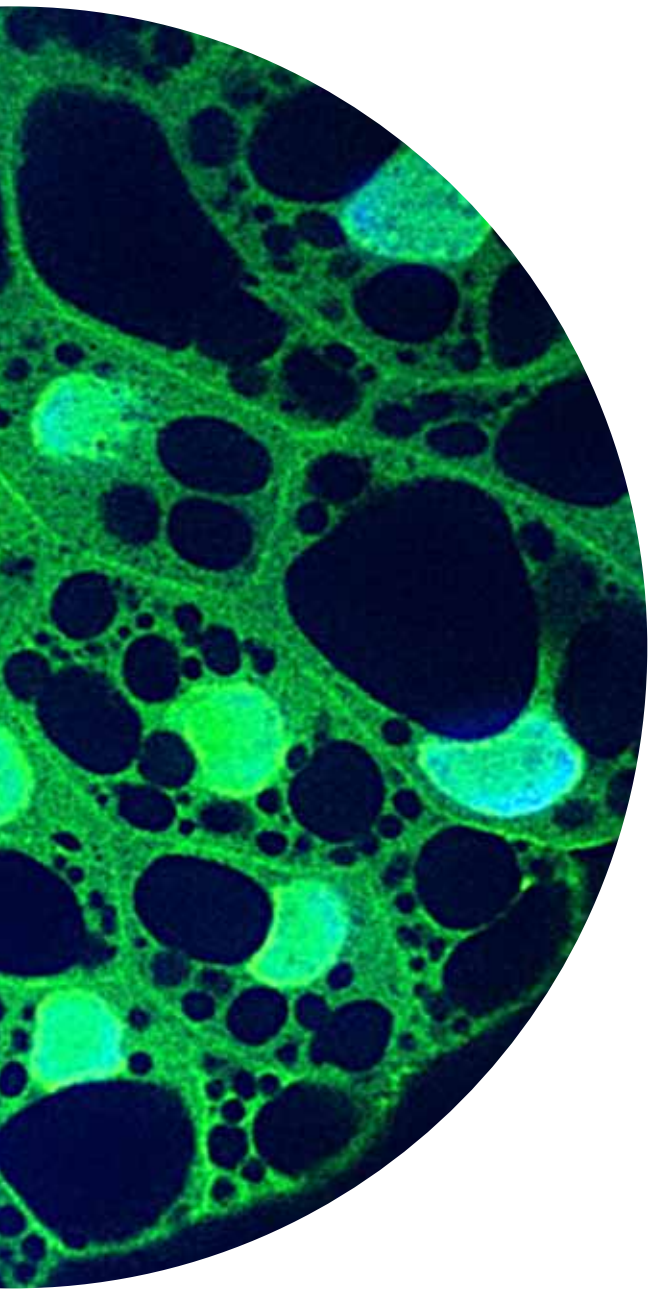


Postgraduate Projects

Centre for Cancer Biology



Building a new generation
of world-leading cancer researchers



Postgraduate Projects

Contents

- 1 Centre for Cancer Biology
- 6 Acute Leukaemia Laboratory
- 7 Cell Signalling Laboratory
- 8 Cytokine Receptor Laboratory
- 9 Drug Discovery and Development Laboratory
- 10 Gastroenterology Research Laboratory
- 11 Gene Regulation Laboratory
- 12 Hepatitis C Virus Research Laboratory
- 13 Leukaemia Unit, Genetics and Molecular Pathology
- 14 Lymphatic Development Laboratory
- 15 Mast Cell Laboratory
- 16 Melissa White Memorial Laboratory
- 17 Molecular Neurogenomics Research Laboratory
- 18 Molecular Pathology Research Laboratory
- 19 Molecular Regulation Laboratory
- 20 Molecular Signalling Laboratory
- 21 Myeloma Research Laboratory
- 22 Neurovascular Research Laboratory
- 23 Translational Oncology Laboratory
- 24 Tumour Microenvironment Laboratory
- 25 Vascular Biology and Cell Trafficking Laboratory
- 27 The Australian Cancer Research Foundation Cancer Genomics Facility

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image Drosophila salivary glands expressing GFP
show vacuolisation in UTX mutants

Centre for Cancer Biology

Building a new generation of world-leading cancer researchers

Our focus is understanding the fundamental causes of cancer to find new ways to prevent and treat the disease. Established within SA Pathology as a hub for innovative science leading to breakthrough therapies, the Centre for Cancer Biology currently hosts 21 full-time research group leaders and their teams, each examining different, but inter-related, aspects of cancer biology.

The translation of new discoveries into clinical practice is strengthened by co-localization of laboratories within a single centre, as well as our proximity and close interaction with the clinical resources of the Royal Adelaide Hospital, and the academic resources of the University of South Australia and the University of Adelaide. The CCB also has alliances with leading pharmaceutical companies to rapidly exploit new discoveries.

The CCB aims to be a hub of internationally recognised cancer research excellence, achieving tangible outcomes for cancer patients. A key platform within this goal is to foster high quality postgraduate studies to build a new generation of world-leading cancer researchers.

Student research opportunities

Each CCB laboratory offers exciting opportunities for research studies at Honours, Masters and PhD level, as well as undergraduate summer student placements. This booklet outlines the research areas of the various CCB laboratories and indicates some available research projects. In most cases many other projects are also available. Please contact the Heads of the laboratories to further explore these opportunities. In most cases research studies can be undertaken in the CCB through enrolment with either the University of South Australia or the University of Adelaide.

Our record of research excellence

One of the key thrusts of the CCB is to maintain cancer research excellence. This can be measured by the high quality of our research publications, as well as in health outcomes. Research excellence is also evident in the success of CCB scientists in obtaining peer reviewed grant and fellowship funding from local, national and international sources.

Core facilities

Our research is underpinned by world class core facilities, including the newly established Australian Cancer Research Foundation Cancer Genomics Facility, Detmold Imaging and Flow Cytometry Facility, Intravital Microscopy Suite, IMVS Animal Care Facility, and the Adelaide Proteomics Facility.

Higher degree research study at the Centre for Cancer Biology

The CCB is internationally recognised for high quality cancer research and provides an excellent environment for students to develop their scientific skills with access to world-class facilities. Completing a postgraduate degree at the CCB will provide a pathway to a career in medical research, translational science or pharmaceutical research. The CCB has a major commitment to training of higher-degree research (HDR) students and aims to provide students with the skills and abilities to succeed in research-intensive settings, and the capacity to work both independently and as part of a highly trained research team. Each year the CCB recognises outstanding HDR student achievement through a number of awards and prizes.

Honours

Students can undertake Honours in any of the CCB laboratories through programs at either the University of South Australia or the University of Adelaide. All CCB laboratory Heads are leading scientists with extensive experience in postgraduate student training and supervision.

During the Honours year students will undertake a specific research project with the technical support and wealth of knowledge of the host laboratory. An Honours degree is necessary for employment in most research laboratories, and is also an essential requirement for further postgraduate studies. After successful completion of the Honours year students are able to apply for entry into PhD and Masters by Research programs.

Entry into the Honours programs at the CCB is highly competitive and students are required to have a strong undergraduate training in science, medical science, applied science or medicine. As part of the selection process any previous research experience will also be considered in support of the application.

The CCB will offer a limited number of scholarships to full-time Honours students.

PhD or Masters research studies at the CCB

Students can undertake Masters or PhD in any of the CCB laboratories through either the University of South Australia or the University of Adelaide. Eligible students need to first identify a suitable CCB laboratory to host their studies. This booklet provides a brief overview of the research in each of our laboratories.

See the CCB website www.centreforcancerbiology.org.au for a more comprehensive description, or contact the CCB Laboratory Heads to discuss possible projects.

