable cancer targets involving protein-protein interactions have been identified. As part of a related CDT proposed project (led by Waring), novel hit peptides will be identified for these projects, which will incorporate perfluorinated amino acids (WP1). Active hits will be selected for further modification and the effects of new perfluorinated amino acids will be assessed.

**Training & Skills**

The recruited PhD student will receive training in synthetic organic chemistry (Cobb), peptide chemistry (Cobb), DNA encoded library synthesis (Waring), biophysical analysis (Cobb/ Kawamura) and biological screening and evaluation (Cobb/ Kawamura, Waring). At the end of their PhD training the recruited student will have all the required skills to work at the interface between the molecular and life sciences. The student will be primarily based at Durham but will spend time in both the Waring and Kawamura labs in Newcastle.

**How to Apply**

To apply for this project please visit the Durham University application portal to be found at: [https://www.dur.ac.uk/study/pg/apply/](https://www.dur.ac.uk/study/pg/apply/)

Please select the course code F1A201 for a PhD in Molecular Sciences for Medicine and indicate the reference MoSMed20-08 in the ‘Field of Study’ section of the application form.

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