Prostate cancer is a leading cause of cancer mortality in men in the Western world. Identifying and understanding the pathways that drive advanced and treatment-resistant prostate cancer will provide important information that will allow prognostication and individualised patient treatments.

Our current research interests lies in understanding the mechanisms of treatment resistance in advanced prostate cancer. Work in our lab together with Hing Leung’s group uses state-of-the-art in vivo models in conjunction with patient samples to interrogate the disease processes in advanced and treatment-resistant prostate cancer. This work will help to provide information on drivers of prostate cancer progression and to identify novel biomarkers of disease and/or drug targets to treat the disease.

As a Consultant Urological Surgeon based at the Queen Elizabeth University Hospital in Glasgow, I have one of the highest-volume robotic prostatectomy practices in the UK for patients with aggressive and locally advanced prostate cancer, allowing me to keep my translational research clinically relevant.

**Sleeping Beauty screen reveals Pparγ activation in metastatic prostate cancer**

Using a murine forward mutagenesis screen (Sleeping Beauty) in a PtenNull background, we were able to identify the gene peroxisome proliferator-activated receptor gamma (Pparγ), which encodes a ligand-activated transcription factor, as a promoter of metastatic prostate cancer. Pparγ is a critical regulator of fatty acid and glucose metabolism, influencing lipid uptake and adipogenesis. In our model, upregulation of Pparγ was associated with an activation of lipid signalling pathways, including upregulation of lipid synthesis enzymes (fatty acid synthase (FASN), acetyl-CoA carboxylase (ACACA)) and lipid droplets (ACLY). Our data suggested that prostate cancer patients could be stratified in terms of Pparγ/FASN and PTEN levels to identify patients with aggressive prostate cancer who might respond favourably to Pparγ/FASN inhibition (low PTEN/high PAKT expression), a finding that has potential to guide the design of future clinical trials. Ongoing research by our group has demonstrated that this lipid synthesis phenotype might be driven through alterations in mitochondrial function and AKT3 activations.

In addition, to our knowledge, we were the first to demonstrate the strength of the Sleeping Beauty transposon model system in successfully determining low-frequency somatic mutations that might drive prostate tumourigenesis. We are further investigating and validating other novel and clinically relevant hits from this screen.

**Role of Arid1a in prostate cancer**

ARID1A was also identified as a potential driver in prostate cancer by the Sleeping Beauty screen. ARID1A is part of the BAF complex, and functions as a key regulator controlling DNA accessibility and organisation by chromatin remodelling. The BAF complex itself is highly mutated in metastatic prostate cancer (CRPC and ERPC).

Our group has been working on characterising its role in cholesterol uptake and synthesis along with regulation of fatty acid synthesis in metastatic prostate cancer.

**Publications listed on page 100**

**MODELS OF ADVANCED PROSTATE CANCER**