Scholarships

A range of scholarships are available for students wishing to undertake Masters or PhD studies at CCB. Both the University of South Australia and the University of Adelaide administer Australian Postgraduate Awards (APA), and offer a limited number of University Postgraduate awards (for Australian students). Scholarships are available for international students through both Universities. Externally-funded scholarship opportunities may also be available for some laboratories and projects. The Universities also provide scholarship opportunities to assist students in specific categories including indigenous students, students who have experienced socio-economic disadvantage, students from rural areas and students with disabilities.

For more details on research scholarships

University of South Australia www.unisa.edu.au/scholarship

University of Adelaide www.adelaide.edu.au/study/postgraduate/research-degrees/scholarships

Fees

Both University web sites provide details of fees for domestic and international HDR students.

How to apply

PhD applications are submitted through the postgraduate application process of the Universities:

University of South Australia www.unisa.edu.au/resdegrees

University of Adelaide www.adelaide.edu.au/study/postgraduate/research-degrees

Summer research placements

Opportunities exist for students to gain research experience during their undergraduate courses via six to eight week research placements in the various CCB laboratories during the summer vacation. Scholarships are available through the University of South Australia, the University of Adelaide, and other sources.

Contacts

For further general information about research studies in the CCB at PhD, Masters, Honours or summer student placement levels please contact our student coordinators:

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Our major focus is to understand the mechanisms underlying normal blood cell growth and differentiation, and the changes associated with myeloid diseases, in particular Acute Myeloid Leukaemia (AML) and pre-leukaemic diseases, including Polycythemia Vera. We have used a number of molecular and biochemical approaches to investigate, in detail, growth factor receptor signaling responses and downstream events occurring during normal myelopoiesis, and associated with the aberrant growth and survival of disease cells.

A significant research effort concerns analysis of receptor signalling mechanisms that control stem and progenitor cell responses to a number of key haemopoietic growth factors, and which are commonly mutated or up-regulated in acute myeloid leukaemia. Additionally, there is growing evidence that altered metabolism in cancer cells presents a novel therapeutic target. We have projects examining genetic changes that lead to altered metabolism and novel therapeutics that exploit the altered metabolism of the cancerous cells as their mechanism of action. Finally, we are using a number of genetic and epigenetic approaches to identify new genes and mutations that contribute to myeloid disease. These include studies of families with inherited predisposition to haematological disease, microarray gene expression profiling, methylation analysis, and exome capture and next generation sequencing from bone marrow and blood of patients. We have identified a number of genes of interest that are the subject of current studies.

Projects

The genetic basis of metabolic changes in AML progression

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GADD45A regulation of epigenetic changes in AML

Dr Michelle Perugini, michelle.perugini@unisa.edu.au

The genetic basis of signal transduction alterations in Polycythemia Vera

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Testing of novel therapeutics for poor prognosis AML

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Our research methodologies include: genetics, genomics, gene expression analysis, bioinformatics, signal transduction analysis, cell and molecular biology and *in vitro* and *in vivo* models of AML. Projects would be suitable for students with knowledge in these areas and an interest in developing further skills.

Cell Signalling Laboratory

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The interest of the Cell Signalling Laboratory is to understand how signals that are normally generated to maintain homeostasis, when dysregulated give rise to disease. Our primary research interest is to understand how a cancer cell progresses from a benign state, with good prognosis, to a malignant state resulting in metastatic disease. In solid cancers, which constitute 80% of human cancers, >90% of deaths are due to metastasis. We recently identified a novel tyrosine phosphorylation-based signalling pathway which regulates the trafficking of growth factors/cytokines and their receptors. Dysregulation of this signalling pathway impacts on cancer progression and developmental programmes. We use cell biological, molecular biological, biochemical, proteomic and live microscopy approaches in our studies and where possible, verify our findings using mouse models of cancer and human clinical samples.

Projects

Identifying Pez substrates that mediate its effects on protein secretion and metastasis.

Cells secrete factors that can act upon themselves or on other cells for normal maintenance. However, cancer cells, through mutations, can have an altered composition of secreted factors which act to alter their immediate microenvironment or to prepare a metastatic niche in secondary organs to facilitate their ability to embed in those organs. Our recent studies in mouse models show that Pez/PTPN14, a protein mutated in a number of cancers, regulates secretion of a plethora of factors that affect metastasis. Using a state-of-the-art differential phosphoproteomic screen, we identified a number of candidate substrates that can affect the cellular secretome. A number of projects exist to understand how these proteins act downstream of Pez to regulate the cellular secretome and metastasis.

Mechanisms of receptor trafficking.

The ability of cells to respond to proliferative and survival signals is dependent upon the repertoire of cell surface receptors. Loss of Pez in humans lead to multiple developmental defects including abnormal development of lymphatic vessels, giving rise to lymphoedema. This finding led us to identify Pez as a key regulator of receptor trafficking to the cell surface in lymphatic endothelial cells and breast cancer cells and consequently of the cell's ability to respond to growth factors. We are currently elucidating the molecular mechanisms by which Pez, its substrates and tyrosine phosphorylation networks regulate growth factor receptor trafficking to the cell surface and their impact on (a) lymphatic development and (b) cancer progression. This will ultimately also lead to discovery of new signal transduction mechanisms in protein trafficking, an area which is currently poorly understood.

miR-200 family microRNAs in neuroblastoma.

Neuroblastoma is a childhood cancer with poor prognosis once the cancer has spread. We have found that the miR-200 family of microRNAs can inhibit cell migration and invasion to limit the spread of breast cancer. We are using our findings in breast cancer to inhibit the spread of neuroblastoma.



Cytokine Receptor Laboratory

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Cytokine receptors transmit signals between the external, cellular environment and the cells internal machinery, stimulating the cells to respond in a variety of ways including maintenance of cell viability, promoting cell proliferation or enhancing cellular function. Abnormalities in this process including enhanced cell survival and growth are hallmarks of cancer while misregulated cellular function is associated with inflammatory diseases.

The Lopez laboratory seeks to understand the mechanism of cytokine receptor activation in health and disease with a focus on the receptors for GM-CSF, IL-3 and IL-5. This will reveal biological rules of receptor activation and will allow the development of new drugs to treat unmet clinical needs in diseases such as leukaemia, asthma and arthritis. Our research program includes structural biology approaches to elucidate structure/function relationships amongst these receptors and inhibitors there of; and cell biology, molecular and proteomics approaches to elucidate the signalling mechanisms and functional consequences of receptor activation.

Projects

Establishing the biological significance of increased IL-3 receptor expression. Having developed an IL-3 receptor-specific antibody that is currently being assessed in clinical trials in patients with leukaemia, we are now seeking to define the biological significance of IL-3 receptor over expression on malignant and normal cells. In a related study we aim to determine the role of the IL-3 receptor in autoimmunity.

Dynamic assembly of the GM-CSF and IL-3 receptors and the mechanism of signalling. We have identified a sequential mechanism of GM-CSF receptor assembly that is required for signalling. This project aims to define the molecular details of this process including the nature of the protein:protein interactions as well as functional consequences.

Determine the signalosome complexes required for GM-CSF and IL-3 signalling. We have identified specific signalling proteins that bind the GM-CSF and IL-3 receptors and are studying how these molecules contribute to the formation of the overall signalosome complex. This project aims to define the contribution of adapter-mediated signalling elements and their contribution to the functions of the cytokine receptors.

These projects will utilise cutting edge structural, molecular, cellular and genetic techniques as well as proteomic and signal pathway analysis.

Recent key papers

Broughton S *et al*: Dual Mechanism of Interleukin-3 Receptor Blockade by an Anti-Cancer Antibody. **Cell Reports** 8: 410-419, 2014.

Busfield S *et al*: Targeting of acute myeloid leukemia *in vitro* and *in vivo* with an anti-CD123 MAb engineered for optimal ADCC. **Leukaemia** 2014: Apr 7. doi: 10.1038/leu.2014.128.

Hansen G *et al*: The structure of the GM-CSF receptor complex reveals a new mode of cytokine receptor activation. **Cell** 134: 496-507, 2008.

