

PROSTATE CANCER BIOLOGY



Group Leader
Hing Leung

Clinical Lecturer
Mark Salji¹

Graduate Student
Maha AlRasheedi

¹NHS Educating Scotland

²Embassy of Kuwait, London;
jointly with Nuclear Medicine,
NHS Greater Glasgow and Clyde



Prostate cancer affects one in eight men in the developed world, and now accounts for more cancer related deaths in men than females dying of breast cancer. Despite improvement in patient survival with novel androgen receptor inhibitors and taxane chemotherapy, a significant proportion of patients with advanced disease still dies within five years of diagnosis. We have a highly comprehensive cross-disciplinary programme of translational research aimed at tackling treatment (hormonal and/or taxane chemotherapy) resistance. At our disposal, we have a wide range of preclinical models and clinical resource to help us discover new treatment targets and understand the molecular mechanisms of how aggressive prostate cancer can resist current treatment.

The Prostate Cancer Biology Group applies cutting-edge technologies and innovative laboratory model systems to enhance our understanding of treatment resistance. We ultimately aim to discover new therapeutic targets and develop better treatment strategies with accompanying clinical biomarkers to support precision medicine in patients with advanced prostate cancer (Figure 1).

Castration-resistant prostate cancer (CRPC) is incurable and remains a significant challenge worldwide. Using a panel of isogenic human prostate cancer models of hormone-naïve and castration-resistant disease, we have developed matching 2- and 3-dimensional *in vitro* cultures and *in vivo* orthografts to model clinical prostate cancer. We initiated deep quantitative proteomic analysis to characterise proteins of interest in CRPC. As a result, we identified several key players in CRPC and reported our findings recently (Blomme *et al.*, 2020, 2022; Martinez *et al.*, 2021).

We further carried out multi-omic analyses (RNA sequencing, proteomics, and metabolomics) of our matched models of hormone-naïve and castration-resistant orthografts. Untargeted metabolomics revealed N-acetylaspartate (NAA) and N-acetylaspartylglutamate (NAAG) commonly accumulating in CRPC across three independent matched models. In addition, proteomics analysis showed upregulation of related enzymes, namely N-Acetylated Alpha-

Linked Acidic Dipeptidases (FOLH1/NAALADL2; also commonly referred to as Prostate-Specific Membrane Antigen/PSMA)(Salji *et al.*, 2022). Of note, PSMA is a highly relevant clinical marker in routine clinical PET imaging to detect metastatic and/or recurrent disease. Here, our findings are pointing to a new research direction in understanding how PSMA-mediated functions may promote treatment resistance.

Our recent extensive research into CRPC collectively points to aspects of altered cancer metabolism to be important in treatment resistance. We were particularly intrigued by the role of abnormal cholesterol metabolism in driving lethal prostate cancer. We recently observed that an androgen self-sufficient form of CRPC depends on cholesterol bioavailability, and SCARB1 (Scavenger Receptor Class B Member 1) mediates tumoral cholesterol uptake to fuel androgen biosynthesis as a resistance mechanism (Patel, *et al.*, 2018). To test the clinical relevance of this observation, we designed a proof-of-concept clinical study, the SPECTRE trial, which is a 6-week long single-arm Phase II treatment trial combining atorvastatin and androgen-deprivation therapy in patients with CRPC. The primary study endpoint was the proportion of patients achieving ≥50% drop of baseline PSA levels at any time over the 6-week period of atorvastatin medication (PSA response). Exploratory endpoints included PSA velocity and mass spectrometrically identified serum metabolites (Rushworth *et al.*, 2022).

