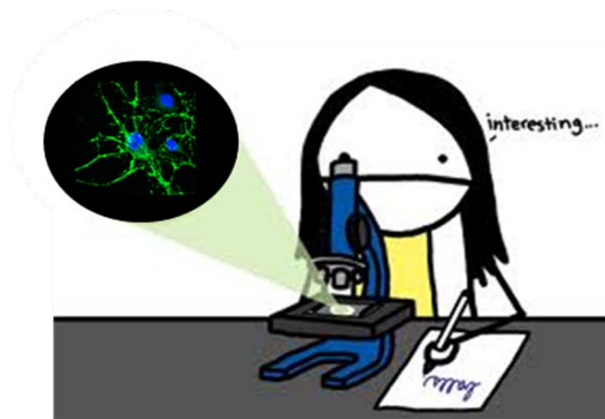


# Pathology HONOURS & RESEARCH HIGHER DEGREE INFORMATION SESSION



**Monday 12<sup>th</sup> September 2011.  
12 to 2 pm**

**Harry Brookes Allen Museum Of Anatomy and Pathology  
(Level 3), Medical Building**

**Meet with prospective supervisors  
Light lunch provided**

[www.path.unimelb.edu.au](http://www.path.unimelb.edu.au)



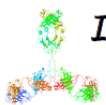
NEURODEGENERATION

TREATMENT



CANCER

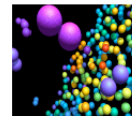
IMMUNOPATHOLOGY



DISEASE PREVENTION



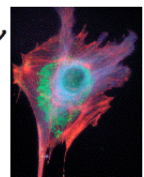
CELLULAR BIOLOGY



MOLECULAR BIOLOGY

GENETICS

EPIDEMIOLOGY



# DISCOVER YOUR RESEARCH POTENTIAL AND ENROL IN THE PATHOLOGY HONOURS PROGRAM STARTING IN 2012

The Bachelor of Science (Honours) and Bachelor of Biomedicine (Honours) program in Pathology provides an introduction to the challenging area of investigation of disease at the cellular and molecular level. This program involves candidates undertaking a full-time research project into one of the various aspects of disease as outlined in the honours project descriptors and under the careful supervision of highly-trained research scientist or clinician who are located either on campus or at one of our affiliated institutes. The objectives of the course include the development of the individual student's skills in the areas of acquisition, interpretation and critical analysis of laboratory data, planning and design of experiments and reporting of experimental data in a concise and scientific manner consistent with that published in scientific journals. The Department of Pathology Honours program will commence in mid February and conclude in late October. Students need to enroll for the following 4<sup>th</sup> year course subjects for 100 credit points –

<i>Pathology Honours Research Project (PATH40001)</i>	25 credit points
<i>Pathology Honours Research Project (PATH40005)</i>	50 credit points
<i>Critical Analysis of Pathology Research (PATH40002)</i>	12.5 credit points
<i>Introduction to Biomedical Research (BIOM40001)</i>	12.5 credit points

Assessment tasks for this subject includes writing a report outlining a critical review of the literature related to the research project, a research thesis, and 2 seminar presentations during the year. Half of the coursework component is run by the MDHS (assessment tasks include the completion of two written assignments) and the other half is run by the Department of Pathology (assessment tasks involve students critically appraising an unseen journal article in an open book exam like conditions).

Honours in Pathology can be undertaken by students with an interest in understanding the nature of disease, with a strong background in Pathology and/or allied disciplines. To undertake the Honours Program in the Department of Pathology, potential candidates should consider the projects being offered (projects will be made available by early September). It is highly recommended and a good idea that students contact supervisors to discuss the project in further detail before making their selections.

For any questions or concerns please contact one of the course conveners.

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**Dr Anthony White** email: [arwhite@unimelb.edu.au](mailto:arwhite@unimelb.edu.au), Phone: 8344 1805

## KEY DATES FOR HONOURS STARTING IN 2012

Dates	Event
<b>Wednesday 7 September 5.15pm – 6.15pm</b>	<b>How to Apply for Honours</b> Venue: Frederic Wood Jones Theatre (Level 3, Medical Building) Students must register by emailing <a href="mailto:sc-mdhs@unimelb.edu.au">sc-mdhs@unimelb.edu.au</a> and include their student ID
<b>Thursday 8 September 3pm – 5pm</b>	<b>Discover Honours Expo</b> Venue: Alan Gilbert Building (1 <sup>st</sup> floor, Executive Lounge) Students must register by emailing <a href="mailto:sc-mdhs@unimelb.edu.au">sc-mdhs@unimelb.edu.au</a> and include their student ID
<b>Monday 12 September 12pm – 2pm</b>	<b><u>Department of Pathology Project Information Session</u></b> <ul style="list-style-type: none"> <li>○ Program overview</li> <li>○ Meet with prospective project supervisors</li> </ul> Venue: <b>Harry Brookes Allen Museum of Anatomy and Pathology, Level 3, School of Medicine Building</b>
<b><u>Opening</u> Mid Sept, 2011</b>  <b><u>Closing</u> 18 Nov, 2011</b>	<b><u>Application to do Honours</u></b> Applications for Honours are lodged to MDHS via one of the following processes. <ol style="list-style-type: none"> <li>1. <b>Current Local and International <u>University of Melbourne</u> Students</b> Apply Online via the student portal webpage</li> <li>2. <b>Local and International <u>non-University of Melbourne</u> Applicants</b> Apply Online - <a href="http://www.futurestudents.unimelb.edu.au/admissions/entry-requirements">http://www.futurestudents.unimelb.edu.au/admissions/entry-requirements</a></li> </ol>
<b><u>Opening</u> Mid Sept, 2011</b> <b><u>Closing</u> 27 Nov 2011</b>	<b><u>Lodge Project Preferences in HATS</u></b> After having decided on a project(s) and received your Application ID number, you will need to lodge your preferences for projects offered within MDHS departments through HATS.
<b>3rd week Dec 2011</b>	<b>First round of offer letters sent by mail to students</b>
<b>1<sup>st</sup> week Jan 2012</b>	<b>Closing date for acceptance/rejection by students of First Round offers</b>
<b>2<sup>nd</sup> week Jan 2012</b>	<b>Second round of selection and mailing of offer letters begins</b>
<b>Mid Feb 2012</b>	<b>Honours 2012 begins</b>

