CANCER PROGRAM

Tumour Progression Group
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Project: Identification of microRNAs regulating cancer stem cell function

Our laboratory investigates the genetic pathways that control differentiation and self renewal during tumourigenesis and metastasis, with the ultimate aim of identifying and characterising "stem-like" cells in cancer. We have recently identified a microRNA that controls the p53 tumour suppressor. We have identified a critical role for this microRNA not only in normal development but in certain cancers.

Using cutting edge in vitro and in vivo models, we now aim to identify other microRNAs controlling these "stem-like" characteristics and test their functional significance to cancer progression.

Breast Cancer Translational Research Group
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Our group is investigating the application of basic scientific findings to improve the diagnosis and treatment of breast cancer. In particular we focus on finding novel targets for treatment and developing and validating markers of resistance to therapy and of prognosis.

Project 1: Investigating developmental pathways Hedgehog, Wnt and Notch in breast cancer

There is increasing evidence that reactivation of pathways that regulate embryonic development also play an important role in the development and progression of breast cancer, possibility due to aberrant regulation of stem cell self-renewal. This project utilises sophisticated mouse models of mammary carcinogenesis to better understand the role of these pathways in breast cancer, and to explore the therapeutic potential of modulating their regulation.

Project 2: The role of BAG-1 in resistance to endocrine therapy and radiotherapy in breast cancer

BAG-1 (bcl-2 associated athanogene) is a pro-survival protein which can influence diverse biological processes including: nuclear hormone receptor function, apoptosis, signal transduction and protein turnover. It has the ability to enhance the actions of the estrogen receptor as well as other key targets involved in apoptosis and cell survival such as bcl-2 and heat shock proteins. We are investigating its role in resistance to hormone treatment and radiation therapy using breast cancer cell line models and human tissue derived from diagnostic tissue biopsies. We hope to identify new biomarkers of responsiveness to treatment and the mechanisms regulating these processes.

Project 3: Investigating mutations in the PI3-kinase pathway in resistance to endocrine therapy

Activation of the PI3K/AKT pathway has been associated to resistance to endocrine therapy in a percentage of breast cancer patients. The project aims to undertake mutational analysis of PIK3CA, and expression analysis of other pathway members to study their association to resistance. A secondary study currently being undertaken is the analysis of Plexin B1 by mutational and expression studies as a potential candidate of tamoxifen resistance.

Integrin and Cell Biology Group
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Project 1: Integrin signalling in breast and prostate cancer

The signalling pathways that control normal development are often disrupted during cancer. Our research aims to understanding the mechanisms behind the regulation of cell fate decisions during these processes and the progression to metastatic disease. Cell-matrix adhesion mediated by integrins, provides cells with both a positional identity and coordinates growth factor and hormone signaling to control cell function. The initiation and progression of cancer is dependent on the ability of a cell to acquire the means to circumvent this regulation and as such modulation of integrin function can alter tumour phenotype. We currently have a number of projects in the lab examining integrin function in prostate and breast cancer. We will use conditional deletion of b1 integrin, focal adhesion kinase (Fak) and integrin-linked kinase (Ilk) in cancer models in vivo, alteration of integrin signalling in normal primary and cancer cells in vitro, with human cancer cell xenografts, to determine the role of b1 integrin, Fak and Ilk in the regulation of cancer progression and metastasis, stem cell function and normal development.

Naylor MJ et al. Ablation of b1 integrins in mammary epithelium reveals a critical role for integrin in glandular morphogenesis and differentiation. *J Cell Biol* (2005) 171:717-28

Project 2: Role of Runx2 in prostate cancer

Breast and prostate cancer preferentially metastasise to bone where they contribute to the morbidity and mortality characteristic of advanced cancer. At present we do not understanding why these cancers preferentially colonise bone and induces its destruction. Signalling pathways or genes that specifically regulate breast/prostate and bone development are of particular interest as they may mediate breast/prostate cancer bone metastasis. The transcription factor Runx2 is a prime candidate for this role. Runx transcription factors are regulators of cell fate and developmental processes and can act as both tumour suppressors and oncogenes. Runx2 is a master regulator of bone development but is also expressed in the prostate and breast where it regulates gene expression. As human prostate cancer advances to metastatic disease Runx2 expression is lost. We are currently investigating the role of Runx2 in breast cancer and mammary gland development. This project will use two new transgenic mouse models we are developing to delete or overexpress Runx2 in the prostate and experimental prostate cancer models, alteration of Runx2 levels in cancer cells in vitro and xenografts to determine the role of Runx2 in prostate cancer.

