BACKGROUND

Human cancers are characterised by a disruption of normal cellular growth due to defects in the control of both cell proliferation and cell death (apoptosis). Apoptosis is a physiological form of cell death with distinct morphological and biochemical characteristics. Current therapies for the treatment of human cancers, including ionising radiation and chemotherapeutic drugs, kill tumour cells by inducing apoptosis, so understanding how the process of cell death is regulated in normal and cancerous cells is an important goal for effective treatment.

Defining the molecular mechanisms of oestrogen - and anti-oestrogen-mediated survival/apoptosis in breast cancer models

As well as stimulating cells to proliferate, oestrogen also acts as a survival factor and protects cells from apoptosis. Consequently, there is some evidence that anti-oestrogens may protect against the development of breast cancer by inducing apoptosis. Therefore, defining how oestrogen and anti-oestrogens influence the apoptotic process, and identifying the genes that mediate their effects, is important in understanding how breast cancer can develop and how some patients may develop resistance to anti-oestrogen therapy.

Characterising the apoptotic effects of novel therapeutics for breast cancer

Plant chemicals have provided an abundant and effective source of novel therapeutics for the treatment of cancer. We are currently studying a novel plant toxin, persin, which is derived from avocado leaves and fruit, and effectively kills cultured human breast cancer cells. To further develop this compound as an anti-cancer agent, it is critical to understand more about its mechanism of action, and how it might interact with drugs currently used in the treatment of breast cancer to enhance their efficacy.

Apoptosis Research Group Selected Publications


Breast Cancer Group

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BACKGROUND

The breast cancer team has established large series of tissue samples from women with breast cancer and early pre-invasive breast disease through collaborations with both local and overseas institutions. The group also has a longstanding collaboration with the Australia and New Zealand Breast Cancer Trials Group which allows access to breast tissue from international treatment trials. This material, in combination with contemporary genomic and molecular pathology tools, is being used to identify new diagnostics, molecular markers of disease outcome and therapeutic responsiveness (including markers of resistance to targeted therapies like tamoxifen, aromatase inhibitor and herceptin) and new targets for therapeutic intervention. Current project areas include:

- Reactivation of developmental pathways in preinvasive breast lesions
- Cell cycle proteins in the development of breast cancer
- c-Myc and oestrogen target genes in the development of anti-oestrogen resistance in breast cancer

Breast Cancer Group Selected Publications


BACKGROUND
Cancer Genetics is the study of the genetic basis of human malignancies. These genetic events may either be inherited, resulting in cancer predisposition or cancer initiation, or may be acquired, resulting in tumour progression. The cancer genetics team at the Garvan are concerned with both inherited and acquired genetic variations within the human genome that influence cancer predisposition, tumour gene activation/inactivation, and/or resistance/response to cancer therapies. Further understanding of the molecular-genetic mechanisms involved in cancer development and progression will lead to advances in cancer diagnosis and treatment.

PROJECT 1
Identification of genetic variants associated with high-risk, early-onset breast cancer

Two-thirds of families with early-onset (<40 years of age) breast cancer do not carry a mutation in a known susceptibility gene. The aim of this study is the identification and characterisation of new candidate genes of hormone metabolism, associated with high risk early-onset breast cancer.

PROJECT 2
Identification of common genetic variants associated with prostate cancer risk

No major predisposition genes have been validated for prostate cancer. The aim of this study is to identify and characterise the role of candidate genetic variation in genes regulating (a) hormone metabolism or (b) the inflammatory network in prostate cancer, and to further characterise the functional consequences of identified variants.

PROJECT 3
Impact of mutational events in bladder cancer progression

The prognosis of patients with bladder cancer is strongly dependent on whether the lesion is superficial or invasive, while some superficial presenting tumours may become invasive. Understanding which cancers progress is therefore of paramount importance for early diagnosis and successful treatment. Our group is interested in determining the molecular-genetic mechanisms (in particular genetic variations) underlying this progression.

Cancer Genetics Group
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Cancer Genetics Group Selected Publications


Colon and Lung Cancer Group
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BACKGROUND
Our laboratory is interested in both translational research and experimental models of colon and lung cancer. We use cancer tissue from retrospective patient cohorts to identify and characterise key markers of prognosis and chemotherapeutic responsiveness, to improve the clinical management of these common cancers. The most promising gene candidates are taken further to functional analysis using mouse and cell line models.