Jin L *et al*: Monoclonal antibody-mediated targeting of CD123, IL-3 receptor alpha chain, eliminates human acute myeloid leukemic stem cells. **Cell Stem Cells** 5: 31-42, 2009.

Drug Discovery and Development Laboratory



Professor Shudong Wang PhD FRSC

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Protein kinases have become the most popular drug targets for innovative drug discovery. Kinase inhibitor blockbuster drugs, including Gleevec® and Tarceva®, have revolutionized the treatment of some forms of cancers. Professor Shudong Wang's research projects are focussed on the discovery and development of novel protein kinase inhibitors as cancer therapeutics. This involves the structure-guided design and synthesis, biological and pharmacological evaluations of inhibitors that target relevant kinases with high potency and specificity. All of the research projects on offer are highly multidisciplinary, and students will work alongside a team comprising computational and medicinal chemists, cell biologists and pharmacologists.

The following projects are specifically designed for postgraduates who have a strong desire to pursue a career in the fields of cancer research, medicinal chemistry and drug discovery.

Projects

Discovery of cell-cycle CDK4 inhibitors as anti-cancer agents. Discovery of cyclin-dependent kinases (CDKs) as key regulators of the cell cycle was made by Hartwell, Nurse and Hunt, which earned them a Nobel Prize in Physiology & Medicine in 2001. Tumour-associated cell-cycle defects are mediated by alterations in CDK activity. Although many CDK inhibitors have been identified, little progress has been made in the discovery mono-specific inhibitors of CDK4. The aim of this project is to design and synthesise a novel class of drug-like molecules that target CDK4 specifically and induce apoptosis in cancer cells.

Mechanic investigation of Mnk inhibitors against metastatic cancers. eIF4E regulates mRNAs that encode proteins involved in cell growth, angiogenesis, invasion, and survival. MAPK-interacting kinases (Mnk1 and Mnk2) phosphorylate and activate eIF4E. Our Mnk inhibitors have been shown to block eIF4E phosphorylation and subsequently inhibit cancer cell growth. This project will further investigate their inhibitory mechanism of colonization, invasion, and migration in metastatic breast and lung cancers.

Targeting transcriptional CDK9 for treatment of prostate cancer. Apoptosis is a cell suicide program essential for the regulation of development and the prevention of tumorigenesis. Evading the apoptotic program is a hallmark of cancer and is often mediated by up-regulation of anti-apoptotic proteins. Metastatic castration-resistant prostate cancer (CRPC) is an incurable condition characterized by impaired apoptosis and increased expression of anti-apoptotic proteins. We have shown that inhibition of CDK9, a key regulator of RNA polymerase II (RNAPII) transcription, can induce CRPC cell apoptosis. This project aims to identify mono-specific CDK9 inhibitors for treatment of metastatic castration-resistant prostate cancer.

Key references

Diab S *et al*: MAP Kinase-interacting kinases—emerging targets against cancer. **Chemistry & Biology** 21, 441-452, 2014.

Lam F *et al*: Targeting RNA transcription and translation in ovarian cancer cells with pharmacological inhibitor CDKI-73. **Oncotarget** 5:17, 7691-7704, 2014.

Shao H *et al*: Substituted 4-(thiazol-5-yl)-2-(phenylamino)pyrimidines are highly active CDK9 inhibitors: synthesis, x-ray crystal structure, SAR and anti-cancer activities.

J Med Chem 56, 640–659, 2014.



Gastroenterology Research Laboratory

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Colorectal cancer (CRC) is the second most common internal cancer in Australia and the second leading cause of cancer death with >4,400 deaths in 2007. Currently there are >14,000 newly diagnosed cases annually in Australia (1,100 new cases in South Australia). Worldwide, there is an annual incidence of almost a million CRC cases with an annual mortality around 500,000.

CRC is a heterogeneous disease as it develops through several molecular pathways, has diverse morphology and different precursors. Early detection of this disease is critical for patient outcome as five year survival for patients with stage I disease is >90%. This contrasts with poor prognosis for advanced disease with distant metastases (stage IV) where five year survival is less than 5%. Unfortunately, 30–50% of patients have occult or overt metastatic disease at presentation diminishing their chances for curative treatment. Better understanding of molecular alterations in CRC precursor lesions and molecular events leading to progression into invasive disease are critical for early detection, prognosis, monitoring and treatment of this disease.

Projects

Molecular characterisation of serrated pathway neoplasia. Most CRCs arise from conventional adenomas, however 30-40% of cancers develop from 'serrated' polyps which until recently were regarded as innocuous, benign lesions without potential for malignant transformation. These polyps, previously grouped within the hyperplastic polyp category are difficult to detect colonoscopically and may pose diagnostic dilemmas for pathologists as their morphology overlap with other serrated polyps. There is growing evidence that failure to identify sessile serrated adenoma during colonoscopy may explain the occurrence of 'interval' cancers in patients with previous negative colonoscopic examination. Molecular alterations in these polyps include frequent BRAF somatic mutations, hypermethylation and microsatellite instability. Using -omics technologies we plan to explore the biology of early precursor lesions and the potential factors that influence the rate of progression of these lesions to carcinoma. Our gene expression data has shown that a unique molecular profile exists which distinguish hyperplastic polyps and sessile serrated adenomas. Our findings will be validated in an independent set of polyps and CRC derived from both the conventional and serrated pathways.

Circulating Tumour DNA in patients with Colorectal Cancer. We have successfully detected somatic BRAF and KRAS mutations in plasma DNA obtained from patients with colorectal cancer where their tumours were characterised on molecular levels using Sequenom MassArray System. We plan to explore this technique assessing its utility as a disease diagnostic, prognostic and monitoring tool.

These projects will involve a range of histopathology methods and cutting edge genomic technologies including next-generation sequencing and gene expression profiling. Our Colorectal Cancer Tumour Bank will be the main source of the human biospecimens used in these projects.



Gene Regulation Laboratory

Professor Greg Goodall PhD

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Metastasis, which is the major cause of death from most cancers, begins with the spreading of cells away from the primary tumour. Cancer cells become invasive and metastatic through a process known as epithelial to mesenchymal transition (EMT). MicroRNAs are small RNA molecules recently discovered to regulate many key processes in the cell. We discovered that the miR-200 microRNA family controls EMT and projects in our lab focus around exploring the regulation and function of miRNAs in EMT and cancer. We use *in vitro* and *in vivo* models of EMT and metastasis, and apply molecular biology, cell biology, genomics and bioinformatics in our studies.

Projects

Characterising the interactions between microRNAs and their targets. We have implemented a method for physical identification of interactions between microRNAs and their mRNA targets on a transcriptome-wide basis, allowing us to refine the understanding of the rules that govern miRNA-mRNA interactions. In this project, the refinements to targeting rules will be tested using gene reporter systems in cultured cells.

Control of alternative splicing during EMT. Regulation of alternative splicing is emerging as a major form of regulation in many cell differentiation processes. We have discovered a splicing regulator that is regulated by microRNAs during EMT. This project investigates the mechanisms and functions by which microRNAs and their targets control alternative splicing during EMT.

Epigenetic control of cytokeratin loci in EMT. Cytokeratin gene expression is highly cell type-specific and thus commonly used as diagnostic cancer markers. By utilising high throughput transcriptome analysis and qPCR, we have found cytokeratins to be among the most significantly down-regulated genes in EMT. Furthermore, using ChIP-Seq we noted that the type II keratins, but not type I keratins, are regulated by histone methylation. This project will examine the mechanisms of cytokeratin gene regulation using ChIP-Seq for transcription factors whose binding sites are enriched in type I keratin promoters and will examine the roles of specific cytokeratins in affecting cell invasiveness and EMT.

Interactions between microRNAs and transcription factors in EMT. This project uses ChIP-Seq technology to investigate transcription factors that are regulated by microRNAs in EMT, and laser capture microscopy combined with RNA-seq to examine their functions at the invasive fronts of tumours.

