4 year PhD studentship in the School of Chemistry, The University of Edinburgh, starting 1st September 2017

Title: Stapled by design: New peptide-based therapeutic leads targeting protein-protein interactions in rheumatoid arthritis

Funding: Medical Research Scotland and UCB Celltech

Academic Supervisors: Dr Alison Hulme, Dr Julien Michel
Industrial Supervisor: Dr Terry Baker

Project Outline:
The interactions between proteins in a cell control many biological processes and so present attractive targets for therapeutic intervention. However, in contrast to the normal "lock and key" analogy for the development of small molecule drugs targeting enzyme activity, the surfaces involved in protein-protein interactions (PPIs) tend to be much larger and have less well-defined binding pockets. Thus PPIs present substantial challenges for therapeutic intervention.

One emerging approach to developing PPI-based therapeutic leads is to examine the available structural information about the interface regions to identify interaction "hot-spots" between protein side-chains. When such hot-spots are found in a alpha-helica region, a peptide may be designed from a contiguous protein sequence extracted from one of the two proteins, thus forming the basis for the design of peptide-based inhibitors of the PPI. To date, this approach has not been widely adopted due to: (i) the lack of secondary structure in the peptide which typically results from a short sequence excised from the parent protein; and (ii) a perceived lack of bio-stability of peptide-based therapeutics. However, stapled peptides - in which a chemical link is made across successive turns of a alpha-helix - show greater helicity, enhanced bio-stability, and improved cellular uptake over their unstapled counterparts. A small number of drugs are currently under development based on this strategy and the arsenal of stapling strategies is rapidly expanding.

Currently a drawback of the technology is that it is difficult to predict whether a given stapling strategy will produce a stapled peptide with the desired bioactive conformation. This project will focus on the synthesis and structural characterisation of a library of peptides stapled via different methodologies. The objective is to determine sequence-structure relationships, and the generated data will be used to validate molecular dynamics simulation methods for the prediction of stapled peptides structure. Both experimental and computational methodologies will be applied to the rational design of stapled peptides which interact with two key proteins of interest to UCB that are important in the inflammatory signalling pathways in rheumatoid arthritis. Overall this work aims to greatly expand prospects for the routine use of stapled peptides in drug discovery.

Eligibility Requirements:
Applicants must be UK or EU nationals and have a 1st class or upper 2nd class MChem or a 1st class BSc (or equivalent) and a strong desire to work at the interface between synthetic medicinal chemistry as well as molecular modelling. Previous experience (an undergraduate project and/or industrial placement) which demonstrates your commitment and motivation is desirable, but not an absolute requirement. Applications including a CV, transcript and names of referees should be sent to Dr Alison Hulme (Alison.Hulme@ed.ac.uk).

Further information:
See: Hulme group web pages: https://hulmegroup.wordpress.com/
Michel group web pages: http://www.julienmichel.net/lab/