BBSRC Industrial CASE studentship: Identification of targets and binding sites of TRPC modulators by chemical proteomics

Supervisors: Dr. Robin Bon (School of Chemistry), Prof. David Beech (School of Medicine) and Dr. Stuart Warriner (School of Chemistry)

Industrial partner: AstraZeneca

Industrial supervisors: Dr. Matthew Burnham and Dr. Richard Ward

Funding covers: Tuition and fees and provides a stipend of ~£14K per annum

Industrial partner annual supplement to BBSRC studentship stipend: £2000 per annum.

Duration: 4 years (including 3-6 months of placements at AstraZeneca)

Eligibility: must be a UK candidate or an EU candidate who has resided in the UK for at least 3 years by 30.9.2014 if starting PhD on 1.10.2014.

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All applications should be submitted online. Please see www.chem.leeds.ac.uk/en/postgraduate-research/how-to-apply for guidelines.

The project

The Bon and Beech groups have recently discovered several small molecule modulators of the canonical transient receptor potential (TRPC) channels.\(^1,2\) TRPC function is implicated in cardiovascular remodelling and inflammation. To validate TRPC channels as drug targets, it would be important to better understand their biology and pharmacology. In addition, because TRPC function is measured in whole cells, the molecular targets of most TRPC modulators are currently unknown and probably diverse.\(^1\)

Potent and selective modulators of the 6 different human TRPC channels would provide valuable fundamental insights into TRPC channel biology and pathophysiology. Furthermore, identification of the molecular targets of TRPC modulators would lead to either the validation of TRPC channels as druggable proteins or the identification of their regulator proteins (either known or newly identified) as druggable potential targets for TRPC modulation.

This project will involve the development of chemical target identification probes suitable for the unbiased pull-down and identification of membrane protein targets of small molecules.\(^3\) This technology will be used to i) identify the molecular targets of a number of TRPC modulators and ii) identify their binding sites through MS analysis of protein digests.

Objectives

- Design/synthesis of chemical probes based on TRPC modulators
- Evaluation of chemical probes in assays of ion channel activity
- Mass Spectrometry-based chemical proteomics workflows for identification of protein targets and binding sites of TRPC modulators

The candidate

You will have or expect to obtain a first class or higher second class degree in Chemistry or Chemical Biology, including relevant practical experience (for example through a laboratory-based research project), and a strong interest in chemical protein labelling and chemical proteomics.

References