These projects involve a range of techniques in molecular and cell biology, including recombinant DNA manipulation, manipulation of gene expression in cultured cells, high resolution microscopy, reporter assays, next-gen sequencing and bioinformatics.



Hepatitis C Virus Research Laboratory

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There are over 170 million persons worldwide infected with HCV that results in significant liver disease (fibrosis/cirrhosis) and cancer in many of those infected. In fact infection with HCV is now the leading indication for liver transplantation in many countries including Australia. Current therapies do not work in all individuals and there is no vaccine. HCV specifically infects liver cells (hepatocytes) and the main focus of our laboratory is to define the host response to infection with HCV using both laboratory based models and clinical samples. We also have a focus on developing models to study the HCV-host interaction in live cells. Through this approach we hope to add to our understanding of how HCV causes disease and identification of novel therapeutics.

Projects

Interferon stimulated gene control of HCV replication. In response to viral infection there is activation of the innate immune system that ultimately leads to the production of the cytokine Interferon (IFN), a potent inducer of gene expression. Hundreds of genes are induced following IFN stimulation and many of these are antiviral although, their exact functions have not been formally characterized. We have identified a number of novel ISGs (Viperin, IFITM family) with anti-HCV activity and determined their mode of action. Potential honors projects will include cloning novel ISGs and testing their antiviral activity not only against HCV but also Dengue. This project will encompass aspects of virology and cellular biology and is highly molecular based.

Live virus imaging of the HCV life cycle. Much of our understanding of viral life cycles and viral host interactions has relied on static microscopic images of infected cells. This represents only a snapshot in time and may significantly distort the actual scenario. We have developed the capability to visualize the HCV life cycle in living cells in real-time through introduction of small fluorescent tags into HCV proteins. This allows us to investigate the trafficking of viral proteins and their interactions with host proteins at various stages of the life cycle. Potential honors projects will include tagging of new HCV proteins for analysis and subsequent investigation of interactions with other HCV and host proteins. These studies will enhance our knowledge of the HCV life cycle using this novel and exciting technology.

The role of Interferon Lambda (IFN- λ) in response to HCV infection. It has been recently described that IFN- λ may play a dominant role in controlling viral infection, as opposed to the other IFN family members (α, β, γ). This project intends to dissect IFN- λ signaling pathways of the hepatocyte in response to HCV infection, with a particular focus on the role of STAT3 in the production of antiviral ISGs. This project will utilize *in vitro* culture models of human cell lines and primary hepatocytes and will focus on both cellular biology and virology techniques.

Leukaemia Unit, Genetics and Molecular Pathology

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Chronic myeloid leukaemia (CML) is an invariably fatal disease within three to five years if untreated. The disease is caused by an activated tyrosine kinase, which is the protein product of the BCR-ABL1 fusion gene. Effective therapy that targets BCR-ABL1 now means that the majority of patients respond and have a substantially prolonged survival. However, some patients have intrinsic drug resistance and their disease progresses within a few months of diagnosis to a rapidly fatal acute leukaemia. New prognostic markers are required to reliably predict the patients who are destined for rapid disease progression. Our laboratory monitors the molecular response to kinase inhibitor drugs of a large number of patients and many are enrolled in national and international clinical trials. The focus of our research is the identification of biomarkers of response to therapy and we have made key correlations between molecular factors and treatment outcome.

Projects

Characterising the rate of leukaemic cell death and the heterogeneity of response to tyrosine kinase inhibitor therapy. Impaired apoptosis is central to tumour development and BCR-ABL1 confers an apoptosis resistant phenotype. Growth and survival signals emanating from BCR-ABL1 regulate the expression and interactions of BCL2 family members of the intrinsic (mitochondrial) apoptotic pathway. Tyrosine kinase inhibitors kill BCR-ABL1 expressing leukaemic cells by upregulation of pro-apoptotic proteins in this pathway. However, leukaemic cell death in response to the inhibitors is highly variable as assessed by differences in the rate of BCR-ABL1 mRNA decline between patients when therapy is initiated.

We have demonstrated that failure to achieve at least a 1 log reduction by three months of therapy is associated with poor outcome (Branford et al, JCO 2012;30:4323). This project will assess the capacity of kinase inhibitors to initiate apoptosis with the aim of identifying patients at the time of diagnosis with an impaired apoptotic response. This may guide therapeutic decisions designed to avoid early disease progression.

Defining the role of additional genomic mutations discovered in BCR-ABL1 expressing cells. BCR-ABL1 is known to be the cause of CML. Other mutations may modulate treatment response and drive BCR-ABL1 independent drug resistance. We have used powerful new genomic technologies, including next-generation sequencing and bioinformatic tools to identify mutations at the time of diagnosis and/or at disease progression. We aim to define the role of these mutations in the disease process using functional studies and a range of cell biology techniques.



Lymphatic Development Laboratory

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Lymphatic vessels are a crucial component of the cardiovascular system. These specialised vessels are important for fluid homeostasis, the absorption of dietary fats and immune cell trafficking. Abnormalities in the growth, development and/or function of lymphatic vessels underlie human disorders including vascular malformations, lymphoedema, inflammatory diseases and cancer.

Despite the integral role that lymphatic vessels play in health and disease, little is known about the signals that direct their construction. The focus of research in the Lymphatic Development Laboratory is to understand how the growth and development of lymphatic vessels (lymphangiogenesis) is controlled during development and disease.

Projects

Defining the role of the transcription factor GATA2 in lymphatic vessel development in order to understand how GATA2 mutations cause primary lymphoedema. In collaboration with Hamish Scott's laboratory, we found that mutations in GATA2 underlie human primary lymphoedema and that GATA2 is localised to lymphatic vessel valves (Kazenwadel et al., 2012). This project aims to understand how GATA2 controls transcription in lymphatic endothelial cells and how loss of GATA2 function impacts on valve development. Ultimately, understanding how valve development and function is controlled should pave the way for the design of much needed new treatments for lymphoedema.

Characterising the role of microRNAs in lymphatic vessel growth and development. We have identified a number of microRNAs that are differentially expressed between blood and lymphatic vascular endothelial cells. This project aims to define the roles of these microRNAs and their target genes in vascular development.

Characterising novel signalling pathways that control lymphatic vessel patterning and morphogenesis. By profiling the genes expressed selectively in lymphatic compared to blood vascular endothelial cells during development, we have identified a number of genes and signalling pathways not previously implicated in the vasculature. We now aim to define the role of each of these genes and pathways in vessel growth and maturation.

Each of these projects will employ a range of cutting edge genetic, molecular and cell biology techniques including the generation and analysis of conditional knockout mice, primary cell culture, high resolution confocal microscopy and high throughput genomics approaches.

Mast Cell Laboratory

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Mast cells are unique immunocytes that normally reside in tissues, particularly those that are exposed to the external environment such as the skin, gut and lung. Historically, they are depicted as major effector cells of asthma and other IgE-associated allergic disorders and immune responses to parasites. However, in addition to their ability to initiate and amplify inflammation, mast cells can also regulate such responses to protect against pathological effects of excessive inflammation and aid the processes of restoring tissue homeostasis (Grimaldeston *et al*, Nat Immunol 2007; Biggs... Grimaldeston, J Exp Med 2010). Research being undertaken by the Mast Cell Laboratory focuses on the novel regulatory abilities of mast cells, with an emphasis on how this dynamic cell contributes to the regulation of inflammation associated with allergy and skin cancer development.

Projects

Defining novel molecular mechanisms that regulate IgE- and toll-like receptor- mediated mast cell activation. Activation of the high affinity receptor for IgE, FcεRI, can be controlled by inherent inhibitory mechanisms in the mast cell. This project aims to understand how certain ubiquitin ligases control mast cell activation following IgE and TLR-mediated stimulation.