**Further information about undertaking honours in Pathology or MDHS**

Go to <http://sc.mdhs.unimelb.edu.au/why-honours>

**For Information about entry requirements into the Pathology Honours program,**

Go to - <http://sc.mdhs.unimelb.edu.au/entry-requirements> and Pathology handbook entry requirements <https://handbook.unimelb.edu.au> (search for Path40001)

**For full project description of all Pathology Honours projects,**

Go to <http://www.path.unimelb.edu.au/> and download honours project list.

# Honours Projects for 2012, Semester I

<b>Department of Pathology (On Campus)</b>	
<b>Dr Joe Ciccotosto</b> , A/Prof Andy Hill, Dr Percy Chu	Investigating the neuronal cell binding of the Alzheimer's Disease A $\beta$ peptide using live cell imaging techniques
<b>Dr Peter Crouch</b> , Dr White, Dr Liddell	Energy metabolism in neurodegenerative diseases
<b>Dr Genevieve Evin</b>	New Methods for Measuring Alzheimer's Disease-Associated BACE
<b>Dr Theo Mantamadiotis &amp; Dr Dabaco</b>	Dissecting the CREB signalling pathway in brain tumour stem cells
<b>Dr Theo Mantamadiotis &amp; Dr Dabaco</b>	Identification and characterisation of stem cells in human brain tumours
<b>Dr Daniel Park</b> , Dr Tu Nguyen-Dumont	Identification of genetic variants which influence breast cancer risk #1
<b>Dr Daniel Park</b> , Dr Tu Nguyen-Dumont	Identification of genetic variants which influence breast cancer risk #2
<b>Dr Anthony White</b> , Dr Kanninen, Dr Crouch	Investigating the molecular pathology of childhood neurodegenerative disease.
<b>Dr Anthony White</b> , Dr Crouch, Dr Liddell	Development of novel metal-based neuroprotective drugs.
<b>Baker IDI Medical Research Institute (Baker)</b>	
<b>Dr Judy de Haan</b> , A/Prof Jandeleit-Dahm	Use of antioxidant mimetics to reduce high-fat and low-salt diet induced atherosclerosis in the GPx1/ApoE <sup>-/-</sup> double knockout mouse.
<b>Dr Tom Karagiannis</b>	Combination therapies for cancer: Chromatin modification and phototherapy
<b>Dr Tom Karagiannis</b>	Molecular mechanisms of action of dietary histone deacetylase inhibitors
<b>Florey Neuroscience Institute (FNI)</b>	
<b>Dr Wah Chin Boon</b>	Effects of Plastic on Brain Development
<b>A/Prof Andrew Gundlach</b> , Dr Brad Turner, Dr Wah-Chin Boon, Dr Qian Sang	Insulin-like peptide 3 (INSL3)/RXFP2 signalling in sensorimotor circuits: trophic modulatory role in developing/mature brain and in neurodegeneration?
<b>Ludwig Institute for Cancer Research (Ludwig)</b>	
<b>A/ Prof Joan Heath</b> , Dr Yeliz Boglev	Examining the connection between U12-type mRNA splicing, development and cancer
<b>Mental Health Research Institute of Victoria (MHRI)</b>	
<b>Dr Gawain McColl</b> , A/Prof Robert A. Cherny	Rapid drug screening for Parkinson's disease.
<b>Dr Blaine Roberts</b> and A/Prof Robert Cherny	Understanding the role of trace elements in Alzheimer's disease
<b>Dr Blaine Roberts</b> and Prof Colin Masters	Characterizing neurotoxic oligomers of the amyloid beta peptide.
<b>Dr Tim Ryan</b> and Prof Colin Masters	New dyes, new insights: spectroscopic detection of A $\beta$ oligomers in pathological samples
<b>Murdoch Children's Research Institute (MCRI)</b>	
<b>Dr Paul Licciardi</b>	Biological effects of probiotic metabolites
<b>Dr Paul Licciardi</b> , Dr Satzke, Dr Dunne	Streptococcus pneumoniae vaccination, carriage, and immunity
<b>Dr Simon Royce</b>	Expression of histone deacetylase enzymes – ontogenic and phylogenetic studies
<b>Dr Simon Royce</b> and Karagiannis	Chromatin modification in chronic models of asthma
<b>A/Prof Mimi Tang</b> , Dr Eileen Dunne, Dr Sung	Microbiota diversity and calprotectin in infant colic
<b>A/Prof Mimi Tang</b> , Dr Paul Licciardi	Investigating the roles of T regulatory cells, intestinal microbiota and early life microbial exposures in the development of allergic disease
<b>A/Prof Mimi Tang</b> , Dr Paul Liccardi	Probiotic and Peanut Oral Immunotherapy (P-POIT) for the Treatment of Peanut Allergy
<b>Dr Jim Vadolas</b> , Dr Bradley McColl	Site-specific integration of gene therapy vectors: Applications in stem cells and gene therapy
<b>Dr Jim Vadolas</b> , Dr Marnie Blewitt, Dr Bradley McColl	Epigenetic modifications of the human $\alpha$ -globin locus: New therapeutic targets for haemoglobin disorders
<b>Dr Jim Vadolas</b> , Dr Wijburg, Dr McColl	How does thalassaemia affect resistance to bacterial pathogens?
<b>St Vincent Institute of Medical Research (SVI)</b>	
<b>Dr Tom Brodnicki</b>	How does Latet affect infectious and autoimmune disease pathology?
<b>Dr Tom Brodnicki</b>	Sleeping Beauty mutagenesis - discovering new genes underlying disease pathology
<b>A/Prof Louise Purton</b> , Dr Emma Baker, Dr Carl Walkley	Identification of osteoblast lineage cells by fluorescence-activated cell sorting in normal and cancerous states.
<b>A/Prof Louise Purton</b> and Mrs Jean Hendy	The involvement of Hoxa1 in blood cell diseases.
<b>A/Prof Louise Purton</b> and Dr Linda Bendall,	Identification of the niche that regulates quiescence in acute lymphoblastic leukaemia cells.
<b>A/Prof Louise Purton</b> and Dr Julie Quach	Impact of TNFalpha in the bone marrow microenvironment in normal and stressed situations.
<b>Dr Nicole Walsh</b> and A/Prof Natalie Sims	The role of Oncostatin M in rheumatoid arthritis and osteoarthritis

