**Company Name:** Australian Prostate Cancer Research Centre-Queensland (APCRC-Q)

**Project Leaders & Contacts**

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**Project Start:** May 2013

**Project Duration:** 8 months

**Disciplines:** Biology, Biochemistry, Biotechnology, Cell biology, Physiology, Molecular biology, Bioinformatics, Genomics.

**Experience required:**

Laboratory experience is essential and should preferably include some experience in the techniques listed below:

* Cell culture,
* Western blotting and QRT-PCR expression analysis,
* Gene knockdown (shRNA)
* Functional assays for migration and invasion with the latest technology
* Real-time cell analysis,
* Confocal microscopy, and
* Bioinformatics and genomics (for certain projects) – including:
  + Analysis and comparison of large datasets on expression profiles, non-coding RNAs and clinical annotation on tumour samples and controls, to discover and characterise the biomolecular networks that drive the appearance and maintenance of cancer, and identify potential targets for intervention.
  + Correlations with genomic parameters, including ChIP, genotype and DNA copy number.
  + Identifying and implementing analytical methods and software.
  + Manipulating, comparing and analysing large biomolecular data, including related computation and data visualisation.

**Salary:** $1,125 (Australian) per fortnight

**Hours/week:** 37.5 hours

**Background**

Prostate cancer is the second most commonly diagnosed cancer, and second leading cause of cancer death in men.

**The Australian Prostate Cancer Research Centre – Queensland (APCRC – Q)** is an integrated, trans-disciplinary, and comprehensive prostate cancer research centre based in the state-of-the-art [Translational Research Institute](http://www.tri.edu.au/) (TRI) at the [Princess Alexandra Hospital](http://www.health.qld.gov.au/pahospital/) precinct, in Brisbane, Australia. The TRI provides a rich multidisciplinary and clinically engaged research environment with over 500 members and additional core research facilities for flow cytometry, genomics, proteomics, histopathology and preclinical models of cancer

This flagship Centre, an initiative of the [Institute of Health and Biomedical Innovation](https://www.ihbi.qut.edu.au/) (IHBI), at the [Queensland University of Technology](http://www.qut.edu.au/) (QUT), in partnership with the Princess Alexandra Hospital (PAH), is home to high level clinician-scientists and research leaders who span the translational spectrum. Our team has an extensive track record of innovative prostate cancer research and a strong background in translating research findings into novel potential therapeutics for prostate cancer and extensive peer reviewed research funding, specifically in prostate cancer. We work in a translational framework that sustains a spectrum of research projects aimed at the development of new prostate cancer biomarkers and therapeutics.

The Centre supports a range of relevant translational activities for the development of prostate cancer therapeutics and biomarkers for genetic predisposition, early detection with differentiation of indolent versus aggressive disease and prognosis, and therapeutic response indicators to inform treatment options/planning and characterisation and evaluation of health services and health economics of their delivery. The APCRC – Q also functions as a focal point for collaborative interactions within Queensland, nationally and internationally.

APCRC-Q’s vision is to seamlessly span the spectrum of prostate cancer research – discovery, therapeutic and diagnostic development – through the expertise and passion of a large, coordinated, multidisciplinary research team. For more information, please visit [www.australianprostatecentre.org](http://www.australianprostatecentre.org).

**Special requirements**

Students are responsible for making their own travel, medical insurance, accommodation, and relocation arrangements.

**Project Descriptions**

A variety of projects are available in the broad area of prostate cancer research covering transcriptomics and related bioinformatics, characterization of pathways underpinning prostate cancer progression, metastasis, and treatment resistance and development of new therapeutic interventions.

Below are some examples of the type of project available:

**Example Project 1**

**Project Title:** *Characterising the role of Epithelial-to-Mesenchymal transition (EMT) in prostate cancer progression and metastasis.*

Androgen-dependent gene pathways regulate the growth and maintenance of both normal and malignant prostate tissue. Androgen deprivation therapy (ADT) in patients exploits this dependence when used to treat recurrent and metastatic prostate cancer (PCa), resulting in tumour regression.

However, the initial regression seen with ADT eventually gives way to regrowth of the prostate tumour from cells which are no longer dependent on testicular androgens. This advanced state of the disease, referred to as castrate resistant prostate cancer (CRPC), is currently incurable. Our research aims to identify the molecular mechanisms that drive progression to CRPC.

Recently, CRPC following ADT has been associated with the epithelial-to-mesenchymal transition (EMT) program. The EMT program allows normally non-motile epithelial cells to acquire motile and invasive properties necessary for metastasis. More recently, EMT has also been associated with therapy resistance and cancer stem cell phenotypes in a number of human malignancies. However, the molecular mechanisms mediating the EMT program and its relevance to androgen independence and metastasis in PCa remains poorly understood. This project aims to identify critical mediators of EMT in PCa by defining a “core EMT” signature and functional testing the relevance of EMT to CRPC and metastasis.

**Hypothesis/Aims**

**Hypothesis:** EMT is a key pathway activated in CRPC that promotes tumour re-growth, treatment resistance and metastasis in PCa.

