



Project Title "Dissecting protein phosphatase 1 regulation"  
Group Leader Iain Hagan  
Research Group Cell Division

***This 4-year PhD studentship will be based in the Oglesby Cancer Research Building, Manchester Cancer Research Centre, adjacent to the Christie NHS Foundation Trust, Withington, Manchester.***

Many of the signalling cascades that convert normal growth to the cancerous state are driven by changes in the phosphorylation landscape of the cell. There has therefore been considerable interest in studying the protein kinases that enforce these changes, many of which are actually the transformatory oncogenes driving the cancer (e.g. *src* and *BRAF*). In contrast to our great insight into how protein kinase activities drive transformation, understanding of the function and regulation of the phosphatases that remove phosphate is remarkably patchy. As the level of phosphate on a protein is a product of the balance between kinase and phosphatase activities, this lack of insight is likely to be leaving some key therapeutic opportunities overlooked.

Protein phosphatase 1 is one of the major serine threonine phosphatases in the cell. It is recruited to over 200 targets to modulate the phosphorylation status of these partners, or nearby proteins. This need to bind so many proteins has led to extreme amino acid sequence conservation between the PP1 enzymes of humans and yeast. This project will exploit this conservation to use fission yeast as a model system in which to characterise the impact of post-translational modifications of fission yeast PP1 enzymes before using these findings to guide focused studies of the human enzymes and the cellular impacts of blocking or enhancing key modifications.

The programme will use a variety of genetic, molecular, biochemical and microscopy approaches that our team has developed over 20 years of studying PP1. We have characterised 4 partners in fission yeast (see references below) and three partners in human cells (unpublished). The project will give experience in all core areas of modern cell biology in a highly dynamic research group that is studying how protein phosphatase/kinase activities cell cycle progression and how these controls are modified in cancer.

Alvarez-Tabares et al. *Journal of Cell Science* 120: 3589-3601. (2007)

Grallert, A. et al. *Current Biology* 23:213-222. (2013)

Grallert A. *Nature* 517:94-98 (2015)