DE BONO Johann EOI 2022 – ICR

Project title: Targeting inflammatory cell mediated fuelling of prostate cancer

Project Summary:

Prostate cancer is the commonest cancer in men in the UK, a leading cause of male cancer mortality and increasing in incidence in Asia and the developing world (Sartor & de Bono, NEJM 2018). Inflammation is believed to play a causal role in prostate carcinogenesis, although the precise mechanisms lead to this remain to be fully elucidated (de Bono et al, Nature Reviews Cancer 2020) Treatment has remained underpinned by drugs impacting androgen receptor (AR) function, leading to what is termed castration resistant prostate cancer (CRPC) which is invariably lethal.

We have generated evidence that prostate carcinogenesis and treatment resistance are induced, at least in part, by myeloid-derived suppressor cell secretion of paracrine oncogenic factors including IL-23 (Calcinotto et al, Nature 2018) which can activate AR signaling through JAK/STAT signalling induced activation of ROR (Calcinotto et al, Nature, 2018; Wang et al, 2016). ROR can become overexpressed in CRPC (Abida et al, PNAS, 2019). Interestingly, RORγ can increase AR and AR splice variant (AR-SV) expression and signalling, while RORγt is implicated in the generation of CD4+FOXP3- T cells with an IL-17-secreting and pro-inflammatory, Th17 phenotype (Wang et al, Nature, 2018, Miossec and Kolls, Nature Reviews Drug Discovery, 2012). We hypothesize that elucidating these tumour cell to stromal cell paracrine relationships can identify novel therapeutic strategies to transform the care of prostate cancer.

This PhD student will:

1) Study whole biopsy and single cell CRPC genomic and RNAseq data to generate data supporting tumour-inflammatory cell paracrine interactions;
2) Generate in vitro data in patient-derived models elucidating the oncogenic roles of implicated inflammatory cell secreted paracrine factors;
3) Pursue in vivo studies with novel anticancer agents in patient-derived xenografts and immunocompetent transgenic models (PTEN-/- TP53-/-) to support this hypothesis;
4) Conduct a biomarker-driven proof-of mechanism and proof-of-concept clinical trial and support biomarker data analyses.

Supervisory Team:

- Professor Johann de Bono, Clinical Studies**,** Institute of Cancer Research
- Dr Adam Sharp, Institute of Cancer Research