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Prostate cancer is a global health issue. Despite the controversy surrounding over-diagnosis and over-treatment, prostate cancer remains a major cause of mortality in men in the developed world. Our laboratory focuses on discovering improved treatments for prostate cancer. Our research examines the molecular control of cell survival (aberrant signalling involving activation of receptor tyrosine kinases and epigenetic silencing of *Sprouty2*), cell death (autophagy and kinesin) and invasion (MEK5-ERK5 signalling). Ongoing *in vivo* models for prostate and bladder cancer have provided us with new model systems and exciting insight into their pathogenesis. *In vitro* and *in vivo* models will be combined with genome-wide methodologies to identify novel biomarkers and targets for therapy.

By integrating the major research themes (survival, death and invasion) with state-of-the-art technologies, we have made the following key discoveries in the past year:

Androgens modulate autophagy and cell death via regulation of the ER chaperone Grp78/BiP in prostate cancer cells (Bennett *et al.*, Cell Death Dis., in press) and Grp78 overexpression potentiates the effects of Hsp70-Hsp90 client proteins such as androgen receptor and HER2 in castrate-resistant prostate cancer (Tan *et al.*, J. Pathol. 2011; 223:81) (collaborative project with Kevin Ryan).

Eg5, a member of the kinesin motor family, is a potential target for therapy in prostate cancer and docetaxel-resistant prostate cancer cells remain sensitive to inhibition of Eg5 function by S-trityl-L-cysteine (Wiltshire *et al.*, Mol. Cancer Ther. 2010; 9: 1730) (collaborative project with Frank Kolzielski).

ERK5 signalling in prostate cancer promotes an invasive phenotype (Ramsay *et al.*, Br. J. Cancer, in press). This, along with our previous work on ERK5 in castrate-resistant

prostate cancer, has identified two key patient cohorts for future clinical application of an ERK5 inhibitor (collaborative project with Laura Machesky, Cancer Research Technology and Newcastle University).

*In vivo* models in prostate and bladder cancer have revealed novel synergistic interactions involving distinct signalling abnormalities, including HER, Wnt and Sprouty (Ahmad *et al.*, Oncogene 2011; 30: 178; manuscript in preparation) (collaborative project with Owen Sansom and Tomoko Iwata, University of Glasgow).

Our ongoing efforts will focus on studies examining interactions important in prostate carcinogenesis that may happen between distinct signalling cascades, and epithelium and stroma. Using sequencing and peptide profiling technologies, we will also characterise gene expression and splice variant utilisation that may underpin these interactions.

**Interactions between Sprouty2, PTEN and HER**  
Sprouty2 (SPRY2), a key regulator of receptor tyrosine kinase signalling, is frequently inactivated in human malignancies. We showed that the role

Figure 1  
Confocal microscopy showing SPRY2 knockdown induces nuclear accumulation of PTEN. GFP-PTEN expressed in vector control and SPRY2 knockdown in PTEN null human PC3 cells.

Figure 2  
Schematic representation of the basis for synergism between PTEN and HER2 in prostate carcinogenesis.

Figure 3  
Schematic diagram of mouse prostate cell compartments.

