2010 PhD PROJECTS

Introduction

The Garvan Institute of Medical Research is one of Australia's leading biomedical research centres, achieving major breakthroughs in the understanding and treatment of such diseases as osteoporosis, cancer, diabetes, mental illness, pituitary disease, arthritis and asthma. Garvan is affiliated with St. Vincent's Hospital and University of New South Wales (UNSW). Annual research expenditure is in excess of $60 million. Students comprise nearly a quarter of our researchers and are enrolled through UNSW. Postgraduate students contribute significantly to our scientific success and Garvan actively seeks high caliber people who demonstrate initiative and independent thought. Major research programs include:

Diabetes and Obesity, Cancer, Immunology, Bone and Neuroscience.

PhD Open Day 25th of August

Our postgraduate student open day will take place on the 25th of August from 10.30 am to 12.30pm. Interested applicants must register to attend at www.garvan.org.au. You will meet with prospective supervisors seeking students. Outside of this period, you may contact specific researchers directly or the graduate student coordinator. The following pages provide details of some of our available PhD projects. Applicants' interest will be matched to suitable laboratories. Information about the postgraduate application process and application forms are available on the last few pages of this brochure or can be downloaded at **http://www.garvan.org.au/education**.

From the Executive Director

Professor John Shine AO FAA
Executive Director

Many professional careers are rewarding, but none are more exciting and fulfilling today than that of biomedical research. With the completion of the human genome sequence and related technologies, the pace of acquisition of new knowledge about fundamental life processes is growing exponentially. Every day, amazing new insights into health and disease are emanating from research labs around the world.

Undertaking advanced postgraduate study in medical research in these exciting times is a very special opportunity. This includes the excitement of discovery, development of an international network of friends and colleagues and the satisfaction of success in your chosen field. The Garvan Institute is well placed nationally and internationally to ensure this success, with state-of-the-art technologies, leading research programs and importantly, a sole focus on research excellence. The institute's role as an integral partner on the St. Vincent's Campus also means that research discoveries have every opportunity to be closely linked to real improvements in the prevention and treatment of disease.

From the Chair, Garvan Higher Degrees Committee

A/Professor Chris Ormandy
Chair, HDC

Medical research has never made such dramatic advances. Revolutions in robotic, electronic and information technologies, coupled with molecular and genetic techniques that operate at the whole genome level, are providing a view of the organism not envisaged just a decade ago. The collection of human clinical samples and the development of medical information systems to capture health outcomes data, now offer an unprecedented opportunity to investigate the cause of disease in relation to new biological understanding. There has never been a better time to make life-changing discoveries.

The Garvan Institute is at the forefront of these advances. Scientists trained here are leaders in medical science, clinical medicine, biotechnology, the pharmaceutical industry and health-related aspects of government. Our students benefit greatly from the strong research focus that comes from our position at the forefront of world medical science. We offer a stimulating and exciting intellectual environment for students pursuing PhD, MSc and BSc Honours degrees via a number of Australian and overseas universities.

The Garvan Higher Degrees Committee provides pastoral care, monitors academic progress and well-being of students during their tenure here. The overall objective of the committee is to assist the executive director in the administration of matters relating to higher degrees. This committee is concerned with all full time and part time students who are undertaking postgraduate research at Garvan, where the principal supervisor is a member of the Garvan scientific staff.

2010 PhD PROJECTS

Cancer Program

Integrin & Cell Biology Research Group

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Project 1: Regulation of stem cells in cancer & development

Stem cells play a critical role in the normal development and functioning of organs. In addition, 'cancer stem cells' may be responsible for tumour growth and resistance to therapeutics. Integrins are cell-matrix receptors that through both adhesive and signalling roles play a critical role in normal development and cancer. Integrin expression has also been used to purify breast and prostate stem cell populations, along with cancer stem cells. This project will determine the role of integrin signalling in the regulation of stem cell function during development and cancer progression using conditional knockout mice, breast and prostate cancer mouse models and alteration of signalling in normal and human cancer cells.

Project 2: The role of Runx2 in breast cancer

We have recently shown a novel role for Runx2 as a critical regulator of mammary gland development. In addition, preliminary data also indicates that deletion of Runx2 can inhibit breast cancer development in an experimental cancer model. These exciting new data identify Runx2 as a new regulator of mammary gland development and potentially as a new gene regulating breast cancer. Building on these findings this project will use whole genome tiling and microarrays, new conditional gene deletion and expression mouse models, primary cell culture and the latest cell biology techniques to characterise and define the role of Runx2 in breast cancer.

Project 3: The role of Runx2 in prostate development & cancer

In addition to its expression in breast and bone, Runx2 is also expressed in the prostate. As human prostate cancer progress to metastatic disease the expression of Runx2 is lost, indicating that Runx2 may act as a tumour-suppressor in the prostate. This project will determine the role of Runx2 in prostate development and cancer using new transgenic mouse models to delete or overexpress Runx2 specifically in the prostate, experimental prostate cancer models and by manipulating Runx2 in xenografts and cancer cells in vitro.

Project 4: Targeting bone cells in inhibit breast cancer induced bone metastasis

During bone metastasis a 'vicious cycle' occurs where tumour cells secrete growth factors that activate and perturb normal bone cell function, in turn 'activated' bone cells secrete and release growth factors that further support tumour growth. The role of bone cells, especially as therapeutic targets, has largely been over-looked in this process. This project will undertake a completely novel approach. Rather than targeting breast cancer cells, we will target bone cells (by inhibit Runx2 specifically in bone cells in metastatic models) to prevent them from responding to the oncogenic signals from tumors cells. By preventing subsequent bone degradation and further growth factor release, we hope to inhibit the 'vicious cycle' of bone metastasis.

