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. Despite improvement in patient survival with novel androgen receptor inhibitors and taxane chemotherapy, patients with advanced disease typically die within five years. We have a highly comprehensive cross-disciplinary programme of translational research aimed at tackling treatment (hormonal and/or taxane chemotherapy) resistance. We have at our disposal a wide range of preclinical models and clinical resources to help us discover new treatment targets and understand the molecular mechanisms of how aggressive prostate cancer can resist current treatments.

Our group applies cutting-edge technologies and innovative laboratory models to enhance our knowledge in treatment resistance. We ultimately aim to discover new therapeutic targets and develop better treatment strategies and improved clinical biomarkers to support personalised medicine in patients with advanced prostate cancer (Figure 1). Mebendazole, an anthelminthic drug, is identified as a clinical candidate to enhance the efficacy of breast ductal medication to treat advanced prostate cancer.

Docetaxel chemotherapy in prostate cancer has a modulated impact on survival. To date, efforts to develop a combination therapy have not translated into new treatment regimes. It is increasingly appreciated that drugs previously developed for a specific indication may be successfully ‘re-purposed’ to treat conditions that were not intended. To this end, we performed a drug repurposing screen using our treatment-resistant prostate cancer cell model. Cells were treated with docetaxel alone, or in combination with drugs. We assayed the viability of cells by nuclear counting using high-content imaging analysis.

Mebendazole, an anthelminthic drug that inhibits microtubule assembly, was selected from hit compounds for mechanistic and functional microtubule assembly, was selected from hit compounds for mechanistic and functional studies of treatment-resistant prostate cancer cell models. We hypothesise that targeting microtubules with more than one agent may improve tumour response. We propose that the concept of combined mebendazole and docetaxel treatment therefore warrants formal clinical evaluation.

Combined docetaxel and mebendazole treatment dramatically reduced cell cycle progression with increased G2/M mitotic block and enhanced cell death. Significantly, following combined treatment, no prostate cancer cells were observed to divide correctly, forming multipolar spindles that resulted in aneuploid daughter cells or arrest in prometaphase.

In collaboration with Dr Christine Dufès (University of Strathclyde), we engineered liposomes to entrap docetaxel and mebendazole at a pre-determined ratio to study evidence of in vivo synergy. Combined treatment indeed drastically suppressed in vivo prostate tumour growth and extended progression-free survival when compared to single drug treatment. Collectively, our data suggests targeting microtubules with more than one agent may improve tumour response. We propose that the concept of combined mebendazole and docetaxel treatment therefore warrants formal clinical evaluation.

AR-mediated rewiring of cancer cell metabolism supports resistance to AR inhibitors in CRPC.

AR-mediated rewiring of cancer cell metabolism supports resistance to AR inhibitors in CRPC. Besides chemo-resistance, we have a major interest in understanding the molecular basis of tumour resistance to hormonal therapy (or androgen deprivation therapy), referred to as castration-resistant prostate cancer, CRPC.

Our team has performed a comprehensive unbiased workflow of proteins consistently associated with treatment resistance, we investigated the impact of candidate proteins in experiments to formally validate the value of the protein panel as biomarkers of CRPC and to probe the role of C7 (complement C7) expression in prostate cancer. In this study, we highlighted the role of C7 in prostate tumourigenesis and its potential as a therapeutic target.

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. Despite improvement in patient survival with novel androgen receptor inhibitors and taxane chemotherapy, patients with advanced disease typically die within five years. We have a highly comprehensive cross-disciplinary programme of translational research aimed at tackling treatment (hormonal and/or taxane chemotherapy) resistance. We have at our disposal a wide range of preclinical models and clinical resources to help us discover new treatment targets and understand the molecular mechanisms of how aggressive prostate cancer can resist current treatments.