<b>Peter MacCallum Cancer Centre (PMCC)</b>	
<b>A/Prof Marc Achen, Dr. Sophie Paquet-Fifield</b>	Analysis of molecules regulating the growth of blood vessels and lymphatics in cancer
<b>A/ Prof Alex Boussioutas and Dr Rita Busuttill</b>	Role of the tumour microenvironment in gastric cancer
<b>A/Prof Alex Boussioutas and Dr Rita Busuttill</b>	Validation of candidate genes involved in the progression of gastric cancer
<b>Prof Bowtell, Dr Etemadmoghadam,Dr Cowin</b>	Molecular analysis of Ovarian Clear Cell Carcinomas
<b>Prof Bowtell, Dr Etemadmoghadam, Dr Cowin</b>	Molecular Analysis of Platinum Resistance in Ovarian Cancer
<b>Prof Bowtell, Dr Etemadmoghadam Dr Cowin</b>	Understanding drivers of a novel molecular subtype of a high-grade serous ovarian cancer
<b>A/Prof Ian Campbell, Dr Kylie Gorringe</b>	Genomic analysis of early breast neoplasms
<b>A/Prof Ian Campbell, Dr Ella Thompson</b>	Identification of highly penetrant genes in familial breast and other cancers using next-generation sequencing
<b>A/Prof Ian Campbell, Dr Kylie Gorringe</b>	Mucinous ovarian carcinoma is a distinct ovarian subtype requiring alternative chemotherapeutic regimes
<b>Dr Michael Cater, A/Prof Ygal Haupt</b>	Manipulating metal ions as a novel approach to cancer treatment
<b>Dr. Nicholas Clemons, A/Prof. Wayne Phillips</b>	Understanding Barrett's oesophagus and oesophageal adenocarcinoma.
<b>Dr Phillip Darcy and Dr Michael Kershaw</b>	Providing "help" for effective cancer immunotherapy
<b>Dr. Delphine Denoyer, Dr. Carleen Cullinane, Prof. Rod Hicks</b>	18F-FPHCys as a reliable imaging biomarker to monitor early efficacy of PI3K/mTOR targeted cancer therapies by Positron Emission Tomography.
<b>Dr Petranel Ferrao, A/Pr Grant McArthur</b>	Assessment of CHK inhibitor therapeutics in Leukaemia
<b>Dr. Ameer George and A/Prof. Ross Hannan</b>	Hijacking growth factor receptor signalling in cancer
<b>Dr Kylie Gorringe, A/Prof Ian Campbell</b>	Functional and genetic characterisation of ovarian oncogenes
<b>Dr Kieran F Harvey</b>	The Hippo pathway, Regeneration and Cancer
<b>Dr Maya Kansara, A/P David Thomas</b>	Role of immunomodulators in the development & progression of osteosarcoma in vivo
<b>Dr Kinross, A/Prof McArthur, Prof. Johnstone</b>	Therapeutic targeting of the PI3K pathway in endometrial and ovarian cancer.
<b>A/Prof. Michael Kershaw and Dr. Phil Darcy</b>	Using cancer to fight cancer
<b>Dr Andreas Moeller</b>	Investigating The Tumour/Stroma Microenvironment In Breast Cancer
<b>Dr Andreas Moeller, Prof Mark Smyth</b>	The identity, role and function of immune cells at sites of metastasis in breast cancer
<b>Dr Paul Neeson &amp; Dr Andy Hsu</b>	Establishing a humanized mouse model of cancer
<b>Dr Belinda Parker</b>	Investigating the mechanisms of immune escape by breast cancer cells
<b>Assoc. Prof. Wayne Phillips</b>	How do PIK3CA mutations cause cancer?
<b>Dr. Normand Pouliot</b>	Mechanisms and therapy of breast cancer metastasis to brain
<b>Dr. Normand Pouliot</b>	Targeting tumour-stroma interactions to treat breast cancer metastasis to bone.
<b>Dr Elaine Sanij and A/Prof Ross Hannan</b>	The Upstream Binding Factor Ubf Regulates Genome Stability
<b>Dr Kaylene Simpson, Assoc/Prof Robin Anderson</b>	Using functional genomics approaches to identify genes that regulate breast carcinoma invasion and metastasis
<b>A/Prof Steven Stacker and Dr. Tara Karnezis</b>	Characterisation of molecules involved in lymphatic vessel function
<b>Dr Daniel Andrews, Prof Mark Smyth</b>	Recognition of h2-m3 by ly49 and subsequent regulation of nk cell responses
<b>Dr Patrick Humbert, Dr Helen Pearson</b>	Functional characterization of the scribble polarity network in prostate cancer metastasis
<b>Dr Patrick Humbert, Dr Nathan Godde</b>	Structural and biochemical characterization of polarity complexes in cancer
<b>Dr Patrick Humbert, Dr Mark Shackleton</b>	The role of polarity regulators in melanoma
<b>Dr Olga Martin, Prof. Stephen Fox</b>	Development of a novel screening test to assess individual radiosensitivity of radiotherapy patients
<b>Dr Jane Oliaro, Dr Sarah Russell</b>	The role of signaling and polarity proteins in asymmetric cell division of t lymphocytes
<b>Dr Richard Redvers, A/Prof Robin Anderson</b>	A functional genomic screen to identify genes that regulate breast cancer metastasis
<b>Dr Richard Redvers, A/Prof Robin Anderson</b>	Regulation of breast cancer metastasis by non-coding rna
<b>Dr Mark Shackleton, A/Prof. McArthur</b>	Characterization of normal melanocyte development
<b>Dr Mark Shackleton, As/Prof. McArthur</b>	Identification of determinants of melanoma progression
<b>Dr Ilia Voskoboinik, Prof Joe Trapani</b>	Regulation and function of perforin, a key effector molecule of cytotoxic lymphocytes

