

Clinical Fellow Proposal

Supervisor: Professor Kevin Ryan, Beatson Institute for Cancer Research
Clinical Supervisor: Professor Jeff Evans, Beatson Institute and BWOSCC.

“Searching for a biomarker of early pancreatic cancer”

Pancreatic cancer is currently one of the most difficult to treat. In the UK, only 3% of patients survive for 5 years after diagnosis and the disease kills around 7,500 per year. One of the main reasons for this extremely poor survival rate is that the majority of patients already have advanced disease at the time of diagnosis. This therefore highlights the need for the development of improved screening strategies that will facilitate the detection of early pancreatic cancer or pre-cancerous lesions such that successful therapy can then be achieved.

Our group works on a cellular process called autophagy that has important roles during tumour development. Autophagy when translated from Greek means ‘self-eating’ and is a process whereby cells break down cytoplasmic proteins and organelles in order to maintain cellular integrity. Due to the fundamental role played by autophagy in regulating cellular homeostasis, it is not a surprise that perturbations in autophagy can promote tumour formation. We have been working with an *in vivo* model of pancreatic cancer driven by the Ki-Ras oncogene which is mutated in approximately 90% of human pancreatic tumours. In the presence of one mutant allele of Ki-Ras, mice develop a small number of pre-cancerous lesions called PanINs (pancreatic intraepithelial neoplasia) which progress to pancreatic ductal adenocarcinoma (PDAC) over a long period of time. However, when autophagy is also blocked in the pancreas, animals develop widespread PanINs that fill the entire organ. Since this is a very unusual situation, we considered it a unique opportunity to search for a clinically-relevant biomarker for the detection of early or pre-cancerous PDAC.

The project will fall in two parts. Firstly, both normal animals and animals with exacerbated PanIN formation will be exsanguinated and the blood compared by mass spectrometry to identify proteins which are different between the two cases. These studies will be undertaken in conjunction with the Beatson Institute’s Mass Spectrometry Facility. Factors identified through this approach will also be analysed in the urine from these animals, to test if the biomarker(s) is also detectable in this way.

In the second part of the project, a simple test will be developed to assay for the biomarker(s) that had been identified by mass spectrometry. If not already available, an antibody to the biomarker(s) will be generated and developed for use in an enzyme-linked immunosorbent assay (ELISA). Mouse material from healthy and diseased animals will be tested using this ELISA to assess if the biomarker and assay can successfully be used to detect both the presence of PanINs and PDAC. If this proves successful, human material (blood or urine) from healthy people and patients with PDAC will also be screened using this approach to determine if the assay is a potentially useful diagnostic tool. We feel this project is scientifically exciting with a clear goal and as such is highly suited to a highly-engaged and ambitious clinical fellow.

Recent selected publications for our laboratory:

Crichton, D., Wilkinson, S., O'Prey, J., Syed, N., Smith, P., Harrison, P.R., Gasco, M., Garrone, O., Crook, T. and Ryan, K.M. (2006) DRAM – a p53-induced modulator of autophagy is critical for apoptosis. *Cell* 126(1): 121-134.

Crichton, D., Wilkinson, S. and Ryan, K.M. (2007) DRAM links autophagy to p53 and programmed cell death. *Autophagy* 3(1), 72-74.

Bell, H.S., Dufes, C., O'Prey J., Crichton, D., Bergamaschi, D., Lu, X., Schätzlein, A.G., Vousden K.H and Ryan, K.M. (2007) A novel p53-derived apoptotic peptide de-represses p73 to cause tumor regression in vivo. *The Journal of Clinical Investigation* 117(4) 1008-1018

Bell, H.S. and Ryan, K.M. (2007) Targeting the p53 family for cancer therapy – ‘Big Brother’ joins the fight. *Cell Cycle* 6(16):1995-2000.

Bell, H.S. and Ryan, K.M. (2008) iASPP inhibition: increased options in targeting the p53 family for cancer therapy. *Cancer Research* 68: 4959-4962

O'Prey, J., Wilkinson, S. and Ryan, K.M. (2008) Tumor antigen LRRC15 impedes adenoviral infection – implications for viral based cancer therapy. *Journal of Virology*, 82(12): 5933-5939

Wilkinson, S., O'Prey, J. Fricker, M. and Ryan, K.M. (2009) PDGFR family kinases promote hypoxia-selective autophagy and cell survival by defining HIF1 α targets. *Genes & Development* 23(11): 1283-1288.

Vousden, K.H. and Ryan, K.M. (2009) p53 and metabolism. *Nature Reviews Cancer* 9(10): 691-700.

Rosenfeldt, M.T. and Ryan, K.M. (2009) The role of autophagy in tumour development and cancer therapy. *Expert Rev Mol Med.* 11:e36.

Helgason, G.V., O'Prey, J. and Ryan, K.M. (2010) Oncogene induced sensitization to death requires induction as well as de-regulation E2F1. *Cancer Research* 70(10):4074-4080.

Ryan, K.M. (2010) Cancer: Viruses' backup plan? *Nature.* 466(7310):1054-5

Ryan, K.M. (2011) p53 and autophagy in cancer: guardian of the genome meets guardian of the proteome. *Eur J Cancer.* 47(1):44-50

Rosenfeldt, M.T. and Ryan, K.M. (2011) The multiple roles of autophagy in cancer. *Carcinogenesis.* 32(7):955-63.

Wilkinson, S., Croft, D.R., O'Prey, J., Meedendorp, A., O'Prey, M., Dufès, C. and Ryan, K.M. (2011) The cyclin-dependent kinase PITSLRE/CDK11 is required for successful autophagy. *Autophagy* 7(11): 1-7.