Characterising the contribution of mast cells during different stages of skin carcinogenesis. In collaboration with Prof Gunnar Pejler (Uppsala, Sweden), we are investigating the important question of whether mast cell function at the peri-lesional interface provides a permissive tumourigenic environment or guards against rapid neoplastic progression during skin carcinogenesis. At the molecular level we have identified that at certain stages of ultraviolet B (UVB)-induced neoplastic progression, mast cells protect against lymphatic vessel dysfunction, detrimental inflammation and tissue changes by secreting IL-10 and the chymotrypsin-like protease, mast cell protease 4. This project will determine whether mast cells maintain anti-tumour functions in settings of skin carcinogenesis where the initiators and promoters of tumourigenesis differ from those caused by UVB irradiation, such as human papilloma virus infection and chemically-induced carcinogenesis.

Elucidating the function of the Rho-ROCK pathway in mast cell function. This project will be carried out under joint supervision with Dr Michael Samuel (Tumour Microenvironment Laboratory, CCB). We have established that mast cells express all components of the Rho-ROCK signalling pathway but the role of this cytoskeletal remodelling pathway is yet to be determined in skin carcinogenesis or settings of allergic inflammation.

Each of these projects will employ a range of sophisticated biochemical, molecular and cell biology techniques and state-of-the-art imaging. Importantly, the contribution of mast cells in certain neoplastic or allergic disease settings *in vivo* will be determined with the powerful tool of conditional mast cell-specific gene knockout mice.



Melissa White Memorial Laboratory

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The primary focus of this laboratory is translational research into Chronic Myeloid Leukaemia (CML), characterised by the constitutively active tyrosine kinase Bcr-Abl, and more recently also Acute Lymphoblastic Leukaemia (ALL). While the majority of patients with these malignancies respond well to current therapies, there is no real cure and a significant proportion of patients are likely to develop resistance to these therapies and/or relapse. Research in The Melissa White Memorial Laboratory strives to understand the underlying biological principles of resistance to therapy, to evaluate the usefulness and clinical relevance of novel targeted therapies and to develop tests to identify poor responders at diagnosis, so that therapy can be altered accordingly.

Projects

Characterisation of signalling and functional properties of BCR-ABL kinase domain mutations.

Tyrosine Kinase Inhibitors (TKIs) that competitively block Bcr-Abl activity have revolutionised CML treatment, however, kinase domain mutations frequently develop. This project will interrogate differences in mutant vs. native Bcr-Abl signalling and include compound mutations that confer resistance to the third generation TKI ponatinib.

Investigate how Bcr-Abl kinase activity affects influx and efflux transporter expression and activity. A longstanding interest of our group is active transport of TKIs in and out of cells critically affecting *in vivo* treatment efficacy (White et al. 2010 JCO). We now aim to pinpoint a potential effect of Bcr-Abl activity itself on transporter expression and activity. In addition, mass spectrometry will be employed to determine the amount of TKIs retained within leukemic cells during treatment.

Identify and characterise novel gene fusions occurring in paediatric ALL patients. Recent research, spearheaded by our close collaborator Charles Mullighan, has identified previously unrecognised gene fusions in a subset of high risk childhood ALL. This project aims to further build on this work by determining the prevalence of reported and new fusions in Australian cohorts and assessing the sensitivity of leukemic cells carrying those fusions to clinically available and novel targeted therapies.

All of these projects will involve a wide range of cell and molecular biology techniques using both established cell culture models as well as primary cells from leukaemia patients, offering students a unique position at the interface between cutting edge science and clinical research aiming to improve patient outcomes.

Molecular Neurogenomics Research Laboratory

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Our group studies a variety of neurological disorders including epilepsy, intellectual disability and autism spectrum disorders. These disorders each have a strong genetic basis and some are associated with abnormal growths in the brain such as tubers and cortical malformations, which have features similar to tumours. We employ a number of different methods to identify the genetic cause of these disorders in patients. Some of these patients are from families with a history of the disorder while others are isolated cases.

The strategies we use include genetic linkage, genome and exome sequencing and targeted re-sequencing of specific genes along with bioinformatics analysis. We have discovered a number of genes involved in neurological disorders including *PCDH19* in epilepsy and intellectual disability in females, *KCNT1* in focal epilepsy with psychiatric features and *DEPDC5* in focal epilepsies with or without brain malformations. We also use animal models including *Drosophila* and Mouse to understand the biological processes by which mutations in these genes lead to neurological disorders. Such knowledge will assist in developing improved treatments for patients.

Projects

Identifying new genes in neurological disorders. We have a large number of families and patients affected with various forms of, for example, epilepsy where we have not yet identified the gene responsible. In this project multiplex families will be analysed by exome sequencing and bioinformatics analysis to identify the causative gene. Once a gene is identified we confirm the finding by looking for further mutations in additional patients with a similar phenotype. We can then begin to investigate any genotype-phenotype correlations.

Using *Drosophila* to understand the biology of neurological disorders. *Drosophila melanogaster* is a powerful model organism which allows sophisticated genetic manipulation directed at revealing the function of uncharacterised genes. This project will utilise *Drosophila* to overexpress, knockout or alter expression of a particular gene. This allows us to explore the role of our newly identified genes in neurological disorders to identify which gene pathways they act in and how perturbation of their function results in human disease. We also use *Drosophila* carrying these disease causing gene alterations as a means to screen for new drugs to treat these diseases.

Mouse models of neurological disease. With the advent of new genome editing technologies it is possible to rapidly generate knockouts and knock-ins of genes that we have identified to be disease causing in our genetic studies in humans. Such knockout mice allow us to conduct powerful genetic and biochemical experiments to determine how these genes work and cause disease. Such knowledge of how genes work *in vivo* is vital in developing strategies to treat the diseases they cause.



Molecular Pathology Research Laboratory

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Hamish Scott heads up the Department of Molecular Pathology where the laboratory situated. The Department is co-located with the ACRF Cancer Genomics Facility, of which he is joint director. The Facility provides access to powerful cutting-edge genetic/genomic technologies including bioinformatics, next-generation sequencing (NGS) and sample preparation robotics. The Department performs both basic and translational research which includes implementing these new technologies into its diagnostic tests for personalized medicine.

Projects

Genetics and pathologic mechanisms of haematological malignancy (HM = leukaemia and lymphoma) predisposition and progression.

Exciting work in our laboratory includes disease gene discovery and confirmation utilizing latest genomic technologies. We have accrued samples from over 90 families with predisposition to HM, which are invaluable resource for the identification of genetic and epigenetic changes leading to these and other cancers. Using a combination of strategies including state-of-the-art whole exome and genome NGS, we have identified new genes that segregate with diseased individuals in some of these families and/or are mutated in sporadic samples. We continue to hunt for additional genes/mutations in families and sporadic samples. Functional studies on potential and identified genes continues *in vitro*, *ex vivo* and *in vivo* in mice to expose mechanisms for predisposition and progression to HM. Opportunities exist for students to be involved in utilising latest technologies to identify new disease genes and how mutations cause disease.

Diagnostic implementation of NGS for personalised medicine.

NGS has the power to dramatically increase diagnostic test efficiencies, including pricing, and help in personalised medicine for genetic diseases and cancer. We are looking for students to work with operational scientists in the implementation of NGS sequencing tests, including panel sequencing for cancers such as lung, melanoma and colorectal cancer, and whole exome sequencing for genetic diseases such as inherited familial cancers.

Genetic autopsy of perinatal death: diagnosis and discovery by whole genome sequencing (WGS).

Perinatal death has an enormous emotional impact on couples, often with long term psychological consequences. The trauma is further compounded in that, despite extensive investigation, a cause is unable to be established in a large number of cases. WGS provides the most sophisticated and complete genetic testing ever available. It is hoped that the use of WGS as a 'genetic autopsy' will provide a definitive diagnosis for the cause of congenital abnormalities and unexplained perinatal death. A precise diagnosis will allow accurate advice to be given to families about recurrence risk, and will open the door to assisted reproductive techniques such as preimplantation genetic diagnosis.