**Project Name**

**Investigating the neuronal cell binding of the Alzheimer's Disease A $\beta$  peptide using live cell imaging techniques**

**Description**

Alzheimer's disease (AD) is an age related neurodegenerative disorder that progressively destroys the brains ability to store memory. The pathology of an AD brain shows abnormal protein deposits, called amyloid plaques and widespread neuron cell death. These amyloid deposits arise from the polymerization of a 4 kDa peptide (A $\beta$ ) which is derived from a precursor molecule called amyloid precursor protein. While the precise mechanism of this A $\beta$  toxicity remains unclear, we have previously reported a clear correlation between A $\beta$  peptide binding to neurons in culture and neuron cell death. We know that when synthetic A $\beta$ 42 is added to neurons in culture, it begins to interact with the plasma membrane surface within a short period of time. At higher concentrations, this peptide will kill the primary cortical neurons within a few days of treatment. We also know that A $\beta$ 42 can bind to the neuronal membrane surface from the cell body to the dendrites and axons. We now wish to monitor the A $\beta$  interaction with the neurons in real time using a live cell imaging microscope. You will undertake a morphological analysis to determine the location of A $\beta$  interaction with the neurons over time. Using organelle specific dyes, you will also monitor changes to the organelle integrity of the cell. You will use a novel microfluidic device that enables us to grow neurons in culture with the axons and dendrites encouraged to grow down through some narrow tubings in isolation from the cell body. You will add A $\beta$  to the cell body or to the axon/dendrites to determine whether this peptide has a region specific effect on the cell.

**TECHNIQUES**

This project will allow the student to learn a broad range of biochemical, cell biological, and confocal microscopy, live cell imaging, primary culture and western blotting techniques.

**References**

Hung, L. W., G. D. Ciccotosto, et al. (2008). "Amyloid-beta peptide (Abeta) neurotoxicity is modulated by the rate of peptide aggregation: Abeta dimers and trimers correlate with neurotoxicity." *J Neurosci* 28(46): 11950-11958.

Ciccotosto, G. D., D. J. Tew, et al. (2011). "Stereospecific interactions are necessary for Alzheimer disease amyloid-beta toxicity." *Neurobiol Aging* 32(2): 235-248.

Taylor, A. M., D. C. Dieterich, et al. (2010). "Microfluidic local perfusion chambers for the visualization and manipulation of synapses." *Neuron* 66(1): 57-68.

Taylor, A. M., S. W. Rhee, et al. (2006). "Microfluidic chambers for cell migration and neuroscience research." *Methods Mol Biol* 321: 167-177.

Poon, W. W., M. Blurton-Jones, et al. (2009). "beta-Amyloid impairs axonal BDNF retrograde trafficking." *Neurobiol Aging*.