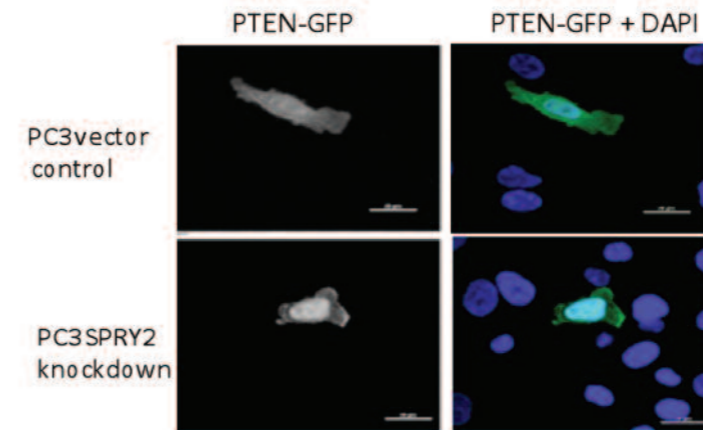


Figure 1

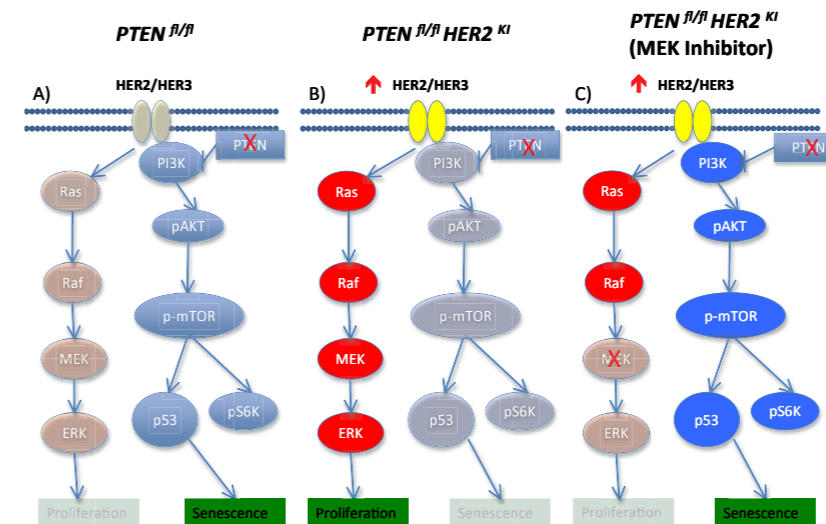


Figure 2

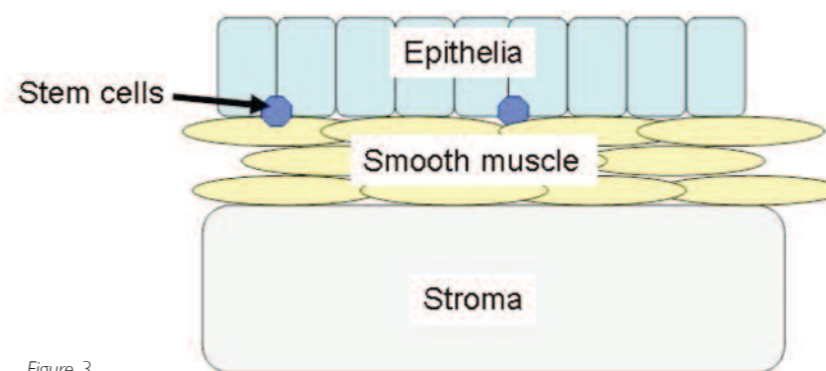


Figure 3

of SPRY2 in carcinogenesis is complex. Its loss can either inhibit or promote prostate cancer depending on PTEN and EGFR status. SPRY2 loss mediates PTEN nuclear translocation (Fig. 1) to induce p53-dependent G1 arrest; this happens despite PI3K activation due to enhanced PTEN phosphorylation. SPRY2 loss exaggerates the response to EGF stimulation by altering EGFR trafficking via the PI3K-p38 pathway in the presence of PTEN. PI3K activation associated with SPRY2 loss enhances EGFR (and HER2) endocytosis to promote carcinogenesis, while concurrent SPRY2 and

PTEN loss drives tumorigenesis via ERK activation. Hence, SPRY2 loss governs prostate carcinogenesis in a PTEN and EGFR (and HER2) dependent context.

We plan to examine the molecular basis of the above observations, which have important impact on patient stratification for targeted therapies. In addition, we have also recently identified a synergistic interaction between PTEN inactivation and HER2 activation that results in aggressive prostate cancer (clinical and *in vivo* model). Interestingly, we found that HER2-driven MAPK activation overcomes PTEN loss-induced cellular senescence (PICS) and that the presence of a MEK inhibitor strongly suppressed proliferation within these tumours by restoring the PICS programme (Fig. 2).

### Importance of stromal micro-environment

Dysfunction of androgen-driven stromal-epithelial interactions is key in normal prostate development and function as well as in prostate diseases such as benign prostatic hyperplasia and prostate cancer (Fig. 3). Previous studies focused on the role of the epithelium but increasing evidence points towards a key role for stromal smooth muscle (SM) cells in androgen-dependent prostate disease and its response to androgen ablation therapy, which can only be considered palliative in nature. Furthermore, androgen receptor expression is often lost from tumour stroma in advanced metastatic prostate cancer. We plan to investigate how the stromal micro-environment differs in prostatic intra-epithelial neoplasia, prostate adenocarcinoma and advanced metastatic prostate adenocarcinoma by examining gene expression in various mouse and human prostate samples. We have also recently developed an exciting new mouse model in which androgen receptor is ablated from prostatic SM (SMARKO) (in collaboration with Lee Smith, University of Edinburgh). These mice demonstrate that SM androgen receptor signalling maintains prostatic cell differentiation and homeostasis and could play a facilitating role in prostate disease. We will now investigate how stromal androgen receptor signalling affects the initiation and progression of prostate cancer. We hypothesise that ablating SM androgen receptor will advance prostatic intra-epithelial neoplasia normally seen in *Pten*<sup>+/-</sup> mice to metastatic adenocarcinoma. We will also examine these mice for expression of genes identified to mediate stroma-epithelial interactions.

**Publications listed on page 79**