PROJECT SYNOPSIS, School of Life Sciences
Director of studies: Dr Alastair Barr

Project title: Characterization of Human Protein Tyrosine Phosphatases

The proposal falls into the following priority area(s), Ageing Research, New technologies for Biosciences

Background to research and synopsis

Cells communicate with each other and respond to their environment via a network of integrated signal transduction pathways that are regulated by protein phosphorylation and the Protein Tyrosine Phosphatase (PTP) family of enzymes. Many human PTPs are associated with diseases such as cancer, diabetes and cardiovascular disease. The objective of this project is to increase our understanding of the regulation, structure and function of specific members of this enzyme family with the aim of defining phosphorylation-dependent signalling events at a molecular level. The findings may lead to novel approaches to pharmacological intervention in these diseases.

Areas of major emphasis include: i) Characterization of the receptor-type PTP CD148 which has been found to play a key role in thrombosis. Techniques will be aimed at identification of ligands, exploring regulation of receptors by dimerization, and analysis of disease associated single-nucleotide polymorphisms (SNPs) and structural biology. ii) Development of small molecule inhibitors of the SHP2 protein-tyrosine phosphatase for breast cancer. Accumulating evidence suggests that this phosphatase plays a fundamental role in progression and metastasis of breast cancer and that inhibition of SHP2 is a potential therapeutic strategy.

Techniques employed that the student will gain experience with include: expression and purification of proteins, mammalian cell culture, immunofluorescence, X-ray crystallography and RNA interference. Membership of appropriate societies, attendance at scientific meetings and presentation and publication of findings will be encouraged to aid in the future career progression of the student.

Supervisory Team and Research Environment

Supervisor Name	Role (DoS, 2nd Supervisor, 3rd Supervisor)	No. of successful PhD/ MPhil supervisions	Current student load for 2011/12 (FTE)	School (for cross School projects)
Alastair Barr	DoS	1	2	
Miriam Dwek	2nd	6	1	

Recent publications relevant to the project:

BARR, A. J., UGOCHUKWU, E., LEE, W. H., KING, O. N., FILIPPAKOPOULOS, P., ALFANO, I., SAVITSKY, P., BURGESS-BROWN, N. A., MULLER, S. & KNAPP, S. 2009. Large-scale structural analysis of the classical human protein tyrosine phosphatome. *Cell,* 136, 352-63.

ELLISON, S., MORI, J., BARR, A. J. & SENIS, Y. A. 2010. CD148 enhances platelet responsiveness to collagen by maintaining a pool of active Src family kinases. *J Thromb Haemost,* 8, 1575-83.

HASHEMI, H., HURLEY, M., GIBSON, A., PANOVA, V., TCHETCHELNITSKI, V., BARR, A. & STOKER, A. W. 2011. Receptor tyrosine phosphatase PTPgamma is a regulator of spinal cord neurogenesis. *Mol Cell Neurosci,* 46, 469-82.

HERMISTON ML, ZIKHERMAN J, ZHU JW. CD45, CD148, and Lyp/Pep: critical phosphatases regulating Src family kinase signaling networks in immune cells. *Immunol Rev*. 2009 Mar;228(1):288-311.

BARR, A. J. 2010. Protein tyrosine phosphatases as drug targets: strategies and challenges of inhibitor development. *Future Med Chem,* 2, 1563-76.

Informal enquiries may be directed to Dr Alastair Barr (a.barr1@westminster.ac.uk) in the School of Life Sciences