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**Pathological Disease Research Topics Matching This Project**

Neurodegeneration

**Select Research Techniques Matching This Project**

Cell culture

Immunofluorescence

Cell biology

Cell death

**Project Name**

**Energy metabolism in neurodegenerative diseases**

### **Description**

Our research group is offering a number of Honours projects for 2012. All projects are distinct, but the central theme is energy metabolism in neurodegenerative diseases as described below. Contact Dr Peter Crouch for details on specific projects.

Neurodegenerative diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic Lateral Sclerosis (ALS) destroy the mental and physical health of millions of people world-wide. Our research team studies these diseases from two distinct but complimentary points of view; we study the fundamental biology that may contribute to the disease pathology, and we develop and test therapeutic agents to treat the diseases. To achieve our research goals our work is based largely on cell culture experiments and testing potential new therapeutics in mouse models of disease.

A common feature of AD, PD and ALS is that specific proteins become abnormally metabolised in disease affected tissues. In AD the protein is amyloid-beta, in PD it is alpha-synuclein, and in ALS it is TDP43 and SOD1. The normal function of some of these proteins is not clear, and it is not known whether their altered metabolism is a cause or consequence of the disease. To help elucidate this, a critical question needs to be answered: "what cellular conditions cause these proteins to be aberrantly metabolised?"

One model we are pursuing is decreased cellular energy metabolism. Neuronal cells have a high demand for energy and a decrease in their capacity to generate energy, as ATP, restricts a broad range of their normal functions. Our research aims to investigate the link between impaired energy metabolism and neurodegenerative disease. Our work also aims to identify the therapeutic potential of compounds we know are activated under conditions of impaired energy metabolism.

This project will utilise a range of cell culture paradigms to model impaired energy metabolism. By modeling these conditions in vitro we will identify the significance of impaired energy metabolism in the pathology of neurodegenerative disease.

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### **Pathological Disease Research Topics Matching This Project**

Neurodegeneration

ALS

Alzheimer Disease

### **Select Research Techniques Matching This Project**

Cell culture

Western blot

Cell biology

Immunofluorescence

**Project Name**

**New Methods for Measuring Alzheimer's Disease-Associated BACE**

**Description**

Alzheimer's Disease (AD) is the most common cause of dementia and a debilitating illness of the aged population. Genetic and experimental evidence support the causative role of amyloid A $\beta$  protein in the disease pathogenesis. A $\beta$  is derived from the amyloid precursor protein (APP) by sequential proteolytic cleavages involving BACE and gamma-secretase. We have shown that BACE levels are increased in the frontal cortex of AD patients (1,2) and that it is elevated in AD cerebrospinal fluid (3). BACE is an aspartyl protease, with characteristic structural features that support its potential as a target for drug development (4). Your project will consist in developing new in vitro and cellular assays for BACE that can be applied to the testing of inhibitors.

**Specific Aims:**

1. To establish and characterize a mammalian cell line stably overexpressing BACE.  
Cells will be transfected with BACE cDNA, and characterized by western blotting for BACE expression and for production of APP cleavage products, sAPP $\beta$  and A $\beta$ .
2. To establish in vitro BACE assays involving synthetic fluorogenic substrates and alternative sources of BACE, including BACE prepared from the cells above
2. To evaluate and compare the effect of candidate BACE inhibitors on the production of sAPP $\beta$  and A $\beta$  from different cell lines, including BACE transfected cells

**References:**

(1) R.M. D. Holsinger, C. A. McLean, K. Beyreuther, C. L. Masters, and G. Evin. Increased expression of the amyloid precursor  $\beta$ -secretase in Alzheimer's disease. *Ann. Neurol.* (2002) 51, 783-786  
(2) C. Santosa, S. Rasche, A. Barakat, S. A. Bellingham, M. Ho, J. Tan, A. F. Hill, C. L. Masters C. McLean, G. Evin. Decreased expression of GGA3 Protein in Alzheimer's disease frontal cortex and increased co-distribution of BACE with the amyloid precursor protein. *Neurobiol Dis* (2011) 43(1):176-83  
(3) R. M. D. Holsinger, C. A. McLean, S. J. Collins, C. L. Masters, and G. Evin. Increased  $\beta$ -secretase activity in cerebrospinal fluid of Alzheimer's disease subjects. *Ann. Neurol.* (2004) 55, 898-899  
(4) G. Evin, A. Barakat, C. L. Masters. BACE: Therapeutic target and potential biomarker for Alzheimer's disease. *Int J Biochem Cell Biol* (2010) 42 (12): 1923-1926.

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**Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Alzheimer Disease