Lung and Colorectal Cancer Group

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The role of MCC silencing in colorectal cancer.

Our laboratory has discovered a new biomarker in colorectal cancer, a methylation defect in the MCC ('Mutated in Colorectal Cancer') gene. Aberrant MCC methylation can be found in early premalignant polyps of the colon, which then develop into cancers. MCC methylation causes gene silencing in up to 50% of bowel cancers (Kohonen-Corish et al 2007). Recently, the MCC gene was identified as a 'driver' of colon carcinogenesis (Starr et al 2009). Our current work aims to identify the normal cellular function of the MCC gene in order to understand how this defect promotes carcinogenesis and whether it is relevant for the treatment responses in patients.

We have several ongoing projects; successful candidates will study both the tumours resected from bowel cancer patients during surgery as well as cancer cell lines grown in the laboratory and mouse models of colorectal cancer.

Project 1

Using bioinformatics and mass-spectrometry techniques we have identified a new role for MCC in the DNA damage pathway. Proficient DNA damage response is crucial to ensure genomic integrity and is commonly deregulated in cancer. Using in vitro and in vivo molecular techniques, we aim to further determine how MCC silencing promotes cancer and how this defect could be exploited to improve treatment. Here we will use ionising radiation to mimic the effects of radiotherapy and analyse whether MCC deficient cancer cells are more radiosensitive than cancer cells with normal MCC. This project also aims to further investigate the cellular mechanism by which MCC controls cell proliferation and its role in the DNA damage response.

Project 2

This project involves mouse experiments to study how bowel cancer develops from an early premalignant tumour to invasive cancer. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin and sulindac, have shown promise in the treatment and prevention of bowel cancer. However, we have shown that when mice receive sulindac mixed in feed, it actually induces new cancers in the proximal colon, while protecting the distal colon against carcinogenesis. This finding was unexpected but now allows us to analyse the very early stages of cancer development, which is difficult to study in human patients. Due to the growing evidence implicating MCC silencing in promoting colorectal cancer, we have engineered an MCC knockout mouse model. The successful candidate will investigate how the MCC deficiency promotes cancer in vivo and have the opportunity to further characterise the role of MCC in a physiologically relevant setting.

References:

Kohonen-Corish MR, Sigglekow ND, et al 2007. Promoter methylation of the mutated in colorectal cancer gene is a frequent early event in colorectal cancer. Oncogene 26:4435-41.

Starr TK, Allaei R, Silverstein KA, et al 2009. A Transposon-Based Genetic Screen in Mice Identifies Genes Altered in Colorectal Cancer. Science 323:1747.

Cell Cycle Group

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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.

Project

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. We are now undertaking genetic screens aimed at identifying which of these genes have roles in the response of breast cancer cells to estrogen and antiestrogens. Projects are available to characterise the roles of individual candidate genes in estrogen action in our well-characterised breast cancer cell line models, using a number of different experimental approaches. Future developments of the project might include investigating the role of selected genes in the response to antiestrogen therapy in breast cancer.

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: 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.

Apoptosis Research Group

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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.

Project 1

The role of survival/apoptosis regulation in the development of endocrine resistance.

In collaboration with the Cell Cycle Group, we have recently identified a group of genes regulating cellular survival/apoptosis that are associated with the response to tamoxifen in breast cancer patients1. This project aims to determine how individual genes in this 'signature' such as the pro-survival protein, BAG-1 can influence both the development of breast cancer and the response to therapy2, and delineate the underlying mechanisms involved.

Project 2

Regulation of apoptosis in normal and malignant breast epithelial cells by the oncoprotein, c-Myc.

The oncoprotein, c-Myc is frequently overexpressed in breast cancers and can confer resistance to antioestrogens in vitro3. However, sustained c-Myc expression not only stimulates proliferation, but can also induce apoptosis directly and sensitise to apoptotic stimuli. Consequently, much interest has centred upon determining how these intrinsic aspects of Myc function are mediated in both the normal and tumorigenic setting, and how they may modulate the response to therapy. Recent studies have identified regions of Myc that can negatively (Myc Box III) or positively (MBIV) regulate its apoptotic function. This projects aims to determine how these domains influence Myc's apoptotic function and subsequently the malignant process in the breast.

1 Musgrove EA, CM Sergio, S Loi, CK Inman, LR Anderson, MC Alles, M Pinese, M Gardiner-Garden, CJ Ormandy, G McArthur, AJ Butt & RL Sutherland (2008) Identification of functional networks of estrogen- and c-Myc-responsive genes and their relationship to response to tamoxifen therapy in breast cancer. PLoS One 3 (8): e2987

2 Millar EKA, LR Anderson, CM McNeil, SA O'Toole, M Pinese, P Crea, A Morey, AV Biankin, SM Henshall, EA Musgrove, RL Sutherland & AJ Butt (2009) BAG-1 predicts patient outcome and tamoxifen responsiveness in ER-positive invasive ductal carcinoma of the breast. Brit J Cancer 100: 123-33

3 Butt AJ, CM McNeil, EA Musgrove & RL Sutherland (2005) Downstream targets of growth factor and oestrogen signalling and endocrine resistance: the potential roles of c-Myc, cyclin D1 and cyclin E. Endo. Rel. Cancer 12: S47-S59

