PROSTATE CANCER BIOLOGY

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Prostate cancer affects one in eight men in the developed world, and now accounts for more cancer-related deaths in men than breast cancer does in women. Recent improvements in hormonal therapy and chemotherapy have brought about modest impact on patient survival. There remains an urgent need to understand treatment-resistant prostate cancer better in order to develop more effective personalised therapies.

We have a highly comprehensive cross-disciplinary programme of translational research aimed at tackling treatment (hormonal and/or taxane chemotherapy) resistance. Our research efforts are revealing novel targets for therapy. Timely validation studies on the identified targets are enabling us to launch 'therapy' discovery campaigns and initiate proof-of-concept clinical trials. Our preclinical and clinical expertise facilitates a seamless transition from laboratory findings to the design of clinical studies, as well as the development of clinical cohort studies.

Target discovery to overcome treatment resistance

We applied three pairs of human isogenic hormone-responsive and -resistant prostate cancer cell models and grew them as orthotopically implanted tumours in a nude mouse model. Collaborating with Dr Sara Zanivan, quantitative proteomic analysis was performed to study the proteome of the tumours. We identified two candidate proteins that were potently upregulated in hormone- (or castration-) resistant tumours. We are now testing the functional impact of the candidate proteins on prostate cancer growth and metastasis. If successful, we will further evaluate the value of these candidates as targets for therapy.

Using a CRISPR screen in an orthograft model, we hope to identify novel genes that may enhance the treatment efficacy of hormone treatment (androgen deprivation therapy) or docetaxel chemotherapy. Hits from the screen are now being validated and further pursued as candidate targets.

A forward genetic screen has been launched as part of Dr Imran Ahmad's CRUK Clinician Scientist Fellowship. This project builds on an earlier screen, which yielded highly informative data, resulting in the nomination of PPARγ as a potential therapeutic target.

Preclinical and clinical validation of novel therapeutics

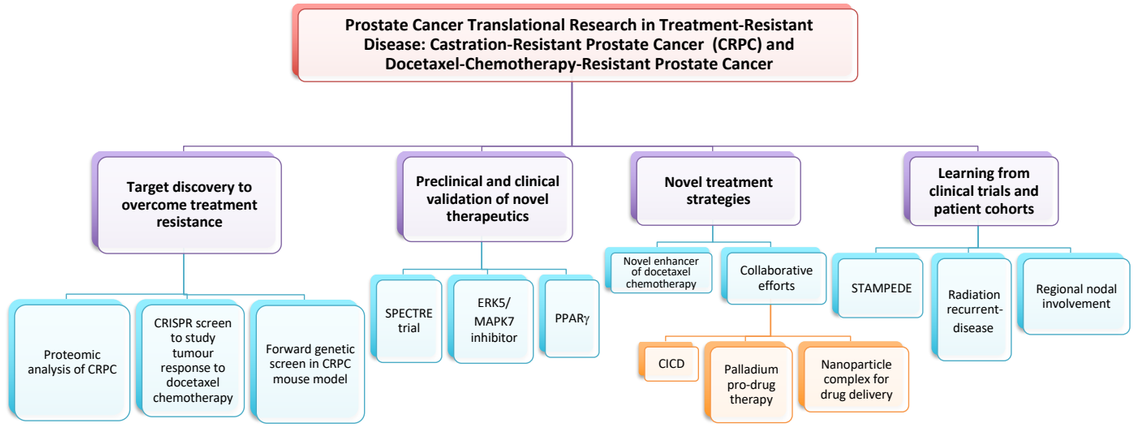
SPECTRE is a proof-of-concept efficacy clinical trial based on our recent publication (Patel *et al.*, 2017), in which we highlighted the importance of tumoural cholesterol uptake by castration-resistant prostate cancer in testosterone *de novo* synthesis.

We have previously proposed ERK5 as a potential target for therapy. Using a genetically modified mouse model of *Pten*-loss-driven prostate cancer, we can confirm that reduced *ERK5* expression suppressed prostate carcinogenesis. This data directly supports the value of ERK5 as a target for therapy. Our plan is to further investigate whether the observed effect on tumour growth depends on the kinase activity of ERK5 or simply depends on its expression status.

PPARγ has a wide-ranging metabolic impact on glucose and lipid metabolism and has been implicated in our earlier forward genetic screen (Ahmad *et al.*, Proc Natl Acad Sci USA 2016; 113: 8290–5). Comprehensive analysis of how PPARγ metabolically and phenotypically contributes to prostate carcinogenesis is now underway.

Novel treatment strategies

Through a number of collaborative projects, we are exploring a number of promising treatment strategies:



From a repurposing screen, we have nominated a drug to combine with docetaxel for enhanced efficacy. We are currently considering the possibility of a proof-of-concept Phase II/III clinical study.

Other collaborative projects include approaches to exploit caspase-independent cell death (in collaboration with Dr Stephen Tait); palladium pro-drug therapy (in collaboration with Dr Asier Unciti-Broceta (University of Edinburgh); and a nanoparticle-based drug delivery complex (in collaboration with Dr Christine Dufes, University of Strathclyde).

Learning from clinical trials and patient cohorts

We successfully applied archival diagnostic materials from the STAMPEDE clinical trial for next-generation RNA sequencing to interrogate the transcriptome of patients receiving chemotherapy within the STAMPEDE trial. Our timely study benefits from the recent publication of (modest) survival benefit combining hormone and chemotherapy upfront at the time of diagnosis (James *et al.*, Lancet 2016; 387: 1163–77). We are working hard to develop a molecular signature to identify patients who would respond unfavourably and therefore may benefit from additional or alternative treatment.

Taking advantage of our clinical expertise, we are developing translational studies focusing on patients who have relapsed from previous radiation-based therapy and those patients with evidence of significant cancer with regional nodal metastasis. We are particularly interested in understanding the tumour microenvironment in recurrent/progressive tumours.

Publications listed on page 99