Alzheimer Disease

**Select Research Techniques Matching This Project**

Protein Chemistry

Cell culture

Western blot

ELISA assays

**Project Name**

**Dissecting the CREB signalling pathway in brain tumour stem cells**

**Description**

One of the most important advances in brain tumour biology has been the discovery that tumours can develop from cells with stem cell-like characteristics. Indeed, the understanding of cancer stem cells has provided a new optimism in the development of novel strategies for cancer therapy. The signalling networks operating in normal neural and brain tumour stem cells involve complex molecular networks. At the hub of these networks are the transcription factors, which determine which genes are expressed, when they are expressed and how much of each corresponding mRNA is expressed. CREB is a transcription factor at the hub multiple signalling cascades, which are active in neural stem cells and CREB regulates the expression of a series of downstream target genes important for stem cell survival and growth. We have previously generated CREB mutant mice which have shown defects in brain stem cells and are now investigating the link between CREB's role in brain stem cell survival and growth and its role in brain tumour development and growth. The aim of this experiment is to identify upstream (eg. growth factors) and downstream (CREB target genes) factors of the CREB pathway in brain tumour stem cells. The experiments undertaken in this honours project will involve the use of human brain tumour cell lines and tumour stem cells and the genetic manipulation of these cells. Specifically, CREB-dependent survival, proliferation and differentiation of these cells will be determined by transfecting a DNA-based CREB-shRNA-expressing plasmid into these cells. This will allow for efficient conditional/long-term silencing of CREB expression. Thus, the effects of CREB silencing can be determined by measuring the survival (Annexin V status), proliferation (MTT cell growth assay) and differentiation (nestin, GFAP, beatIII-tubulin IF) potential of these cells. Preliminary studies in two human brain tumour cells lines using CREB-siRNA, which allows transient silencing of CREB expression, show CREB-dependent effects on growth. A change in one of these parameters (survival, growth, differentiation) has direct implications on the effects of CREB on brain tumour development and growth. The generation of these lines will also provide the opportunity to perform a microarray/gene screen to determine the BTSC CREB-dependent transcriptome. Moreover, this project will also provide an opportunity to become involved in collaborations between the Department of Pathology, the Royal Melbourne Hospital neuro-oncology groups and the new Melbourne Brain Centre.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Stem Cell

Cellular Growth & Proliferation

**Select Research Techniques Matching This Project**

Cell culture

Molecular biology

Cell biology

RNA silencing

**Project Name**

**Identification and characterisation of stem cells in human brain tumours**

### **Description**

This project is part of a larger focussed study on understanding the molecular genetic mechanisms involved in brain tumours and novel paths toward improving patient therapies. It will also provide an opportunity to become involved in collaborations between the Department of Pathology, the Royal Melbourne Hospital neuro-oncolgy groups and the new Melbourne Brain Centre.

Gliomas are a type of aggressive brain tumor which exhibit complex cellular and genetic heterogeneity, limiting effective targeted therapy approaches. Understanding the complexities of such tumors requires knowledge of the cell types and factors contributing to the development and progression of the tumour. In this project various state of the art labeling techniques will be performed on brain tumour cells and tissues, with aim of characterising the stem cells which give rise to the tumour. A panel of fluorescently labelled antibodies will used to double or triple label the cells and tissues, which will identify the stem cells and determine subsets of stem cells expressing various markers important for stem cell survival, growth and differentiation. Specific experiments to be performed include immunofluorescence analyses which will be performed on human patient brain tumour biopsies using commercial tumour tissue arrays (US Biomax) or tissue sourced from the Royal Melbourne Hospital neuro-oncology group. Some of the factors to be investigated will be: epidermal growth factor receptor (EGFR), PTEN, p53, CD133, nestin, GFAP, betaIII-tubulin, CREB. These factors comprise key genes/proteins known to influence brain tumour cell biology and pathology. The study will involve confocal microscopy, cell/tissue culture, histology and histochemistry.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Stem Cell

Cellular Growth & Proliferation

### **Select Research Techniques Matching This Project**

Cell culture

Immunofluorescence

Immunohistochemistry

Histology

**Project Name**

**Identification of genetic variants which influence breast cancer risk #1**

**Description**

We are one of the first groups in Australia to publish on the application of massively parallel sequencing ("next generation sequencing") to the study of human disease [Park et al., 2011]. We have established a sequencing and bioinformatics pipeline for the discovery of breast cancer predisposition genes via 'whole-exome' sequencing of highly selected familial breast cancer cases. Indeed, by using this approach, we have discovered and validated a new breast cancer predisposition gene [manuscript in preparation]. The Project(s) offered will 'plug-in' to this 'discovery' workflow to characterise other promising candidate breast cancer risk genes.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

**Select Research Techniques Matching This Project**

Molecular biology

Next generation sequencing

Bioinformatics

Epidemiology

**Project Name**

**Identification of genetic variants which influence breast cancer risk #2**

**Description**

We are one of the first groups in Australia to publish on the application of massively parallel sequencing ("next generation sequencing") to the study of human disease [Park et al., 2011]. We have established a sequencing and bioinformatics pipeline for the discovery of breast cancer predisposition genes via 'whole-exome' sequencing of highly selected familial breast cancer cases. Indeed, by using this approach, we have discovered and validated a new breast cancer predisposition gene [manuscript in preparation]. The Project(s) offered will 'plug-in' to this 'discovery' workflow to characterise other promising candidate breast cancer risk genes.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

**Select Research Techniques Matching This Project**

Molecular biology

Next generation sequencing

Bioinformatics

Epidemiology

**Project Name**

**Investigating the molecular pathology of childhood neurodegenerative disease.**

### **Description**

Neuronal ceroid lipofuscinosis (NCLs) or Batten disease is a group of childhood neurodegenerative disorders. Batten disease is caused by mutation in one of 10 genes of unknown function. The mutation results in slow but progressive deterioration of visual, cognitive and motor functions resulting in death in early childhood. Collectively, NCLs are the largest form of neurodegenerative disease affecting children. At present there is no effective treatment or cure and research efforts to date have yet to identify a unifying disease-specific pathway.