Molecular Regulation Laboratory

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We study cellular and molecular biology of disease with a focus on programmed cell death (PCD) and protein homeostasis by ubiquitination. PCD plays a fundamental role in cell and tissue homeostasis and too little or too much of it can lead to many human diseases including cancer.

We study the mechanisms and regulation of PCD in normal homeostasis and during animal development, with a particular emphasis on the roles of the cell death and survival machinery in cancer and ageing. Ubiquitination is a common type of protein modification that is involved in the regulation of protein stability, degradation, localisation and trafficking. We are studying the physiological and pathological functions of a group of ubiquitin-protein ligating enzymes (Nedd4 family of ubiquitin ligases) using cellular and gene knockout (KO) approaches.

Projects

Regulation of iron homeostasis by the Nedd4 adaptor proteins Ndfips and Arrdcs. Our current research is focused on iron metabolism and how the Nedd4 adaptor proteins maintain the correct balance between iron uptake, usage and storage in the body. Defective iron metabolism is one of the most common illnesses in humans, and is also a common side-effect of other illnesses such as cancer and inflammation. Dissecting out the root causes of this issue is vitally important in designing effective treatments. In this project, students will characterize the role of Nedd4 adaptor proteins in preventing iron imbalance.

Studying Nedd4-2 function using gene KO models. Recently we have shown that Nedd4-2 is a critical *in vivo* regulator of ENaC in the lung, and that the absence of Nedd4-2 leads to perinatal lethality in Nedd4-2 knockout mice. Projects in this area will utilise these Nedd4-2 knockout mice to characterise the mechanism by which Nedd4-2 regulates ENaC and other ion channels such as the chloride channel CFTR (cystic fibrosis transmembrane regulator), and will include proteomic studies to identify novel substrates of Nedd4 and Nedd4-2, and the characterisation of these interactions.

Caspase-2 as a tumour suppressor protein. Our laboratory recently discovered that the loss of the cell death protease, caspase-2, enhances the ability of cells to transform readily by oncogenes and that caspase-2 deficiency increases the potential of tumourigenesis in some mouse models of cancer. In addition, our recent work has shown that caspase-2 is important to maintain genomic stability, which is commonly disrupted in cancer. In this project the prospective students will help decipher the molecular pathways by which caspase-2 functions as a tumour suppressor, and how it acts to prevent genomic instability.

Studying the function of caspase-2 in oxidative stress response and ageing. We have discovered that loss of caspase-2 enhances oxidative stress and animal ageing and results in possible metabolic defects. We are now characterizing this phenotype to understand the pathways that are affected in caspase-2 KO mice. The project utilises animal work, as well as biochemical, proteomics and cellular approaches to profile the differences between the wild type and KO animals.

Role of autophagy in cell death during animal development. To understand the mechanisms of developmentally programmed cell death (PCD) we are using the model organism *Drosophila*. Our studies have led to the discovery of an alternative mechanism of PCD that utilises the catabolic process of autophagy. Using genetic and cell biology approaches we are now examining the transcriptional regulation and mechanisms of autophagic cell death in *Drosophila* and in mammalian cells, and further aims to determine how cell growth and death signals are integrated.



Molecular Signalling Laboratory

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The Molecular Signalling Laboratory examines cell signalling pathways that contribute to cancer and other diseases. In particular, the primary focus of our work is on the sphingolipid pathway, which can trigger increased cell survival, increased cell proliferation, and new blood vessel formation; three of the classic hallmarks of cancer. Indeed, we and others have established that sphingosine kinase, a central enzyme in the sphingolipid pathway, plays an important role in many different cancers, and is an attractive target for anti-cancer therapy.

Our studies are directed in 3 main areas: (i) to understand the molecular mechanisms regulating sphingosine kinase in cancer, (ii) developing agents that target sphingosine kinase, or its regulation, as anti-cancer agents, and (iii) defining the downstream pathways important for sphingolipid-mediated cancer cell signalling.

Projects

Defining the role of novel binding proteins in oncogenic signalling by sphingosine kinase.

We have previously established that localisation of sphingosine kinase to the plasma membrane is critical for oncogenic signalling by this enzyme. This project aims to understand how this localisation of sphingosine kinase is regulated via characterisation of the roles of a number of proteins we recently found associate with this enzyme. Understanding how sphingosine kinase is regulation in this manner may identify new targets for anti-cancer therapy.

Characterising the anti-cancer activity of novel sphingosine kinase inhibitors. We have recently developed novel chemical inhibitors of sphingosine kinase that show exciting anti-cancer activity in various cancer models. This project aims to further assess and develop the existing, and second-generation inhibitors as anti-cancer and chemotherapy-sensitising agents.

Characterising downstream effectors of sphingosine and determining their role in cancer biology. Cancer cells adopt multiple molecular mechanisms to evade cell death, one of which is the pro-survival 14-3-3 proteins. We have recently identified that the survival function of the 14-3-3 proteins is regulated by sphingosine. We are elucidating the molecular mechanisms involved in this new signalling pathway with the aim of harnessing this process to develop new anti-cancer agents.

These projects will employ a range of cutting edge biochemical and molecular cell biology techniques, that range from cloning, generation, purification and analysis of recombinant proteins, to cell culture and *in vitro* assays of neoplastic transformation, to cancer models in mice.



Myeloma Research Laboratory

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Multiple myeloma (MM) is an incurable haematological malignancy characterised by the clonal proliferation of malignant plasma cells (PC) within the bone marrow (BM). MM is the second most common haematological malignancy after non-Hodgkin's Lymphoma, with approximately 1,400 newly-diagnosed patients each year in Australia. Despite recent advances in treatment, MM remains almost universally fatal with a 10 year survival rate of approximately 17%. The main clinical manifestations of MM are the development of osteolytic bone lesions, bone pain, hypercalcaemia, renal insufficiency, suppressed immunoglobulin production and increased BM angiogenesis. It is now widely accepted that most, if not all, MM is preceded by a premalignant MGUS (monoclonal gammopathy of uncertain significance) stage. However, the genetic factors which trigger the progression from asymptomatic MGUS to overt malignant MM remain to be determined.

Projects

Defining the role of the bone marrow microenvironment in the development MM. There is a growing appreciation of the role played by the non-cancerous or microenvironmental cells in the development of malignancy. One area of our research is dedicated to identifying factors in the BM microenvironment that contribute to the development of MM. We have previously compared the gene expression and cellular characteristics of two strains of mice; the commonly used laboratory strain C57BL/6 and the related strain C57BL/KaLwRij. Although very similar, subtle differences have developed over time, the most striking being the susceptibility of C57BL/KaLwRij mice to the development of MM. The cause of this difference in susceptibility remains to be determined. The project is aimed at identifying genetic differences between KaLwRij and C57BL/6 mice that may underlie the propensity of each strain to succumb to, or resist myeloma disease development, respectively.

Determining the effects of myeloma plasma cells on mesenchymal stem cell (MSC) differentiation. Lytic lesions are a common feature of MM. Notably; these lesions persist beyond disease remission, suggesting that MM PC mediate long-term changes to the normal bone remodeling process by inhibiting osteoblast function. Osteoblasts are specialised bone forming cells derived from precursor pluripotent mesenchymal stem cells (MSCs) that reside within the bone marrow microenvironment. We hypothesise that infiltration and proliferation of MM plasma cells in the BM could potentially alter the differentiative potential of MSCs leading to a deficiency in bone forming function of osteoblasts. Using gene expression profiling of MSC prior to and following exposure to MM PC we aim to identify the molecular mechanisms by which MM plasma cells influence stem cell biology.

Identification of genetic factors which trigger the progression from asymptomatic MGUS to overt malignant MM.

