



Call for applications: EASTBIO DTP PhD studentship:

"Accelerated chemical probes development with hybrid NMR/molecular dynamics methodologies"

Supervisors: Dr Julien Michel, School of Chemistry, University of Edinburgh, and Dr Alessio Ciulli, School of Life Sciences, University of Dundee

A fully funded 4-year EASTBIO PhD studentship (fees and stipend at the standard rate) is available **from September 2016** for candidates with a strong academic record and that satisfy **BBSRC studentship eligibility requirements** (see <http://www.eastscotbiotdp.ac.uk/> if you are unsure).

The use of chemical probes to interrogate the function of biomacromolecular assemblies *in vitro* and *in vivo* is of crucial importance to basic and applied research in molecular biosciences. With advances in our understanding of cellular processes, there is a pressing need for developing new chemical probes to tackle previously unexplored protein families. In this context a significant hurdle is that many proteins are currently considered "unligandable", meaning that high-throughput screens or conventional *in silico* screen approaches have failed to yield chemical probes suitable for cellular and animal studies.

We propose to tackle this challenge by incorporating protein dynamics in the assessment of the ligandability of a protein. There is abundant evidence that ligands often bind and stabilise minor protein conformational states. Such minor states are often called 'cryptic binding sites' because they are not apparent in the structure of unliganded proteins readily solved by structural methods. New methodologies that anticipate the existence of such cryptic binding sites could significantly expand opportunities available to develop chemical probes.

This objective will be here pursued by combining state-of-the art molecular dynamics simulation protocols with cutting-edge biomolecular NMR methods to detect, and stabilise, minor but ligandable conformational states of proteins. The overall goal is to deliver an efficient methodology to generate new chemical matter suitable for further optimisation into high-value chemical probes that will advance basic and applied molecular biosciences research.

The Michel lab at the University of Edinburgh will provide advanced training in computational methods and acquisition/analysis of NMR datasets. The Ciulli lab at the University of Dundee will provide advanced training in biochemical methods for protein expression and purification, and use of NMR methods for structure-guided design of chemical probes. The methodology will be applied to challenging protein families (epigenetic reader domain proteins, E3 ubiquitin ligases) for which the Ciulli lab is developing new chemical probes and for which significant structural and biochemical data has already been generated in-house.

To apply, please send initially a cover letter and CV to julien.michel@ed.ac.uk or a.ciulli@dundee.ac.uk. Informal enquiries are encouraged. Nominated candidates will be invited to apply formally to the EASTBIO DTP. Complete applications must have been received by the EASTBIO studentship panel by December 14th 2015 and contact with the proposed supervisors should be made at least one week before that deadline.

For further information please visit:

<http://www.julienmichel.net/>

<http://www.lifesci.dundee.ac.uk/groups/alessio-ciulli/>