Previous research has shown that many of the proteins associated with Batten disease are localized in the endoplasmic reticulum, either as their normal location or as a mutated form. Our preliminary research has identified substantially elevated zinc levels in the brain regions affected in an animal model of CLN6 late infantile Batten disease. As the endoplasmic reticulum is also a key site for regulation of zinc homeostasis in neurons, we are investigating the link between altered biometal homeostasis and the mutated CLN6 protein. In addition to this, we are mapping the downstream pathological consequences which involve a series of changes to cell signaling molecules. We are investigating the link between changes to signaling kinases such as PI3K/Akt and ERK and changes to synaptic markers as an early indicator of neuronal degeneration.

The current project will investigate these underlying molecular events in cell culture models as well as small and large animal models of Batten disease. The objective will be to delineate the early molecular changes that lead to neuronal cell death in the affected brain regions of animals with Batten disease mutations. The findings can then be further investigated in tissues from human patients with Batten disease. This knowledge may help in the development of novel therapeutic treatments for the disease.

The research project will involve the use of cell culture models including primary and secondary cultures, immunoblot, immunofluorescence, RT-PCR and additional molecular techniques. These will be applied to several models associated with the CLN6 form of the disease including natural mutation models in mice and sheep.

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### **Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Oxidative Stress

### **Select Research Techniques Matching This Project**

Cell culture

Cell biology

Immunofluorescence

DNA cloning & PCR

**Project Name**

**Development of novel metal-based neuroprotective drugs.**

### **Description**

Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD) and motor neuron disease (MND) are characterized by protein accumulation, oxidative stress and neuronal degeneration. Together, these diseases have an enormous impact both financially and socially worldwide, yet there are no effective treatments for any of these diseases. Growing evidence supports a key role for abnormal biometal homeostasis in the onset and progression of these neurodegenerative diseases. In many cases, there is strong evidence to support a loss of normal intracellular copper, a key biometal in many cell functions including energy production in the mitochondria and anti-oxidant function. Therefore, therapeutic treatments designed to restore normal neuronal and glial copper homeostasis have the potential to restore activity of these functions in the brain.

Together with collaborators, our laboratory has developed novel copper-based compounds termed bis (thiosemicarbazones). These copper complexes are readily taken up into neurons and glia and deliver bioavailable copper to the cells. Our research has demonstrated that these compounds have potent neuroprotective effects in animal models of AD, PD and MND. While, the protective function is related to copper delivery, we still know little about the mechanisms of cell uptake, release and trafficking of the copper inside neurons and glia and how this induces strong neuroprotective responses. At present we are investigating these exciting aspects of copper complex action in cell culture and animal models.

This project will investigate the neuroprotective actions of new copper complexes with the aim of identifying structure-activity relationships that can be used to design more potent compounds. In addition, the project will investigate the mechanisms by which neurons and glia metabolize the copper complexes and how this relates to neuroprotective outcomes. This research will contribute important findings to the developmental process of our metallo-drug development program, a research project that has been included in the National Health and Medical Research Council (NHMRC) Ten Of The Best Research Projects, 2010 (<http://www.nhmrc.gov.au/guidelines/publications/r48>).

The project will apply a range of techniques including primary and secondary cell culture, enzyme assays, viability assays, immunoblotting, immunofluorescence, ICP-MS metal analysis, RT-PCR and additional biochemical and molecular techniques.

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### **Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Motor Neuron Disease

Alzheimer Disease

### **Select Research Techniques Matching This Project**

Cell culture

Cell biology

Immunofluorescence

DNA cloning & PCR

**Project Name**

**Use of antioxidant mimetics to reduce high-fat and low-salt diet induced atherosclerosis in the GPx1/ApoE<sup>-/-</sup> double knockout mouse.**

**Description**

Research Focus: Our laboratory is focused on delineating the role of antioxidant defence in the prevention of diabetic complications such as diabetes-associated-atherosclerosis (DAA). We have previously shown an important role for glutathione peroxidase-1 (GPx1), an endogenously expressed antioxidant enzyme that is part of the body's natural defence against oxidative stress, in preventing DAA in murine models lacking GPx1. By using synthetic mimetics of GPx1, we have demonstrated significant reductions in DAA in our murine models. We are also interested in the role of GPx1 mimetics in non-diabetic settings to establish whether a more targeted approach to antioxidant defence is applicable to cardiovascular disease in general.

**Project:**

Title: Use of antioxidant mimetics to reduce high-fat and low-salt diet induced atherosclerosis in the GPx1/ApoE<sup>-/-</sup> double knockout mouse.

Randomised GPx1/ApoE<sup>-/-</sup> mice, will be fed diets rich in saturated fats and cholesterol for 7 and 14 weeks. A second HFD-fed group will be given GPx1-mimetics by daily gavage. Thereafter mice will be killed and examined for extent of lesions within the aorta (lesion area after staining with Sudan-4) as well as markers of atherosclerosis (increased cellularity by assessing SMC proliferation and macrophage infiltration) and inflammation. A second model will also be investigated based on the novel finding that low salt diets accelerate atherosclerosis. GPx1/ApoE<sup>-/-</sup> mice will be fed low salt diets for 6 weeks. A second group will receive GPx1-mimetics by gavage. Mice will be killed and assessed for plaque, markers of atherosclerosis and inflammation as detailed above. Techniques will include an assessment of plaque size and histology (cryostat sectioning and staining through the aortic sinus as well as an analysis of the entire aorta by the en face technique), immunohistochemistry and a range of molecular biology techniques such as RT-PCR to assess expression of various antioxidant and pro-inflammatory genes, Western blotting to determine protein levels, and biochemical assays to determine ROS such as superoxide and hydrogen peroxide.

