



Urological Research

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We are a laboratory-based group with a strong surgical focus on prostate cancer.

We have the largest NHS practice in robotic prostatectomy in the UK, which has proved to be very important in contributing to a well-characterised human biorepository at the CRI. In the past year this has led to a new Cancer Research UK project, the CancerMaP project, jointly run with Colin Cooper of the Institute of Cancer Research (ICR), which will generate DNA, mRNA and miRNA from prostate cancers stratified by TMPRSS2-ERG status. Over the past year, the project team has grown with the appointment of Vincent Gnanapragasam (HEFCE funded Senior Lecturer; and Cancer Research UK Clinician Scientist). We are a multi-disciplinary group, which includes a substantial number of clinical academic trainees in addition to biologists. The main purpose of the group is to identify the mechanisms that underpin castration independent prostate cancer, with the intention of identifying potential therapeutic targets or markers that might predict clinical outcome of prostate cancer. A critical component over the past year has been to further develop the clinical material required for testing out new potential markers. This has included establishing tissue microarrays, and collections of serum, plasma and urine in addition to fresh frozen material.

Castration-independent prostate cancer

Androgen receptor (AR) signalling is maintained in most men with castration-independent prostate cancer and new management and therapeutic approaches are needed. Our goals are to identify and characterise markers that better predict progression, and to identify more effective ways of targeting this disease. The AR as a transcription factor remains the primary target for treatment and the rationale remains strong for better targeting of this pathway and to

uncover biomarkers. Because it is unlikely that any single protein will prove to be critical as a marker or a therapeutic target a rational approach is to unravel transcriptional networks by integrating chromatin immuno-precipitation (ChIP), expression, and SNP data. Over the last five years, we have characterised AR binding sites and gene targets using ChIP and expression arrays (Figure 1). The same approaches are now being applied to other transcription factors (Ascl1 and Hes6) and co-regulators (HIP1) which we have shown to be over-expressed and, in the case of HIP1 and Hes6, to associate with the AR. It is possible that targeting transcription factors/co-regulators other than the AR may reduce AR signalling sufficiently to produce a therapeutic response. To test this idea further we need more appropriate models and better characterised sets of clinical material, which we hope to have in the near future.

Main discoveries

Our main discoveries are highlighted below.

(1) We have shown how the AR binds to the human genome and using ChIP-on-chip have found that it usually binds in a half-site (rather than as a palindromic dimer) and that frequently there is co-enrichment for other transcription factors such as Foxa1, ETS and GATA, several being of functional importance (Massie et al., *EMBO Rep.* 2008; 8:871; Massie and Mills, *EMBO Rep.* 2008; 9:337).

(2) A neuro-endocrine profile is associated with castration-independence. We have found that a pro-neural expression signature, including over-expression of Ascl1, Hes6, and neurotensin is associated with advanced and castration-independent prostate cancer, and that Hes6 silencing reduced neural gene expression and invasiveness of prostate cancer (Vias et al., *Prostate* 2007; 67:190; Vias et al., *BMC Med. Genomics* 2008; 1:17; Vias et al., *Trends Mol. Med.* 2008; 14:486).

*Joined during 2008 †Left during 2008