2010 PhD PROJECTS

Immunology & Inflammation Program

Mucosal Autoimmunity Research Group

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The cells in our bodies use a system, known as immunity, for protecting themselves from any "foreign" substance (e.g. viruses and bacteria). When our immune system damages our own tissues, this is termed autoimmunity. Diabetes is the name given to disorders in which the body has trouble regulating its blood glucose levels. There are two major types of diabetes: type 1 and type 2. Type-1 diabetes (T1D) is a chronic autoimmune disease in which the T cells of the immune system attack and destroy the insulin-producing beta cells in the pancreatic islets of Langerhans. An estimated 140,000 people in Australia have T1D and the incidence has increased by 37% in the last decade. T1D is a disease involving multiple genes that are under strong environmental influence. Broad based immunosuppression is commonly used to treat autoimmune diseases and transplant recipients but has many drawbacks since we need a functioning immune system in order to thrive. The aims of our research are to identify specific molecules that can be targets for selective immunosuppression of autoreactive T cells whilst ensuring the maintenance of our healthy immune cells.

Our research is focused on how the environment impacts upon the genes that confer susceptibility to autoimmune disease. Interactions with environmental antigens and cytokines help to nurture and educate the immature immune system. The factors that promote self-destructive T cells in place of healthy T cells are a subject of great interest to our group.

Project : Mucosal tolerance and type-1 diabetes

The proximity of the pancreas to the gut and their intimate connections via the pancreatic ducts make the pancreas a potential target for T cells primed in the gut associated lymphoid tissue (GALT). We have shown that the T cells infiltrating the pancreas express the mucosal homing receptors CCR9 and (a4b7), express high levels of the cytokine IL-21. In addition, T cells from the GALT can cause diabetes in a transfer model. This project is focused on whether T cells that cause diabetes originate from a defect in self-tolerance at mucosal sites.

During a crucial period just after birth, the immune system is "taught" to tolerate the many harmless bacteria and food molecules that constantly pass through the gut. One of the basic mechanisms of protection involves the highly selective permeability of the gastrointestinal epithelium. We hope to understand how interactions between the environment and the immune system in early life can cause or prevent the subsequent development of autoimmune disease. Specifically, we intend to see whether Type 1 Diabetes can be explained by inappropriate immune responses to harmless environmental antigens in the gut, using a mouse model of diabetes to track this putative loss of tolerance in the gastrointestinal tract.

There are a number of testable hypotheses for the involvement of the GALT in autoimmune diabetes and they include: (1) The T cells that destroy the insulin-producing cells (diabetogenic) are primed in the gut to insulin or other islet antigens (2) diabetogenic T cells are created following inappropriate responses to commensal flora or (3) diabetogenic T cells remain unregulated because of the inability of NOD mice to undergo normal neonatal tolerance to environmental antigens. Each of these hypotheses can be tested using a simple system whereby a known antigen (Ovalbumin) is expressed by a commensal bacteria such as e.coli, is delivered to NOD mice that either do express or don't express specific antigen in the islet beta cells of the pancreas (driven by the insulin promoter). These mice are already available for our use and we have the reagents necessary to track these cells through their diabetogenic transformation. We anticipate that these studies will define the role of the mucosal immune system in the development of type-1 diabetes and define new avenues for therapeutic intervention

Antibody Engineering Research Group

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Project: Antibody therapeutics

Our laboratory is working on the development of novel antibody therapeutics. Monoclonal antibodies have revolutionised the treatment of many conditions. In fact, they are the most common class among recently approved drugs, with more than 150 candidates currently in clinical trials. While early monoclonals were generated by immunisation of animals, they are now increasingly produced by in-vitro evolution technologies. These technologies have allowed the development of novel, cutting-edge biological therapeutics. Domain antibodies, consisting of a single variable chain, are a promising new class of such fragments. Domain antibodies can be produced in large quantities in bacteria and open up promising new routes for non-intravenous applications, imaging and therapy. We are applying our technology to targets in cancer and inflammatory diseases.

Gene Therapy & Autoimmunity Research Group

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The Autoimmunity and Gene Therapy Group is focused on the study of inflammatory diseases including autoimmune diabetes and rejection of transplants. Our research involves basic science research as well as clinical studies and trials in the field of human islet transplantation. A number of projects are available that would suit highly motivated and ambitious students. Our research includes analysis of gene expression and regulation, molecular signaling pathways that regulate inflammation, cellular immunology, and animal models of type I diabetes and organ graft rejection. Cutting edge technologies used in our research include transgenic and knockout animals, RTqPCR, micro-array and laser capture microscopy.

Project 1: B lymphocytes and autoimmunity (type 1 diabetes)

B lymphocytes have been identified as critical players in the development of type 1 diabetes. By using soluble compounds to deplete B cells during disease development, and through the use of newly created knockout and transgenic NOD mouse lines, we are continuing to elucidate the functional role of B lymphocytes in type I diabetes development.

For background see:

- Mariño E, et al., Diabetes. 2008 Feb;57(2):395-404;
- Mariño E, et al., Diabetes 2009, (in press)
- Silveira PA, Grey ST. B cells in the spotlight: innocent bystanders or major players in the pathogenesis of type 1 diabetes. Trends Endocrinol Metab. 2006 May-Jun;17(4):128-35.

Project 2: Gene therapy for islet transplantation

Transplantation of pancreatic islets is one potential therapeutic option to restore normal blood sugar regulation in subjects with type 1 diabetes. However, the transplanted islets are destroyed by an autoimmune response, as well as by an aggressive immune response directed against the tissue graft, referred to as the 'allo'-immune response. Genetic engineering of islet cells to be resistant to immune-mediated destruction, or modulating the immune response to accept a graft, may allow permanent long-term graft survival.

