ICR The Institute of Cancer Research

The Institute of Cancer Research
PHD STUDENTSHIP PROJECT PROPOSAL

FUNDER DETAILS	
Studentship funded by:	Prostate Cancer Foundation
PROJECT DETAILS	
Project title:	Dissecting the prostate cancer-stromal interface
SUPERVISORY TEAM	
Primary Supervisor	Professor Johann de Bono
Associate Supervisor(s)	Dr Adam Sharp Dr Jon Welti
Secondary Supervisor	Professor Udai Banerji
DIVISIONAL AFFILIATION	
Primary Division	Clinical Studies
Primary Team	Cancer Biomarkers
Site	Sutton

ABSTRACT

Prostate cancer is the commonest cancer in men, increasing in incidence in Africa and Asia, and a major cause of male cancer morbidity and mortality. While many prostate cancers are indolent and need no treatment, and some others are curable, a substantial proportion are aggressive, advanced at diagnosis, and lethal despite multiple treatment advances. Research from our laboratories and others have identified cytokines including IL-23 and NRG-1 that are secreted by stromal cells including myeloid cells that fuel prostate cancer growth. This work is identifying novel therapeutic strategies to advance prostate cancer therapy and providing insights into means for improving outcomes from prostate cancer. We have hypothesised that the study of these complex interactions existing between prostate cancer cells and various immune cell types, as well as other stromal cells, will allow us to continue to transform prostate cancer care. To support this work, the student will utilise generated patient-derived in vitro and in vivo models, namely patient-derived organoid cultures as well as xenografts. The student will also study co-cultures of these organoids with various stromal cells and acquiring immune cells from patients to evaluate how these can impact prostate cancer cells. Mining of genomic data including exome, whole genome and RNAseq data as well as single cell RNAseq analyses will be a key part of these efforts. It is envisioned that broad validation of acquired data will require the use of various orthogonal experimental efforts. These studies may also involve testing novel therapeutic strategies deemed to impact tumour growth that can then be pursued in clinical and translational parallel research which is a major strength of this team.

BACKGROUND TO THE PROJECT

Prostate cancer is a leading cause of morbidity and mortality in men[1]. Although recent treatment advances have extended overall survival (OS), men with advanced prostate cancer invariably develop lethal advanced castration resistant disease. In addition to risk factors such as age, ethnicity and a

family history of prostate cancer, modifiable risk factors including infection, obesity and diet have been implicated in causing prostate inflammation and carcinogenesis. Recent advances in this field are providing novel mechanistic insights regarding the environmental, genomic and immunological factors driving the 'inflammatory storms' that generate prostate cancer cells and how these contribute to progression to prostate cancer. This complex biology highlights the need for an integrative approach to prostate cancer research, prevention, and drug development strategies.

Chronic inflammation, commonly observed in pre-neoplastic and malignant prostates, has been implicated as a driver of prostate carcinogenesis and progression. Although the exact stimuli required in order to initiate and maintain prostatic inflammation are not fully understood, microbial infection (perhaps from urinary microbiota), chemical irritation, physical trauma, obesity and diet are all postulated to play roles. Tumour progenitor cells of an intermediate phenotype, which co-express basal and luminal cell markers and are purported prostate cancer precursors, expand in the context of inflammation. This inflammatory response consists of the recruitment and expansion of leukocytes including myeloid cells, macrophages and lymphocytes in the prostate. In advanced prostate cancers, high peripheral blood neutrophil-to-lymphocyte ratios, reflecting an expanded circulating myeloid compartment, correlate with worse overall survival and decreased sensitivity to anti-androgens and chemotherapy. As such, we have reported that myeloid-derived suppressor cells (MDSCs) can secrete IL-23 and NRG1, which in a paracrine fashion activate IL-23 and HER3 receptors on tumour cells, driving downstream androgen receptor (AR) target genes through STAT3–RORγ signalling as well as AKT activation. MDSCs also produce free radicals that can cause DNA single- and double-strand breaks (DSBs), which can induce cellular senescence (probably through ATM activation) and fuel further inflammation through senescence and the senescence-associated secretory phenotype (SASP), with vicious cycles fuelling 'inflammatory storms' that drive prostate carcinogenesis and fuel prostate cancer growth.

PROJECT AIMS

- Establish co-culture systems of patient-derived models and stromal cells;
- Elucidate paracrine interactions between these cells; *and*
- Identify and validate actionable therapeutic strategies.

RESEARCH PROPOSAL

Hypothesis

Tumour-stromal cell interactions fuel tumour growth through paracrine cytokines.

Aims

To identify actionable and druggable targets to block prostate cancer growth.

Methods

1. Mining genomic and RNAseq data acquired from clinical biopsies of prostate cancer.
2. Generating and analysing single cell RNAseq data from stromal cells acquired from patient biopsies.
3. Validating RNA data analyses by hyperplex immunocytochemistry.
4. Pursuing functional in vitro and in vivo studies utilising patient-derived models (organoids and xenografts) as well as prostate cancer cell lines, and available transgenic and syngeneic models (eg PTEN -/- TP53 -/-).
5. Validating novel therapeutic strategies for pursuit in clinical trials.

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LITERATURE REFERENCES	
de Bono J et al, Nature Reviews Cancer 2020. Gil V et al, Cancer Research 2020.	
CANDIDATE PROFILE	
Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).	
Pre-requisite qualifications of applicants:	BSc
Intended learning outcomes:	• Cell culture; • Co-culture studies; • Organoid cultures; • Tumour genomic analyses; • Immunocytochemistry; *and* • Single cell RNAseq analyses.
ADVERTISING DETAILS	
Project suitable for a student with a background in:	☒ Biological Sciences ☐ Physics or Engineering ☐ Chemistry ☐ Maths, Statistics or Epidemiology