What causes an individual patient to progress from MGUS to MM is still incompletely understood. Our group is in the unique position of having assembled a biospecimen bank comprised of a large number of matched MGUS and MM clinical samples taken from patients at the time of diagnosis. Using a comprehensive genomics approach, we will identify structural and gene expression changes between paired MGUS/MM samples and to investigate the biological roles of the candidate 'myeloma genes' using established *in vitro* models and a mouse model of myeloma that recapitulates human disease.



Neurovascular Research Laboratory

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Understanding development of the neuronal and vascular systems at the molecular level presents a major challenge to developmental biologists. Recent advances, including our own, conclusively show that similar molecules are recruited by both systems to coordinate development. We are particularly interested in understanding the signaling pathway centered on VEGF and its Neuropilin receptors in neuronal development. Neural stem cells possess the exceptional ability to self renew and differentiate in to multiple cell types. During embryonic development, transient populations of neural stem cells give rise to the entire central and peripheral nervous systems.

We have recently identified essential roles of key signaling molecules in neuronal development and are now using genome-wide studies to characterise their functions in neuronal migration and differentiation. The Neurovascular Development Laboratory offers an ideal opportunity for postgraduate training in developmental biology, embryology and molecular biology, with an overall focus on understanding the molecular biology of human disease.

Projects

Investigating the molecular control of neural crest stem cell (NCSC) development

NCSCs are a transient population of stem cells that give rise to all cells types in the peripheral nervous system. We have recently identified a novel role for the Neuropilin (Nrp) family of receptors in NCSC migration. To understand how these receptors function we are now undertaking experiments to characterize the intracellular signaling pathways that control neuronal migration.

Identifying the embryonic origin of the childhood cancer Neuroblastoma

Neuroblastoma is the most prevalent extracranial solid tumour in childhood and arises from incorrect NCSC differentiation. We have recently shown that the Nrp1 receptor is expressed in a subset of NCSCs that from neuroblastoma. This now gives us the unique tools to dissect the aberrant genetic programs initiating tumour formation.

Investigating the role of 14-3-3 ζ in schizophrenia

14-3-3 proteins are expressed abundantly in the brain and are thought to control survival and developmental pathways. We have recently generated mice deficient in one of the 14-3-3 isoforms, 14-3-3 ζ . These KO mice appear small but outwardly normal and display various patterning defects in brain development and neuronal migration. Our preliminary findings suggest that these mice have behavioural issues akin to schizophrenia. We are now analysing the development of cerebral and hippocampal neurons in mouse models of 14-3-3 ζ .

Translational Oncology Laboratory

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Professor Michael Brown operates the Royal Adelaide Hospital Cancer Clinical Trials Unit and is a senior consultant medical oncologist in the Royal Adelaide Hospital Cancer Centre. He has tumour subtype interests in melanoma and lung cancer. His research is focussed on the pre-clinical and clinical development of novel cancer immunotherapies for the diagnosis, monitoring and therapy, and associated laboratory evaluations. Some mechanism-based research occurs in collaboration with other laboratories within the Centre for Cancer Biology.

Projects

Preclinical development of an imaging agent for detection of tumour cell death. We have preclinical proof of concept for a novel method of detecting cancer cell death based on the APOMAB[®] monoclonal antibody that is specific for a ribonucleoprotein overexpressed in malignancy. Non-invasive methods for the detection of cancer cell death are useful both for prognostication (where necrotic tumours have a worse prognosis) and prediction of therapeutic response (where increased rates of tumour apoptosis and necrosis are associated with improved patient outcomes). The APOMAB[®] monoclonal antibody will be adapted for use in immuno-positron emission tomography (immunoPET) with the long-lived positron emitter, Zirconium-89. This form of immuno-PET will be tested in a new set of murine tumour models for a tumour type-specific indication able to be developed commercially.

A generous PhD scholarship top-up is available to help support this work.

Antibody-drug conjugates for bystander treatment of lung cancer. Antibody-drug conjugates (ADCs) are an emerging class of cancer therapeutic with two recent US FDA approvals in Hodgkin disease and HER2-positive breast cancer. We are investigating ADC versions of APOMAB[®] based on the premise that dead tumour cells are ingested by viable tumour cells. We have *in vitro* evidence that phagocytosis by viable tumour cells of APOMAB[®] bound dead tumour cells results in bystander killing of the viable tumour cells. These experiments have been extended to *in vivo* tumour models in which significant bystander tumour killing has been demonstrated.

Chimeric antigen receptor T cells for leukaemia and glioblastoma with Prof Tim Hughes, Prof Angel Lopez and Dr Agnes Yong. This newly commencing project funded by the Beat Cancer Hospital Support Package will investigate the design and implementation of chimeric antigen receptors targeting ephrin family members using *in vitro* and *in vivo* model systems. The ephrin receptors are important molecules involved in the pathogenesis of acute myeloid leukaemia and glioblastoma multiforme, the most aggressive and common form of primary brain tumour. In addition, the targeting of endothelial cells and a possible role in vasculogenic mimicry will also be studied.



Tumour Microenvironment Laboratory

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The Tumour Microenvironment Laboratory studies the mechanisms by which the tissue microenvironment is co-opted by tumours to facilitate their growth. This stems from accumulating evidence that the microenvironment is fundamentally changed in many of its key characteristics during tumourigenesis. We seek to identify the mechanisms by which properties of the tumour microenvironment impact on the initiation and progression of cancers, and conversely how the cancer acts to remodel its microenvironment, resisting the organism's attempt to normalise it.

The Rho signalling pathway is well-known to regulate the contractility of the cellular actomyosin cytoskeleton and promote cell migration and invasion. Less well-understood is its role in remodelling the tissue microenvironment. Using conditionally gene-targeted models, we showed that activation of the Rho-signalling pathway within the skin caused over-production and abnormal remodelling of collagen, the most abundant component of the microenvironment. The resulting increase in tissue density disrupted normal tissue homeostasis and promoted tumourigenesis (Samuel *et al Cancer Cell* [2011]). We are now working to determine how signalling through the Rho pathway effects these changes, and the impact of these changes on human cancers (Ibbetson *et al Am J Path* [2013]).

Projects

Determining the functional consequences of transcriptional changes that occur downstream of ROCK activation in the epidermis. Gene expression analysis of ROCK activated skin using microarrays has demonstrated that several genes with tentative links to regulation of the ECM are differentially regulated upon ROCK activation. This project will apply state of the art imaging techniques including confocal microscopy and two-photon microscopy to determine the functional effects of differential regulation of these genes upon skin physiology using *in vitro* cultured primary keratinocytes and epidermal fibroblasts and *in vivo* cancer models.

Determining the pathological effects of ROCK activation in normal murine intestinal tissue. We have determined that the Rho signalling pathway is aberrantly activated in most human colorectal cancers, as evidenced by ROCK substrate phosphorylation. To determine the function of the Rho pathway in normal intestinal homeostasis and cancer, we have generated a strain of mice in which ROCK can be activated conditionally within the intestinal epithelium. This project will apply immunofluorescence and biochemical approaches to determining the function of ROCK activation within the normal intestinal epithelium and also in a mouse model of intestinal cancer.

These projects will utilise a range of cell, molecular and tissue biology techniques including the derivation and culture of primary cells, state of the art 2-photon and confocal imaging techniques and the use of sophisticated, conditionally gene-targeted mouse models.

Vascular Biology and Cell Trafficking Laboratory



Associate Professor Claudine Bonder PhD

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With a focus on immune dysfunction and disease we study the intricate network of blood vessels that carry white blood cells throughout our body. Blood vessels contribute to life threatening diseases but are also essential for tissue regeneration and organ transplantation. A major interest of our group is to (i) investigate blood vasculature in normal and disease states and (ii) better define blood vessel progenitor cells for clinical application. Our work may provide new opportunities to (i) treat debilitating diseases such as allergy, (ii) assist blood vessel repair in patients with cardiovascular disease and diabetes and (iii) block blood vessel development in cancer patients.