For background see:

* Grey ST, et al., J. Immunol. 2003 Jun 15;170(12):6250-6;
* Walters S, et al., J Immunol. 2009 Jan 15;182(2):793-801;
* Webster K, et al., J Exp Med. 2009 Mar 30.

Project 3: The role of NF-kappaB and graft inflammatory responses in transplant rejection

It is recognized as a given that the major cause of graft rejection is the induction of a vigorous immune response directed to the graft itself. Emerging evidence shows that the graft can contribute to this process through the release of soluble factors that in turn enhance the immune response. Many of these pro-inflammatory graft responses are regulated by the transcription factor NF-kappaB. Understanding the molecular networks that control tissue graft responses after transplantation may lead to novel ways to prevent graft rejection.

For background see:

- Grey ST, et al., J. Exp. Med. 1999, 190 (8): 1135-1145;
- Hartman MG, et al., Mol Cell Biol. 2004 Jul;24(13):5721-32;
- Liuwantara D, et al., Diabetes. 2006. Sep;55(9):2491-501.

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Project: Mechanisms of action of intravenous immunoglobulin (IVIG)

IVIG is a crude antibody preparation, isolated from plasma collected from large numbers of healthy donors. While it has traditionally been used for replacement therapy in immunodeficiencies (such as HIV), it is now increasingly used as a powerful immunomodulatory reagent in over 35 autoimmune and inflammatory conditions (such as ITP). The use of IVIG has increased dramatically over the past decade to a degree that its supply is now critically limited and its use represent a significant cost to the community. However, despite its clear efficacy in the clinic, the mechanisms of action of IVIG remain unknown. To tackle this problem, we use cutting-edge biochemical techniques and models of disease. Our approach includes biochemical fractionation of IVIG components, their analysis in in-vitro and in-vivo models, and the development of antibody fragments as a recombinant substitute. Together, these studies will provide insights into the molecular mechanisms of immunomodulation and will allow a more efficient use of this costly form of therapy.

2010 PhD PROJECTS

Neuroscience Program

Neurodegenerative Disorders Group

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PhD Studies in Dr Bryce Vissel's group allow you the opportunity to learn and develop cutting edge technologies and approaches that will contribute to a deeper understanding and treatment of Parkinson's disease, Alzheimer's disease or spinal cord disorders. The group uses sophisticated approaches to understand how synaptic dysfunction leads to neurodegeneration and to identify potential approaches to reverse the disease process. In addition to studying mechanisms of neurodegeneration, the group studies stem cells and the mechanisms underlying regeneration in the nervous system. The goal of this work is to

identify approaches that could drive recovery in the brain in diseases such as Parkinson's and Alzheimer's disease. All our projects will train you in a wide range of cutting edge approaches, including anatomy,physiology, animal behavior, cell culture, high-end microscopy, surgery and so on. Our group is helpful, friendly and highly motivated. These are kinds of studies you could undertake:

Project 1: Neural regeneration research and studies of stem cells

Students will have the opportunity to study neural regeneration in our group. Adult neurogenesis is the process by which the brain generates new nerve cells in the adult central nervous system (CNS) from stem cells that naturally exist in the brain. Stimulating neurogenesis may potentially offer a therapeutic approach for neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and spinal disorders. In our group, we are working to identify mechanisms that regulate adult neurogenesis (neural repair mechanisms) in the normal and diseased brain, to determine if manipulating these mechanisms may offer

therapeutic potential. The students who are interested in research projects in this area will learn advanced techniques in the study of neurogenesis and neural stem cells. Techniques learned will include: (1)Stereotaxic survival surgery and gene therapy approaches, (2) Immunohistochemistry combined with advanced confocal microscopy and stereology for analysis of regeneration. (3) Use of in vitro cell systems, including neural stem cells, for studying neurogenesis. (4) Behavioural testing to determine the capacity for functional recovery in animal models (5) molecular biology. Research into mechanisms and role of neural regeneration is a cutting edge area of research worldwide and the research has significant potential to lead to important discoveries.

Project 2: Neurodegeneration research and studies of synapses

When neurons in the brain that secrete dopamine die, this causes Parkinson's disease, which leads to a profound loss of motor function and eventually death. The biology of dopamine neurons, which is absolutely critical to a range of diseases such as Parkinson's disease, is poorly understood. We are researching dopamine neuron synapses to develop a greater understanding of the role that dopamine synaptic function in normal behavior and in disease and we have several cutting edge projects available for students.

The student will learn advanced techniques in studying dopamine synaptic function, including: (1) Culture of

primary cells from mouse neural tissue, including glial cells, dopamine neurons and hippocampal neurons (2) Immunocytochemistry combined with advanced confocal live imaging microscopy (3) Advanced methods in microscopy for analysing active synapses formed by live neurons. (4) New concepts and techniques that few labs worldwide are able to achieve. The available research projects have significant potential to lead to important discoveries.

Hearing Research Group

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Project 1: Using Adult Stem cells to Repair Hearing Loss

Ever wondered if your music player is too loud? Studies have shown that listening to loud music for extended periods can cause long-term hearing loss. The hearing loss results from damage to the sensory receptors for hearing, the hair cells in the inner ear. This project will explore whether adult stem cells can replace the damaged hearing cells. Mouse sensory stem cells from the nose, tongue and balance organ will be transplanted into the inner ear of deaf mice. Hearing levels will be tested before and after cell transplantation. All techniques are well established and currently functioning in our laboratory. Future studies with human stem cells offer a clinically relevant progression from animal studies.

