

4 Year BBSRC Ph.D. Studentship in collaboration with UCB Biopharma

Academic Supervisors: Dr Matthew Crump

Industrial Supervisors: Dr. Richard Taylor, Ian Whitcombe

“Investigation of the scope and limitations of capillary flow NMR as a medium throughput screening technology for generation of positional information in ligand-protein and protein-protein complexes”.

This project is the continuation of a highly successful collaboration which has already demonstrated that in principle mass spectrometry can be employed as a fast method for screening ligands which are weakly and non covalently bound to proteins of therapeutic interest with considerable potential in high throughput screening within the pharmaceutical industry. In parallel robust NMR methods have been developed for the timely delivery of structural information allowing rapid and informed follow up of “hits” identified by mass spectrometry.

This project will build on this solid foundation in exploring the application of capillary flow NMR technology as a primary fragment screening tool. NMR spectroscopy can provide atomic resolution binding location information avoiding the need for crystallization and is exquisitely sensitive to the small changes in magnetic environment making it ideally suited for studying very weak interactions. Compared to mass spectrometry, however, the relative insensitivity of an NMR experiment tends to increase protein consumption thereby precluding the use of NMR as a tool for the primary triage of hits. Recently capillary flow NMR technology has become available at Bristol and this has the potential to significantly reduce both the amounts of isotopically labeled protein required per ligand screen and/or the NMR experimental acquisition time. The project will explore the application of capillary flow NMR hardware to protein (e.g. ^1H - ^{13}C HSQC, 2D NOESY) and ligand detect (e.g. saturation difference spectroscopy) NMR experiments that are typically applied in fragment screening. In-line automated fluidics will enable the development of an NMR based assay platform for screening larger sample sets (up to ~500) and the automation of the generation of protein-ligand dissociation constants. The results will be cross-validated using a cryoprobe equipped 600 MHz instrument (both at UCB and Bristol) and there will be scope to extend protein-ligand interaction studies to full solution structure determinations. In tandem the project will develop new methods for measuring protein-protein interactions in pharmaceutically relevant targets using biological mass spectrometry in conjunction with H/D exchange. Mass spectrometry will be performed at UCB using a state of the art WATERS 2nd generation SYNAPT high resolution mass spectrometer. *The combination of the two techniques will provide critical structural information on the binding of small molecule fragments to target proteins.*

The successful candidate should have a minimum of an upper second class degree in Chemistry or Biochemistry and you will receive advanced training in the use of both NMR and mass spectrometry in protein structure elucidation as well as experience in protein expression and purification with access to state-of-the-art NMR and mass spectrometry facilities both at

the University and at UCB. The student can expect to spend several months working at the UCB site, where their work will be focused on live therapeutic projects.

For further information please contact Dr Matthew Crump (matt.crump@bristol.ac.uk) or Dr Richard Taylor (Richard.Taylor@UCB-Group.com). Applicants must be resident in the UK or EU to be eligible to apply. The anticipated start date is the 1st October 2011. An online application form is available at <http://www.bristol.ac.uk/prospectus/postgraduate/2011/intro/apply.html>. The stipend will consist of a BBSRC contribution (£13590 p.a.) and an additional Industrial supplement (£3500 p.a.).