Projects

A new target to treat allergy. Rapid recruitment of neutrophils to a site of inflammation is associated with severe and difficult to manage allergy. We are currently examining the role of sphingosine kinase (SK) in histamine-induced neutrophil recruitment and how attenuation of this enzyme, with topical application of an SK inhibitor, is proving to be a new treatment option for allergic inflammation in humans. Clinical translation of this work is a major focus of the laboratory.

Endothelial progenitor cells (EPCs) in disease. EPCs circulate in peripheral blood and migrate to a site for vascular formation and repair. We recently identified a new population of immature, non-adherent human EPCs along with over 100 new surface expressed biomarkers that may well be new targets to control vasculogenesis in diseases such as cancer, heart disease and diabetes.

EPCs in islet transplantation. Pancreatic islet transplantation is an emerging cure for Type 1 Diabetes but success is limited by death of insulin producing beta cells post-transplantation. We have recently shown that EPCs improve islet engraftment, function and cure rate of diabetic mice. Further development of an EPC:islet interaction will advance the cure for diabetes in humans and we are utilising cutting edge technology of smart surface biomaterials to expedite this process.

Vasculogenic mimicry in melanoma. (Principal supervisor Dr Lisa Ebert, lisa.ebert@health.sa.gov.au). Tumours need a constant supply of oxygen and nutrients to grow and metastasis. The sprouting and extension of pre-existing blood vessels represents one way to provide for these requirements. However, recent findings suggest that tumour cells themselves can also form vessel-like structures in a process known as vasculogenic mimicry (VM). We have identified new molecular mechanisms that control melanoma VM, and are studying the impact that they and VM have on melanoma progression. Our ultimate aim is to develop new treatment options for cancer patients.

A novel regulator of tumour cell growth in Multiple Myeloma. (Principal supervisor Dr Lisa Ebert, lisa.ebert@health.sa.gov.au). We recently identified a new surface marker expressed on human stem and progenitor cells, including haematopoietic and endothelial progenitors. New data suggests that this surface marker is closely associated with poor prognosis in multiple myeloma (MM), a malignancy of terminally differentiated plasma cells. Accordingly, we aim to analyse the expression and function of this molecule in MM cells in detail, and assess a potential function in regulating interactions with the bone marrow microenvironment.



The Australian Cancer Research Foundation Cancer Genomics Facility

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Over the last 10 years numerous technological developments have greatly accelerated our understanding of genetics and genomics of both inherited diseases and cancer. Advancements in microarray, microfluidics and next-generation sequencing (NGS) technologies have ushered in a new era of genomics research and the prospect of genomics-based personalised medicine.

The Australian Cancer Research Foundation (ACRF) Cancer Genomics Facility was opened in October 2012, underpinned by grants totalling more than \$6 million from the ACRF, Therapeutics Innovation Australia (TIA) SuperScience Fund (Federal Government), MedVet Laboratories, the Cancer Council of South Australia, the State Government of South Australia and the Co-operative Research Centre for Biomarker Translation and through a partnership of SA Pathology and the University of Adelaide. It is equipped with the latest instrumentation for next-gen sequencing, including NGS from Illumina, Ion Torrent and Roche; microarrays from Affymetrix and Illumina; as well as Fluidigm equipment for the study of single cells. We have substantive automation, and have been first in Australia for several of these technologies, such as automation of epigenomics.

Importantly, in collaboration with eResearch SA, South Australia's high performance computing node, we have started to build our in-house capability to analyse and interpret the vast amounts of data generated by these new technologies. This includes not only 'super'-computer infrastructure, but also bioinformaticians, people skilled in analysing and interpreting this data. The prominence and promise of studies using these technologies is shown in high profile international publications, which are changing cutting edge clinical practice for both inherited genetic diseases including cancer predisposition, and many forms of 'sporadic' cancer.

Projects

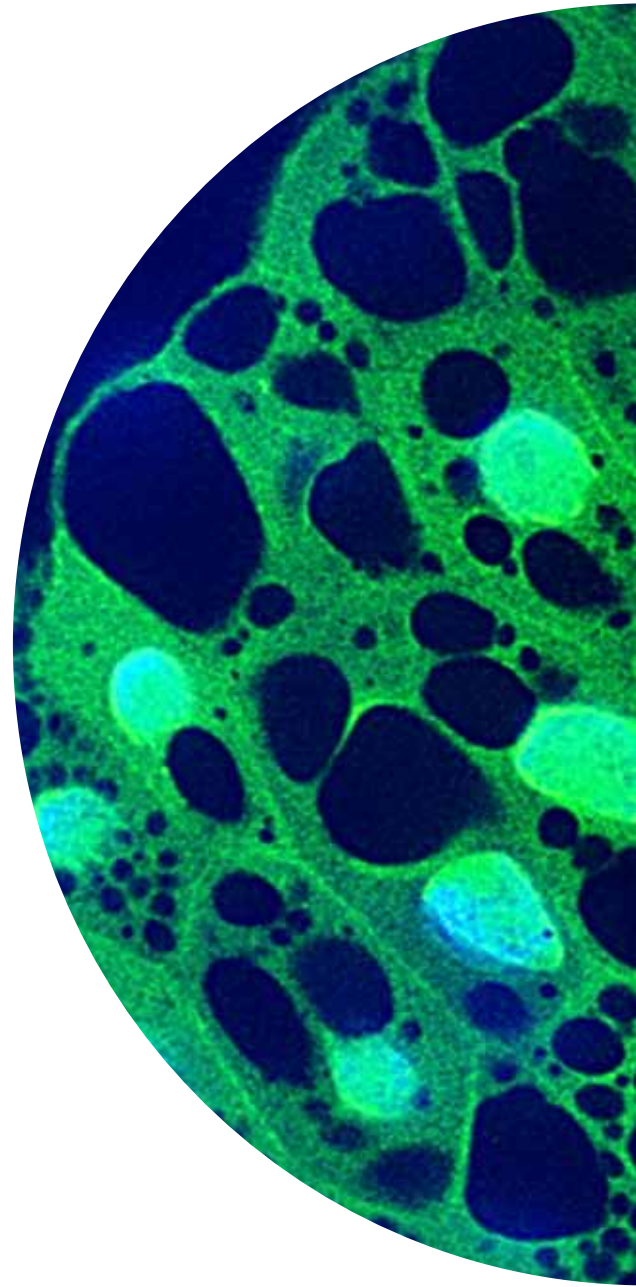
Data analysis, integration and visualization for cancer genomics (Dr Andreas Schreiber). Next generation sequencing (NGS) techniques produce prodigious amounts of data allowing interrogation of DNA sequence, mRNA expression, transcription factor binding and/or DNA methylation on a genome-wide scale. NGS is routinely used by groups within the CCB for discovery of genetic variants, the development of markers for diagnosis and/or prognosis, as well as a tool for understanding the developmental programs underlying cancer progression. The key bioinformatic challenge associated with NGS is to combine, organize and understand this flood of data, within the context of the underlying biology, to facilitate meaningful biological interpretation and to thereby correlate the underlying biology with phenotypic and clinical outcomes. Visualization, network and statistical techniques are some of the tools that can be used to accomplish this task and we have projects available, in collaboration with other labs at the CCB, to use and develop such techniques. These projects are suitable primarily for students with a background in the mathematical, statistical or computing sciences.

Building regulatory networks from EMT datasets (Dr Andreas Schreiber and Professor Greg Goodall). The Epithelial to Mesenchymal Transition (EMT) is a cellular differentiation process that is crucial in driving cancer metastasis. We currently have, and continue to expand, a collection of datasets from mRNA-seq, ncRNA-seq and ChIP-seq of laboratory EMT models that can be individually mined for discovery of regulatory interactions and can be integrated to develop higher order control networks that can subsequently be tested in the Gene Regulation Laboratory. This project will involve the use of existing bioinformatics tools and pipelines as well as the development of in house scripts for data analysis and visualisation. The project can be undertaken by students from either a computing, statistics or biology background.

Centre for Cancer Biology



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