Project 2: Brain Pathways for Locating Sound in Space

Can't hear in a noisy pub or restaurant? Hearing loss affects one in five Australians, many of whom experience difficulty in understanding speech in noisy spaces. The pathways in the brain that help us locate sounds and recognise speech are not fully understood. This research project will study the brain pathways and nerve cells involved in hearing using electrical recordings in brain slices. The goal is to improve treatment strategies for individuals with hearing loss, users of hearing aids, and deaf persons with cochlear implants.

A wide range of skills is available to students, including stem cell biology, immunohistochemistry, molecular biology, cell culture, electrophysiology, fluorescent confocal microscopy, and hearing testing. Laptop and conference travel are guaranteed.

Note: Honours projects (1 year) are available before commencing a PhD project (3 years). Both Honours and PhD projects are carefully designed to achieve positive outcomes in the allotted time.

Diabetes & Obesity Research Program

Metabolic Systems Biology

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Disruptions in metabolism have become the hallmark of numerous diseases including cardiovascular disease, diabetes, obesity, cancer as well as a number of infectious diseases. This presents a fascinating biological problem because metabolic control is extremely robust and involves a complex interplay between several major biological systems that are constantly changing in harmony with the external environment. To begin to dissect the control of metabolism and how it goes awry in disease it is essential to consider not just the individual molecules or small groups of molecules that comprise individual molecular machines but rather to consider many thousands of molecules and how they work together within the living cell or organism in real time. To accomplish this it is necessary to establish technologies that are capable of interrogating cellular behaviour and how this might change in response to changes in the environment.

To address this goal we have established quantitative mass spec methods to dissect changes in cellular protein phosphorylation on a global scale in response to various stimuli such as insulin or altered nutrient status. This will provide a detailed snapshot of cellular behaviour because every cellular process is precisely regulated by changes in protein phosphorylation. If we can follow changes in the pattern of protein phosphorylation during transitions from one environmental state to another this will enable us to define the overall features of the metabolic network that would otherwise not be intuitively apparent from studying individual molecules in isolation. These data can then be integrated with other data sets such as gene expression or metabolites to build a sophisticated model of the interaction between environment and cellular metabolism ultimately leading to a better understanding of disease processes.

Recent Publications

Yip MF, Ramm G, Larance M, Hoehn KL, Wagner MC, Guilhaus M, James DE CaMKII-mediated phosphorylation of the myosin motor Myo1c is required for insulin-stimulated GLUT4 translocation in adipocytes. Cell Metab. 2008 8:384-98.

Stöckli J, Davey JR, Hohnen-Behrens C, Xu A, James DE, Ramm G.

Regulation of glucose transporter 4 translocation by the Rab guanosine triphosphatase-activating protein AS160/TBC1D4: role of phosphorylation and membrane association. Mol Endocrinol. 2008 22:2703-15.

Hoehn KL, Hohnen-Behrens C, Cederberg A, Wu LE, Turner N, Yuasa T, Ebina Y, James DE. IRS1-independent defects define major nodes of insulin resistance. Cell Metab. 2008 7:421-33.

Ng Y, Ramm G, Lopez JA, James DE. Rapid activation of Akt2 is sufficient to stimulate GLUT4 translocation in 3T3-L1 adipocytes. Cell Metab. 2008 7:348-56.

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Obesity and Insulin Resistance

Obesity is associated with the development of a number of serious and common diseases such as heart disease, stroke, type 2 diabetes, liver disease, arthritis and cancer. The broad aim of our projects is to understand how different tissues and different genes contribute to the way the body balances food intake and energy expenditure to maintain healthy body weight and what goes wrong when this balance breaks down and obesity develops.

Project 1: Mitochondrial metabolism and insulin resistance

This project is aimed at determining the role of mitochondrial oxidative capacity in regulating glucose and lipid metabolism. Mitochondria are the major site for fuel oxidation in cells and strategies that stimulate mitochondria to burn more calories may prove beneficial for preventing fat accumulation and insulin resistance. This project will use both genetic and pharmacological approaches to increase fuel oxidation in mitochondria. We will over-express mitochondrial transcription factors or specific mitochondrial proteins to accelerate mitochondrial respiration and determine if this can improve insulin action in muscle. We will also examine whether drugs targeting specific mitochondrial pathways have potential as anti-obesity treatments.

Project 2: Liver metabolism and energy homeostasis.

The liver plays a central role in the regulation of glucose and lipid metabolism. During fasting, the liver secretes glucose into the bloodstream to ensure adequate fuel is available for the brain. Following a meal, the liver becomes an integral component of the body's energy storage network, with its major function switching from the production of glucose to the conversion of excess glucose to glycogen or triglyceride for storage. When the appropriate integration of these hepatic functions fails, metabolic diseases such as type 2 diabetes, cardiovascular disease and fatty liver disease ensue. This project aims to better understand the intricate system of regulation of these processes in liver by hormonal and nutrient signals.

Recent publications:

Hegarty BD, Turner N, Cooney GJ, Kraegen EW. Insulin resistance and fuel homeostasis: the role of AMP-activated protein kinase. Acta Physiol (Oxf). 2009, 196:129-45.

Kraegen EW, Cooney GJ. Free fatty acids and skeletal muscle insulin resistance. Curr Opin Lipidol. 2008 19:235-41.