PROJECT 1
Prognostic factors in colorectal cancer

This study will analyse tumours from bowel cancer patients who have had a potentially curative operation, to identify which patients are at a high risk of relapse and would benefit from chemoradiotherapy treatment at the time of their operation. We have already identified a new gene that is frequently silenced in colon tumours through promoter methylation and will further characterise its clinical significance. This project will involve the study of a colorectal cancer patient cohort from the Concord Hospital, which has an excellent patient Database with...
clinical follow-up and access to surgical specimens over the last 30 years.

**PROJECT 2**

**Molecular genetics of lung cancer**

Lung cancer is a leading cause of all cancer-related deaths but why current chemotherapeutic regimes are not effective is poorly understood. Therefore there is an urgent need to establish the molecular basis of chemoresistance and identify new gene targets for chemotherapy as well as new DNA-based circulating tumour markers. This is being undertaken through collaboration with clinicians at the Royal Prince Alfred Hospital/University of Sydney who have access to a tumour bank with almost 3000 primary lung cancers using techniques including gene methylation and mutation analysis and immunohistochemistry.

**Colon and Lung Cancer Selected Publications**


**BACKGROUND**

Cancer is a disease characterised by both genetic and epigenetic changes. Genetic changes involve alterations in the DNA sequence and subsequent gene expression changes, whereas epigenetics relates to a higher level control over gene expression, which is independent of the DNA sequence. Both DNA methylation and chromatin modification are important players in epigenetics. It is now clear that DNA methylation and histone methylation are common hallmarks of all cancers and are associated with the silencing of tumour suppressor genes.

Our laboratory is interested in the mechanism that initiates aberrant hypermethylation and chromatin remodelling in early development and in cancer. Unlike DNA mutations or gene deletions, methylation is a reversible modification of the DNA; therefore, an understanding of the process that initiates aberrant methylation could lead to the discovery of novel therapeutic options. These are likely to include ways to reprogram the methylation state and reactivate critical tumour suppressor genes. Deciphering DNA methylation patterns in normal and cancer cells will also provide the foundation for a new type of marker for cancer diagnosis and prognosis.

**Mechanism of Epigenetic Reprogramming in Cancer**

Cancer cells undergo multiple genetic and epigenetic lesions during tumour progression and metastases. Tumour suppressor genes are often silenced in cancer cells by mutation, deletion and/hypermethylation of the gene leading to immortalisation and local proliferation. Conversely activation of oncogenes is also a common hallmark in cancer progression, but the mechanism responsible for activation is less understood. Progression, in which cancer cells become invasive and eventually metastatic, is the key event leading to morbidity and mortality in patients.

**PROJECT 1**

In this study we seek to uncover the mechanism responsible for the expression of the pro-oncogene c-fms, which encodes a growth factor receptor, in breast cancer epithelial cells and the relationship between c-fms activation, demethylation of the c-fms enhancer and tumour progression. Understanding the processes leading to c-fms expression in breast cancer will have important implications for tumour staging and treatment options.

**PROJECT 2**

In this study we plan to profile the epigenetic changes that occur during the early stages of oncogenesis using progenitor cells derived from normal breast tissue. We will use tiling arrays to map the changes in gene expression chromatin modification and DNA methylation to determine the relationship between stem cell marks and susceptibility to epigenetic silencing.

**Epigenetics Research Group Selected Publications**


Pancreatic Cancer Group
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BACKGROUND
Pancreatic Cancer is the fourth leading cause of cancer death in our society, with a 5 year survival rate of less than 5%. There are currently no effective systemic therapies for pancreatic cancer. The Pancreatic Cancer Research Group utilises both basic science and translational research approaches to develop novel diagnostic and therapeutic strategies. Recent work in the laboratory has focussed on the role of signalling pathways important in vertebrate pancreas development in the evolution and progression of pancreatic cancer. The group uses human biological material as well as in-vitro and in-vivo murine models of pancreatic cancer.

Retinoids in pancreatic cancer
Hedgehog signalling in pancreatic cancer
Haematopoietic stem cells in pancreatic cancer
Musashi in pancreatic cancer

Pancreatic Cancer Group Selected Publications:


Signal Transduction Group
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BACKGROUND
Receptor tyrosine kinases (RTKs) provide cell surface receptors for a variety of hormones and growth factors, such as insulin and EGF. As their name suggests, RTKs initiate intracellular signal transduction cascades and the assembly of multiprotein signalling complexes via the phosphorylation of specific proteins on tyrosine residues, and thereby regulate cellular proliferation, differentiation, survival, motility and metabolism. Importantly, aberrant signalling by particular RTKs underlies a variety of disease states. In cancer, this can be due to mutation or overexpression of specific RTKs and identification of such events has led to the development of novel, highly-selective therapeutic strategies that avoid the side-effects of conventional chemotherapy. For example, Herceptin is a monoclonal antibody against a RTK, erbB2, that is commonly overexpressed in breast cancer, and is used for treatment of patients with advanced, erbB2-positive disease.