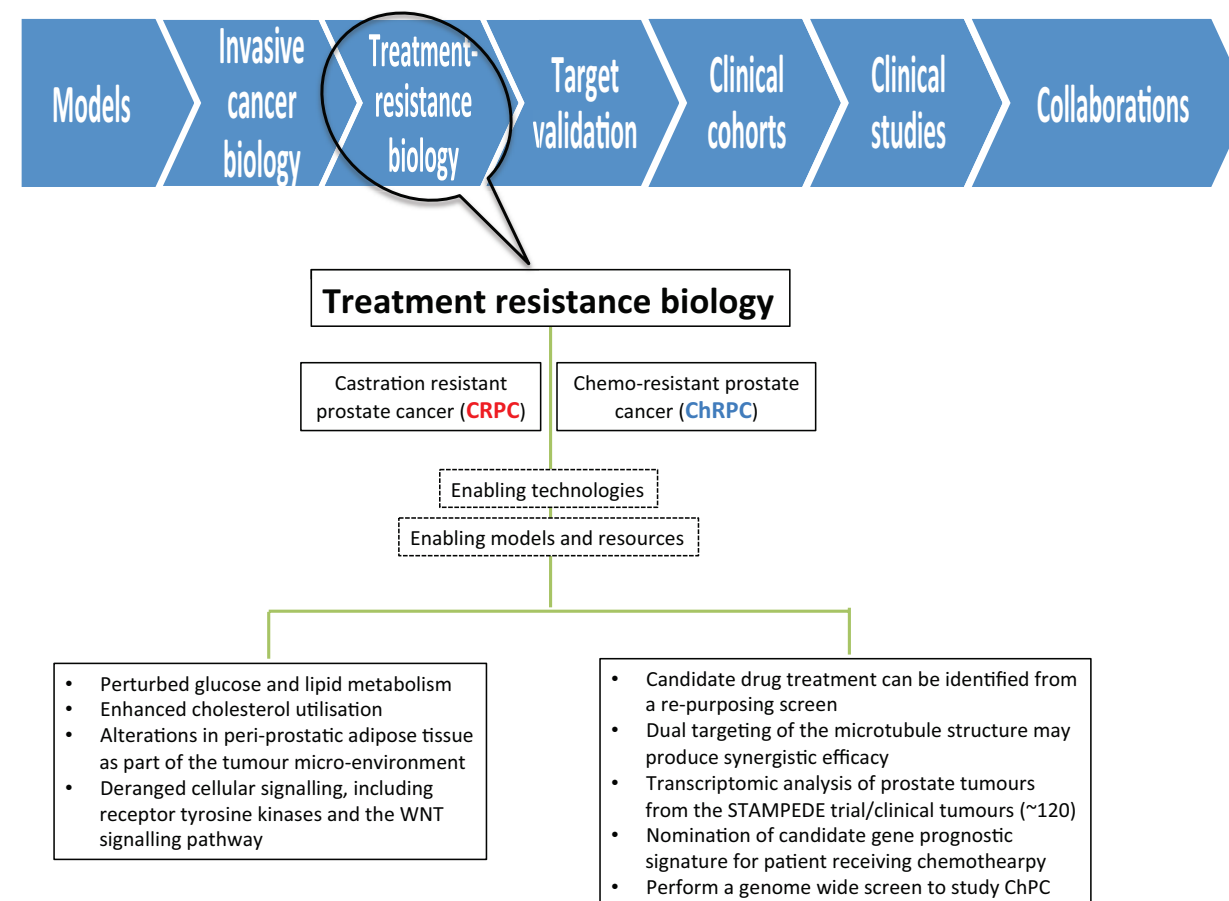


Figure 1

The research programme in the Prostate Cancer Biology Group comprehensively spans multiple aspects of translational cancer research, including basic discovery cancer biology studies, validation of novel druggable targets, collaborative drug discovery campaigns, clinical cohort studies and clinical trials of novel therapeutic agents. In this report, we highlight recent research milestones in our studies of treatment-resistant prostate cancer, particularly for castration-resistant disease. (Enabling technologies - e.g. transcriptomic, proteomic and metabolomic analyses; Enabling models and resources - e.g. genetically engineered mouse models, orthotopic xenograft models, primary cultures; Tissue microarray of clinically resected prostate tumours; Bio-repository from clinical trials and biobanks).

At scheduled interim analysis, all twelve recruited patients experienced, as expected, substantial falls in serum cholesterol levels following statin treatment. While all patients had comparable pre-study PSA velocities, 6 out of 12 patients showed decreased PSA velocities following statin treatment, suggestive of stabilised disease. Unbiased metabolomics analysis of serial weekly blood samples identified tryptophan as a dominant metabolite associated with statin response. Hence, our data from the SPECTRE study provides the first evidence of statin-mediated effects on CRPC and early sign of disease stabilisation. Our data also highlights the

possibility of altered tryptophan metabolism as a potential biomarker for tumour response to statins.

Concluding comment

The use of a multi-omics approach on our panel of preclinical treatment-resistant prostate cancer models reveals novel treatment strategies. Based on our proof-of-concept clinical study, targeting cholesterol metabolism in CRPC warrants further investigations.

[Publications listed on page 106](#)