Turner N, Bruce CR, Beale SM, Hoehn KL, So T, Rolph MS, Cooney GJ. Excess lipid availability increases mitochondrial fatty acid oxidative capacity in muscle: evidence against a role for reduced fatty acid oxidation in lipid-induced insulin resistance in rodents. Diabetes. 2007 56(8):2085-92.

Sanders MJ, Ali ZS, Hegarty BD, Heath R, Snowden MA, Carling D. Defining the mechanism of activation of AMP-activated protein kinase by the small molecule A-769662, a member of the thienopyridone family. J Biol Chem. 2007, 282:32539-48.

2010 PhD PROJECTS

Cooper Group - Cell & Molecular Biology/Genetics

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Project 1: Identifying the underlying molecular mechanism(s) of Parkinson's Disease (PD)

PD is a neurodegenerative disease affecting >50,000 Australians who have already lost ~ 40% of dopamine producing neurons at time of diagnosis. Earlier diagnoses and new treatments are needed as current therapies are only partially effective. Synuclein is a natively non-toxic protein of unknown function that associates with synaptic vesicles. Synuclein is also the central component in PD as its aggregated form is the main component of Lewy bodies, the primary pathological hallmark of PD. Although the underlying cause of PD is unknown in >90% of cases the propensity of Synuclein to become cytotoxic likely results from a complex interaction of unknown predisposing genes (risk factors). Identifying these inherited risk factors will enhance our understanding of how Parkinson's disease develops and is an important step towards preventing the disease or to develop therapeutic agents that may inhibit the degeneration of neurons. Using a new model system expressing nontoxic levels of Synuclein, we screened for Synuclein dependent toxicity upon loss of function of 5000 genes (the potential risk factors). We have identified that defects in major signaling pathways play critical roles in Synuclein toxicity. These genes/proteins will then be investigated in human neural cell lines using a broad array of genetic, cell and molecular approaches to both confirm their association with PD and identify the underlying molecular mechanism(s) responsible for contributing to PD prior to testing in human brain samples.

Project 2: How does mutant LRRK2 cause Parkinson's disease?

LRRK2 is a novel 250-280kDa complex enzyme that has been identified as critically involved in PD pathogenesis. Genetic mutations in LRRK2 are the most common pathogenic mutations currently linked to neurodegenerative disease (accounting for 5-40% of familial PD) and genetic polymorphisms in LRRK2 markedly increase the risk of sporadic PD (up to 16 fold). Our exciting new findings and an innovative model, combined with cell and molecular approaches, will use live human neurons derived from LRRK2 PD patients to identify the mechanisms by which LRRK2 dysfunction can cause PD.

Project 3: The role of PARK9 in Parkinson's disease.

PARK9, a PD recessive susceptibility gene, is predicted to encode a P-type ATPase ion pump of unknown specificity. PARK9 is most highly expressed in PD sensitive regions of the brain and surviving dopaminergic neurons in this region of sporadic PD patients' express PARK9 at 10-fold higher levels than healthy controls. We have discovered an exciting relationship between PARK9 and Synuclein and this project will use (i) quantitative mass spectrometry (SILAC) (ii) metabolomics (iii) cell and molecular biological approaches in both PD model systems and live human neurons derived from a PARK9 PD patients to identify and dissect the mechanism by which PARK9 mutations contribute to PD.

Project 4: Mitochondrial dysfunction in Parkinson's disease.

Mitochondrial dysfunction plays an intimate role in neuronal degeneration in PD and a number of reasons have been proposed including: enhanced production of reactive oxygen species [ROS], diminished ATP production, enhanced apoptosis rates. This project focuses on using PD models to consider these and other possible mitochondrial defects and to determine which is the initiating event and therefore a prime target(s) for therapeutic intervention.

Selected recent publications:

Gitler et al. "Alpha-synuclein is part of a diverse and highly conserved interaction network that includes PARK9 and manganese toxicity." Nat Genet. 41:308-15 (2009). Impact Factor = 25.5

Cooper et al "Alpha-synuclein blocks ER-Golgi traffic and Rab1 rescues neuron loss in Parkinson's models." Science. 313:324-8. 2006. Impact Factor= 30.927

Joint Projects

The Australian Pancreatic Cancer Genome Initiative

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Advances in nucleic acid sequencing technology now make it feasible to rapidly, and exhaustively sequence an entire genome within days. These advances are dramatically changing approaches to cancer research, and in the longer term, will alter clinical practice for many diseases including cancer. The aim of this proposal is to use cutting edge technologies to perform massive scale sequencing of a large number of pancreatic cancers as part of the International Cancer Genome Consortium (ICGC). A comprehensive catalogue of aberrations in the genome, epigenome and transcriptome of ~400 individual pancreatic cancers will be developed in order to: 1. Identify novel candidate "driver" mutations that play a significant role in the development and progression of pancreatic cancer, 2. Correlate these abnormalities with aberrations in RNA expression and epigenetic modification, 3. Use these data to define clinically and biologically relevant subtypes (phenotypes) of pancreatic cancer by examining their relationship to clinico-pathological, treatment and outcome data, and 4. Identify novel potential molecular mechanisms of importance in pancreatic carcinogenesis amenable to the rational design of novel therapeutics. This ambitious project is a collaborative effort between several institutes nationally and internationally with Prof Andrew Biankin from the Garvan Institute's Pancreatic Cancer Research Group leading the clinical and translational aspects of the work for the Australian consortium. The sequencing and assembly of the genomes will be done by University of Queensland's Institute for Molecular Bioscience, and the Peter Wills Bioinformatics Centre at the Garvan will be involved in the analysis of the completed genomes.