Cell Cycle Group
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Project: Functional analysis of estrogen target genes

The female hormone estrogen is centrally involved in the normal physiology of the breast and in the development and progression of breast cancer. Our aim is to develop a better understanding of how hormones like estrogen, their receptors and signalling pathways are involved in the normal control of cell proliferation and differentiation, how these mechanisms are lost in cancer and how these pathways can be manipulated to treat and prevent breast cancer.

In a collaboration between the Steroid Hormone Action Group and the Cell Cycle Group we have used genome-wide transcript profiling to identify genes regulated by the proto-oncogene c-Myc and/or estrogen. We have then identified networks of functionally-related estrogen target genes with roles in the cell cycle, cell growth and cell death, which are associated with poor outcome in breast cancer patients treated with the antiestrogen tamoxifen. Projects are available to characterise the roles of these target genes and networks in estrogen action. This would involve a number of experimental approaches, including well-characterised *in vitro* models, genetically engineered mouse models, contemporary gene discovery tools and functional characterisation.

Signal Transduction Group
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In Australia, approximately 1800 diagnoses of basal breast cancer are made each year. These cancers are resistant to endocrine or herceptin therapy and represent a major treatment dilemma. Therefore, the overall aim of this research proposal is to identify components of tyrosine kinase signalling networks that represent potential therapeutic targets and/or prognostic markers for basal breast cancers.

Project: Tyrosine kinase profiling of basal breast cancers
The specific aims of this project are:

To identify perturbations in tyrosine kinase signalling networks associated with basal breast cancers
We will utilize both a candidate-based and global screening approach. Strong candidates are Src family kinases, and these will be evaluated using specific inhibitors and siRNA. In addition, we will perform mass spectrometry-based profiling of tyrosine-phosphorylated proteins in cell lines and primary cancers in order to identify activated tyrosine kinases. Mechanisms underpinning activation of specific tyrosine kinases will be characterized.

To characterize the functional role of particular tyrosine kinases in basal breast cancer cells
We will use 3D culture of basal mammary epithelial cells and inducible retroviral expression constructs to dissect the functional role of individual tyrosine kinases and their signalling pathways. This work will be complemented by studies on mouse models of basal breast cancers.

To determine whether particular tyrosine kinase pathway components can be used to subclassify basal breast cancers and stratify them according to prognosis
The expression profile of particular activated tyrosine kinases, or tyrosine-phosphorylated proteins, in human basal breast cancers will be characterized by immunohistochemical staining of breast cancer tissue microarrays. This will reveal whether particular markers, or marker combinations, associate with the basal subset and if they can be used to stratify basal breast cancers according to outcome.

Pancreatic Cancer Research Group
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Pancreatic cancer is the fourth leading cause of cancer death in Western societies, with a five-year survival rate of less than 5%. The treatment and survival of patients with pancreatic cancer has not changed for over thirty years and there has been little research into the molecular and cell biology associated with the disease.

The Pancreatic Cancer Research Group (PCRG) undertakes basic, clinical and translational research into pancreatic cancer. The PCRG manages the New South Wales Pancreatic Cancer Network (www.pancreaticcancer.net.au), which is a multidisciplinary team of clinicians and scientists from over 10 teaching hospitals and research institutions. This network provides clinico-pathological data and biological material for translational research purposes. As such, we possess one of the world's largest pancreatic tissue resources.

Project: Molecular pathology of pancreatic cancer
Our project focuses on:
- understanding the role of embryologic signaling pathways, such as retinoic acid signaling, in pancreatic cancer and defining new diagnostic and treatment strategies.
- defining the role of bone marrow derived stem cells in the development of the normal exocrine pancreas and pancreatic cancer.
- developing novel mouse models of pancreatic cancer
- developing novel imaging methods for the detection of pancreatic cancer
- discovering novel diagnostic and prognostic biomarkers, and biomarkers of response to therapy.