The research focus of this group is the characterization of RTK signalling mechanisms and how they are altered in disease states, particularly cancer. Ultimately this research may identify new drug targets and markers that predict patient prognosis and their responsiveness to particular therapies.

Mechanistic and functional studies on the Gab2 proto-oncogene

Gab2 acts as an assembly platform downstream of RTKs and integrins that localizes, integrates and amplifies signals. Overexpression of Gab2 occurs in a subset of primary breast cancers. We will use 3D culture of mammary epithelial cells to examine the functional consequences of Gab2 overexpression in the absence or presence of co-operating oncogenes. In addition, we will use mass spectrometry and protein-protein interaction assays to characterize pathways that negatively regulate Gab2, and confocal and fluorescent imaging techniques to examine spatiotemporal aspects of Gab2 signalling.

The role of the Grb10 adaptor protein in human cancer

Recently we have used gene knock-out mice to identify Grb10 as a negative regulator of signalling by...
the insulin and insulin-like growth factor 1 (IGF-1) receptors. Since IGF-1 promotes the proliferation and survival of cancer cells, this suggests that Grb10 may function as a tumour suppressor. In this project we will determine how loss of Grb10 affects tumour development by crossing the Grb10 gene knock-out mice with genetically-modified strains exhibiting increased tumour susceptibility. We will also use Grb10-deficient cells and RNA interference to characterize the role of Grb10 in regulating specific signalling pathways and cellular responses including sensitivity to chemotherapeutic drugs. Finally, we will assay Grb10 expression in particular cancers by immunohistochemistry and determine how this relates to clinicopathological parameters and patient survival.

### Signal Transduction Group Selected Publications


### Steroid Hormone Action/Cell Cycle Group

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### BACKGROUND

Sex steroid hormones - estrogens, progesterins and androgens - play a pivotal role in the development and normal physiology of the breast, prostate, ovaries and uterus. They are also centrally involved in the development and progression of cancers of these organs, which make up ~30% of all newly-diagnosed cancers. Since loss of normal proliferation controls is one of the hallmarks of cancer, our aim is to develop a better understanding of how sex steroid hormones, 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 built on the demonstration that induction of the proto-oncogene c-Myc mimics the downstream molecular effects of estrogen on cell proliferation. We have used genome-wide transcript profiling to identify pathways regulated by c-Myc and/or estrogen: cell growth, cell cycle progression and apoptosis. Degregulation of these pathways is associated with endocrine resistance and may play a role in breast cancer development and progression.

#### PROJECT 1

**Identification and functional analysis of estrogen and c-Myc target genes**

Ongoing analysis of our transcript profiling data has identified several networks of functionally related genes, as well as a series of largely uncharacterised estrogen and/or c-Myc targets. 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 characterization.

#### PROJECT 2

**Mechanisms of endocrine resistance**

Loss of responsiveness to endocrine therapies, i.e. antiestrogens (Tamoxifen), and aromatase inhibitors, is a common feature of breast cancer and a major limitation to successful treatment and prevention. Overexpression of c-Myc confers resistance to antiestrogens in vitro, with the implication that c-Myc targets may also contribute to resistance. Projects are available to undertake functional characterisation of selected estrogen and/or c-Myc targets identified in our transcript profiling and evaluation of their relationship to endocrine resistance in the clinical setting.

### Steroid Hormone Action/Cell Cycle Group Selected Publications


Cancer Research Program

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**BACKGROUND**
The hypothesis that guides our work is that most if not all human cancers arise from damage to genes and hence identification and characterisation of these genes is the first step in improving cancer prognosis and treatment. We use cutting edge techniques and *in vitro* and *in vivo* models to assess the involvement of genes in cancer development and metastatic spread. This is a young group and prospective students have the opportunity to shape our future research direction.

Current projects are:

**PROJECT 1**
Regulation of the p53 tumour suppressor pathway by oncogenes and microRNAs

**PROJECT 2**
Identification of the cellular mechanisms regulating breast cancer metastasis

**PROJECT 3**
Defining the molecular basis of the “premature senescence” tumour suppressor pathway