Project:

The Peter Wills Bioinformatics Centre and the Pancreatic Cancer Research Group are looking to take on PhD students to get involved in this momentous project. We face many challenges that include:

1. Catalogue the full repertoire of somatic DNA mutations in pancreatic cancer.
2. Define the associated epigenome and transcriptome aberrations to facilitate identification of novel driver mutations.
3. Define "driver" genomic aberrations and phenotypes of pancreatic cancer by examining the relationships between data generated from 1 and 2 above to clinico-pathological, treatment and outcome variables which are available for all patients used in the study.
4. Identify novel potential molecular mechanisms of importance in pancreatic carcinogenesis amenable to the rational design of novel therapeutics.

Suitable candidates will have strong backgrounds in bioinformatics or a related discipline, and also have good programming skills and sound knowledge of molecular biology.

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Project: Regulation of body composition and glucose homeostasis by the adaptor protein Grb10

An important risk factor for Type 2 diabetes is the development of insulin resistance. Many factors contribute to insulin resistance including the decrease in muscle mass associated with reduced physical activity and ageing. Consequently, understanding how the signalling pathways involved in insulin action and maintenance of muscle mass are regulated is of major significance. Our recent characterization of growth factor receptor bound (Grb)10 gene knock-out mice demonstrates a tissue-specific role for Grb10 in regulating insulin action, since these mice exhibit increased insulin signalling in skeletal muscle and adipose tissue. Furthermore, Grb10-/- mice also display increased skeletal muscle mass and reduced adipose tissue content. However, since these mice have 'global' Grb10 ablation (ie Grb10 is absent from all tissues) it is unclear whether Grb10 has roles in both muscle and adipose tissue, or whether the effect in one tissue is an indirect consequence of its role in the other. In addition, if Grb10 is to be targeted therapeutically, it is important to determine whether the beneficial effects of ablating Grb10 require the absence of Grb10 during development, or whether they can be achieved via more 'acute' ablation of this adaptor in adult mice.

To address these issues we will utilize a conditional Grb10 allele (Grb10fl/fl) to determine how Grb10 ablation in a tissue-specific and developmental stage-specific manner affects phenotype. The corresponding mouse strain is under development and should be available in late 2009. Grb10fl/fl mice will be crossed with mice expressing Cre recombinase, or tamoxifen-regulated Cre, in muscle or adipose. This will enable us to 'knock-out' Grb10 expression in muscle and adipose throughout development and adulthood, or alternatively from a particular developmental stage (by timed addition of tamoxifen, which induces the gene deletion). The resulting strains will be characterized for their muscle, fat and metabolic phenotypes, as well as for effects on signalling by insulin and other hormones/growth factors. This will determine whether the effects on body composition in Grb10-/- mice reflect autonomous roles for Grb10 in muscle and/or adipose, and whether an increase in relative lean mass and improvement in glucose homeostasis can be achieved by Grb10 ablation during adulthood.

Bone and Mineral Program

A/Professor Jackie Center
& Dr Grahame Elder
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Phone: 02 9295 8271

Dr Grahame Elder has collected data on patients on dialysis about to undergo kidney and kidney-pancreas transplantation. It is a tremendous resource and there are some very exciting questions that can be explored through this database with issues related to bone and renal bone disease, vascular calcification, diabetes and so on. Projects are available for PhD, Masters and Honours students.

Project

Since 2003, patients entering the kidney and the national kidney-pancreas transplant program at Westmead Hospital have been comprehensively assessed for abnormalities of bone and mineral metabolism, both immediately before and following transplantation. Over 430 patients have now been entered into this data base, which provides cross sectional data on a relatively healthy (fit for transplantation) dialysis population as well as longitudinal data from just pre-transplant onwards.

Bone densitometry and spinal X-rays (including lateral lumbar spine / abdomen; which is a validated means of assessing vascular calcification) are undertaken yearly and multiple laboratory investigations including bone turnover markers and hormonal levels are collected at baseline, 1, 3 and 12 months and at 2 and 5 years. Quality of life assessments at baseline, 3 and 12 months after transplant, using a KDQOL-SF that is validated for dialysis and transplant patients, have recently been added to the data collected. This is one of the most comprehensive bone resources available for patients following kidney and kidney pancreas transplantation and is a useful cross sectional database for patients on dialysis; in particular, those with type 1 diabetes. It provides opportunities to study changes to BMD, biochemistry, sex hormones, bone regulating hormones, vascular calcification, prevalent and incident fracture and QOL from dialysis through transplantation. A post-transplant bone biopsy study, together with high resolution pQCT, is planned to commence in 2009-2010.

The patients on dialysis study (which has been approved and funded) aims to assess the value of supplemental vitamin D vs placebo in patients who are vitamin D deficient and on dialysis. Endpoints include patient-level outcomes such as muscle strength and mobility, in addition to biochemical endpoints and the evaluation of novel bone turnover markers.

You have a postgraduate application form and want to study at Garvan: What now?

1. **Complete the application and send it in after discussions with your proposed supervisor. Remember to include your CV and a copy of your most recent academic transcript.**

   All applications are considered by the Garvan Higher Degrees Committee (HDC) twice a year at times that coincide with the lodgement of Australian Postgraduate Award (APA) applications and National Health and Medical Research Council (NHMRC) scholarships. Applications outside these times will only be considered in exceptional circumstances.

   As Garvan is a not-for-profit organisation, it is unlikely that a research program would have the funds to take on a postgraduate student without scholarship funding of some kind. However, there are many different sources of funding available for postgraduate research students.