**Aims:** To identify critical mediators of EMT in PCa and its relevance to androgen independence and metastasis.

1. *Utilize novel PCa cell lines with conditional expression of EMT-inducing transcription factors to generate a “core EMT” gene expression signature.*
2. *Identify key mediators of EMT in PCa using gene silencing (lentiviral shRNA-mediated knockdown) and cDNA overexpression techniques.*
3. *Functionally assess the effects of gene knockdown and overexpression on biological properties associated with EMT (eg. Mesenchymal gene expression, invasion, stem cell properties, drug resistance).*

**Example Project 2**

**Project Title:** *Characterising the effects of insulin and EMT in prostate cancer progression.*

While ADT provides effective anti-cancer response in advanced patients, the side effects include key features of metabolic syndrome including hyperinsulinaemia. Hyperinsulinaemia appears to precede other metabolic changes and increases in adiposity, and may be a direct result of androgen deprivation and is associated with poor outcomes including more rapid progression to CRPC and increased cancer mortality.

We have identified a novel and intriguing network by which insulin may initiate a process of epithelial-to-mesenchymal transition (EMT). This project will aim to characterise the mechanisms by which insulin drives prostate cancer progression via a program of epithelial-to-mesenchymal transition as part of a wider project to investigating biological pathways by which ADT-induced hyperinsulinaemia have the potential to drive PCa progression.

**Hypothesis/Aims**

**Hypothesis:** In a model of androgen deprivation, insulin can stimulate an epithelial to mesenchymal transition in prostate cancer cell lines, contributing to disease progression. **Aims:** Characterise the mechanisms by which insulin drives PCa progression via a program of epithelial to mesenchymal transition.

1. *Confirm insulin activates the EMT program in PCa cells using QRT-PCR and western blotting,* *immunofluorescent microscopy and functional assays of invasion and migration.*
2. *B. Identify key mediators regulating insulin-stimulated EMT in PCa using gene silencing techniques (lentiviral shRNA-mediated knockdown).*
3. *C. Functionally assess the effects of gene knockdown on insulin stimulated invasion and migration.*

**Approaches**

Cell culture, western blotting and QRT-PCR expression analysis, gene knockdown (shRNA)

Functional assays for migration and invasion with latest technology real-time cell analysis

Confocal microscopy

**Example Project 3**

**Project Title:** *Investigating the potential role of tumour necrosis factor (TNF) in prostate cancer EMT and**progression to CRPC.*

TNF is a pleiotrophic cytokine with seemingly paradoxical roles in cancer biology. On the one hand, there is evidence it promotes carcinogenesis through its involvement in chronic inflammation and tumour angiogenesis, whilst on the other hand, it may induce prostate cancer apoptosis, inhibit tumour vascularisation and stimulate anti-tumour immunity. Much of the confusion relating to the function of TNF in cancer can be attributed to the dependence of its effects on the biological context. Variables such as cytokine dose, target cell type, hormone sensitivity of the cell type, and the complexity of the system (*in vitro* versus *in vivo*) can greatly influence the type of activity seen to be exerted by TNF.

Recently, there have been isolated reports in the literature suggesting that TNF may be involved in prostate cancer EMT as well as progression to CRPC. This project will follow-up on this direction by first confirming these findings and then identifying the molecular mechanisms that mediate such effects. This knowledge would form the rational basis for targeting TNF as a therapeutic strategy for CPRC.

**Hypothesis/Aims**

**Hypothesis:** Chronic exposure to low doses of TNF promotes prostate cancer EMT and progression to CRPC.

**Aims**:

1. *Determine expression level of TNF and its receptors on PCa cell lines, with and without androgen deprivation (cell culture, qPCR, flow cytometry, western blot, ELISA).*
2. *Determine the effects of different doses of TNF on the expression of a “core EMT” gene expression signature (qPCR, western blot)*
3. *Assess the impact of TNF on tumour cell behaviour associated with EMT (cell migration, invasion, drug resistance) (lentiviral shRNA-mediated knockdown, real-time cell analysis)*
4. *Investigate the effects of TNF antagonism in a mouse model of spontaneous prostate cancer development (in vivo studies)*

**Example Project 4**

**Project Title:** *Characterising the role of exosomes in prostate cancer progression.*

Cancer cells secrete vesicles called exosomes whose sizes (30-200 nm in diameter) vary, depending on their cell origin. Exosomes contain mRNA, microRNA (miRNA) and proteins associated with multivesicular bodies as well as transmembrane proteins from their cells of origin. These contents suggest involvement of exosomes in cell to cell communication and membrane exchange between cells. The release of exosomes is exacerbated in tumors leading to their increased presence in plasma, ascites and other bodily fluids of cancer patients. In addition to shared common proteins, these tumor-derived exosomes express an array of tumor antigens that reflect the originating tumor cells. Our hypothesis is that exosomal contents will undergo changes associated with hormonal changes, antihormonal treatment and/or drug treatments or progression of PCa and that analysis of these changes will provide biomarkers indicative of patient response and/or progression. As cancer progresses, exosomes from cancer cells are increasingly shed into the patient’s blood current findings suggest that exosomes content can influence cancer progression.

**Hypothesis/Aims**

**Hypothesis:** Exosome secreted by cancer cells are affected by drug treatment and it can influence prostate cancer progression that eventually may promote treatment resistance and metastasis in PCa.

**Aims:** To identify changes in exosomal content caused by drug treatments

*1. To assess whether hormonal changes, antihormonal treatment and/or drug treatments alter exosome content of androgen-receptor positive PCa cell lines in vitro*

*2. Identify key mediators of exosome secretion in PCa using gene silencing (lentiviral shRNA-mediated knockdown) and cDNA over-expression techniques.*

*3. Functionally assess the effects of gene knockdown and over-expression on gene associated with secretion of exosomes.*

**Approaches**

Cell culture 2D and 3D, western blotting and QRT-PCR expression analysis, gene knockdown (shRNA), over-expression.

Functional assays for proliferation with latest technology real-time cell analysis

Confocal microscopy