Identification and optimisation of small molecule inhibitors of proteins for use as chemical probes or therapeutics

Ian Yule, Jeff Plante, Rachael Tennant, Jayakanth Kankanala, Rachel Trowbridge, Charlotte Revill, Joseph Thompson, Adam Nelson, Colin Fishwick and Richard Foster

Introduction

Our group is interested in the design, synthesis and optimisation of small molecules for therapeutic application or their use in the elucidation of biological function. By combining tools and techniques in medicinal chemistry, computer-aided drug design and chemical genetics we aim to identify and optimise targeted small molecules as key modulators of specific biological function to support both basic target validation of proteins implicated in disease and as potential starting points for future drug discovery.

The group has capabilities in a number of areas for which bioactive molecules may be identified, optimised and/or targeted, including:

Medicinal chemistry, probe synthesis and chemical genetics

- Bio-targeted small molecules
- Targeted imaging agents
- Small molecule microarrays

Computational-aided drug design

- Ligand- and structure-based design
- Virtual screening

High-throughput screening

- 30k member diverse lead-like small molecule library
- Fragment library
- Assay transfer/assay development

The activities are managed through the Medicinal Chemistry and Chemical Biology (MCCB) Technology Group as part of the Biomedical Health Research Centre (BHRC) at Leeds. Several new projects have been initiated during 2012.

Small molecule therapeutics

1. Development of a novel anticoagulant with minimal bleeding risk

We have identified potent, novel small molecule inhibitors of a key enzyme involved in regulation of the coagulation cascade with exceptional *in vivo* efficacy. The inhibitors have been identified by a number of parallel approaches incorporating virtual drug design, chemical synthesis and HTS of drug-like small molecule libraries and fragments. Presently, we are optimising the inhibitors for target potency, specificity and drug-like physicochemical properties using iterative rounds of medicinal chemistry development and screening using a panel of orthogonal bioassays.

2. Identification of novel inhibitors of TRP ion channel function as potential therapeutics

We have identified a series of novel inhibitors of a TRP ion channel implicated in cardioprotection. The compounds have been developed as agents to support detailed understanding of the role of the protein target and its relevance in disease as well for future development of small molecule-based therapeutics. These dual aims are being achieved through iterations of directed chemical synthesis aided by pharmacophore-based design and screening *via* a panel of orthogonal assays.

Diagnostics

Targeted contrast agents

We are designing and synthesising modular targeted high relaxivity MRI contrast agents for protein targeted cardiovascular disease monitoring and prevention.

Electrochemical microarrays

We are developing a small molecule electrochemical microarray for detection of protein-small molecule binding interactions. We are designing multiplexed small molecule microarrays to detect binding of proteins by electrochemical impedance. This approach constitutes a highly promising and flexible method towards the label-free detection of small molecule-protein interactions and has a number of potential therapeutic and translational applications, including micro- HTS and point-of-care diagnostics.

Funding

This work is funded by the MRC, EPSRC, Parkinson's UK, BBSRC, AICR, CRUK, BHF and BHRC.

Collaborators

Leeds: H. Philippou, R. Ariens and C. Fishwick (novel anti-coagulants), L.-H. Jiang, D. Beech, R. Sivaprasadarao (TRP channel inhibitors), R. Bon, S. Gilbert, S. Plein, A. Maqbool (targeted contrast agents), S. Johnson (Electrochemical microarrays).