   Prospective students must also lodge an application for admission to UNSW online at: www.grs.unsw.edu.au/futurestudents/apply.html

2. **Apply for postgraduate funding.**

   Scholarships such as APA, UPA and IPRS should be applied for through the UNSW Graduate Research Office which will also provide additional information about other research scholarships offered by the university.

   NHMRC scholarships should be applied for through the Garvan Grants Administration Office once you have been accepted by the Garvan. For more information email: b.youakim@garvan.org.au.

Key Dates

Late April (TBA)	**Garvan HDC Application deadline**
Late April (TBA)	HDC PhD application interviews & notification to students of acceptance (subject to APA success)
30 April	APA lodgement
June	APA notification
August	NHMRC (Dora Lush) scholarship due first Friday in August
Late October (TBA)	**Garvan HDC Application deadline**
Late October (TBA)	Garvan HDC PhD application interviews & notification to students of acceptance (subject to APA success)
31 October	APA lodgement
December	APA notification

Garvan Institute of Medical Research

Application to undertake postgraduate study

If you are interested in commencing postgraduate study at Garvan, please fill in the details on this form, attach the following information, and send back to Garvan.

- A copy of your most recent academic transcript
- A CV and synopsis
- 2 academic referee reports (sealed)

Personal Details

Title: ☐ Mr ☐ Ms ☐ Mrs ☐ Miss

First Name: _____ Surname: _____

Address: _____

Suburb: _____ State: _____ Post Code: _____

Phone (day): _____ Mobile: _____

Email: _____ DOB: _____

Education

Please list all university qualifications achieved:

Qualification	University	Date Completed

List any University qualifications currently being undertaken or completed:

Qualification	University	Subject Majors

If applicable, please provide a title and short description of your honours project (or you can attach your thesis abstract to this form):

_____

_____

_____

_____

_____

Other Information:

List any awards you have received:

_____

_____

_____

_____

List any relevant memberships:

_____

_____

_____

_____

Provide details of any scientific work experience (paid or unpaid) you have gained outside your university studies (include details of any publications):

_____

_____

_____

_____

Please indicate fields of research interest (you may tick more than one):

- ☐ Cell Biology
- ☐ Bioinformatics
- ☐ Immunology
- ☐ Physiology
- ☐ Pharmacology
- ☐ Genetics
- ☐ Neuroscience
- ☐ Others (Please specify) _____
- ☐ Biochemistry
- ☐ Proteomics
- ☐ Clinical Medicine

Garvan Institute of Medical Research

Are there any Garvan researchers you has discussed your proposed research with or research groups you would like to work with in particular?

1. _____

2. _____

3. _____

What funding have you, or do you intend on applying for?

_____

_____

_____

_____

How did you hear about the Garvan Institute postgraduate program?

☐ Garvan PhD Student Day ☐ Garvan website ☐ Other (please specify) _____

Please return with required information for consideration to:

Higher Degrees Committee

C/- Dr Ebi Cocodia

Garvan Institute of Medical Research

384 Victoria Street

Darlinghurst NSW 2010, Australia

Referee Report

Postgraduate Application

Section A – For the Applicant to complete

Please note that it is your responsibility to ensure that 2 referee reports are returned to the Garvan Institute with the application form, in a sealed envelope, by the due date.

Title: ☐ Mr ☐ Ms ☐ Mrs ☐ Miss

First Name: _____ Surname: _____

Please tick what type of degree you intend to undertake: ☐ PhD ☐ Masters by Thesis

Section B – For the Referee to complete

Please complete Section B, including the questions that follow, and return the completed report to the applicant, in a sealed envelope.

Title: ☐ Dr ☐ Prof ☐ Mr ☐ Ms ☐ Mrs ☐ Miss

First Name: _____ Surname: _____

Your Institution:

Name: _____

Address: _____

Suburb: _____ State: _____ Post Code: _____

Phone (day): _____ Fax: _____

Email: _____

Garvan Institute of Medical Research

1. How long have you known the applicant?

☐ 3-6 mths ☐ 6-12 mths ☐ 1-2 yr ☐ 2 yrs or more

2. In what capacities have you known the applicant?

☐ Lecturer ☐ Course coordinator ☐ Head of School /Department

☐ Dean of Faculty ☐ Coursework Master's supervisor ☐ Research degree supervisor

☐ Examiner of his/her thesis ☐ Other_____

3. How would you rate your knowledge of the applicant as the basis for providing a reference?

☐ Very Good ☐ Good ☐ Adequate ☐ Limited

4. Please indicate your ranking of the applicant relative to other students you have known and/or supervised:

☐ Top5% ☐ Top 8% ☐ Top 10% ☐ Top 15% ☐ Top 20%

5. How would you rate the applicant's writing skill?

☐ Average ☐ Above Average ☐ Very good ☐ Excellent

6. How would you rate the applicant's laboratory skills?

☐ Average ☐ Above Average ☐ Very good ☐ Excellent

7. How would you rate the applicant's knowledge of discipline?

☐ Average ☐ Above Average ☐ Very good ☐ Excellent

8. How would you rate the applicant's ability to plan?

☐ Average ☐ Above Average ☐ Very good ☐ Excellent

9. How would you rate the applicant's initiative and motivation?

☐ Average ☐ Above Average ☐ Very good ☐ Excellent

10. How would you rate the applicant's ability to meet deadlines?

☐ Average ☐ Above Average ☐ Very good ☐ Excellent

11. How would you rate the applicant's team work?

☐ Average ☐ Above Average ☐ Very good ☐ Excellent