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Vascular disease

Cardiovascular Disease

Oxidative Stress

**Select Research Techniques Matching This Project**

Biochemistry

Immunohistochemistry

In vivo animal models

Western blot

**Project Name**

**Molecular mechanisms of action of dietary histone deacetylase inhibitors**

**Description**

It is emerging that a controlled equilibrium between histone acetylation and deacetylation is essential for normal cell growth and perturbations in histone acetylation status have been associated with various diseases. Therefore, HDAC inhibitors are emerging as a new class of cancer chemotherapeutics and are being investigated in inflammatory models including asthma and diabetes.

The anti-cancer effects of conventional HDAC inhibitors such as Trichostatin A, SAHA and valproic acid (induce differentiation, cell cycle arrest, apoptosis, growth inhibition and cell death, which are more pronounced in transformed cell-lines than in normal cells) have been relatively well investigated. However, numerous HDAC inhibitors found in the human diet (e.g. isothiocyanates found in cruciferous vegetables and diallyl disulfide found in garlic) have recently been identified.

Our hypothesis is that dietary and conventional HDAC inhibitors will have analogous effects in model systems of disease. The aim of this project is to investigate cellular (e.g. cell-death, apoptotic effects) and epigenomic (e.g. histone acetylation status) responses to the dietary HDAC inhibitors, sulphoraphane and diallyl disulphide, in comparison to those observed with the prototype HDAC inhibitor Trichostatin A, in vitro. The project will involve mammalian cell culture, flow cytometric analysis of cellular viability (using a membrane permeability marker such as propidium iodide) and apoptosis (Annexin V), Western blot analysis (histone hyperacetylation) and specific gene modulation by real-time PC. In vitro models of cancer (human leukemic cells), cardiovascular disease (rat hypertrophic cardiomyocytes) and normal cells will be investigated.

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**Pathological Disease Research Topics Matching This Project**

Epigenetics

Breast Cancer

Oxidative Stress

**Select Research Techniques Matching This Project**

Cell culture

Molecular biology

Immunofluorescence

Western blot

**Project Name**

**Combination therapies for cancer: Chromatin modification and phototherapy**

### **Description**

The overall aim of this research area is to develop a platform technology for receptor-targeted isotope radiotherapy / diagnostic imaging and for UVA phototherapy. For the UVA phototherapy component of the project, we have developed, UVASens, an ultraviolet light (UV) photosensitiser, which is ~1000 times more potent than compounds used clinically for the treatment of cutaneous T-cell lymphoma.

Our approach involves the use of a DNA minor groove binding ligand to target the radioisotope (radiotherapy / imaging) or iodine atom (phototherapy) to DNA. The DNA binding ligands used for these projects are based on the structure of Hoechst 33342, a well known DNA stain. The aim of this project is to develop appropriate vehicles for the delivery of the DNA ligand to specific target cells. This will be performed by encapsulation in antibody-coated nanoparticles. Given the safety concerns with the use of radioisotopes, unlabelled DNA ligands will be used for the initial proof-of-concept experiments in this project. In this context the fact that these DNA ligands are intrinsically fluorescent is an advantage. It will enable the determination of the efficiency of targeting by fluorescence microscopy / flow cytometry (fluorescence yield of DNA bound ligand increases by ~30-fold).

The project will involve preparing the antibody-coated nanoparticle-based formulations and targeting specific receptors on cancer cells. Receptor systems that will be evaluated will be the anti-carcinoembryonic antigen and SNU-16 overexpressing the receptor, and epidermal growth factor receptors and A431 cells. Evaluation of the efficacy of the constructs will involve flow cytometry (FACS), cell viability and apoptosis assays.

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### **Pathological Disease Research Topics Matching This Project**

Epigenetics

Leukemia

Metastasis

### **Select Research Techniques Matching This Project**

Cell culture

Molecular biology

Immunofluorescence

Western blot

**Project Name**

**Effects of Plastic on Brain Development**

**Description**

Everyday experience tells us the hormones affect behaviour. In fact, sex hormones such as androgens (e.g. testosterone) and estrogens are essential for normal behaviour as well as brain development. Recently, it has been brought to attention that plastics interfere with the actions of sex hormones. Due to the ubiquitous exposure of plastic, it will be important to understand how plastics when ingested during gestation will affect brain development.

The project aims to address the issue how plastic affects brain development using transgenic mice, immunohistological techniques and molecular biology.

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**Pathological Disease Research Topics Matching This Project**

Epigenetics

Cellular Growth & Proliferation

**Select Research Techniques Matching This Project**

In vivo animal models

Immunohistochemistry

Molecular biology

Cell culture

**Project Name**

**Insulin-like peptide 3 (INSL3)/RXFP2 signalling in sensorimotor circuits: trophic modulatory role in developing/mature brain and in neurodegeneration?**

**Description**

These studies will focus on the peptide/(hormone) insulin-like peptide 3 (INSL3) and its receptor RXFP2 and aim to determine the role of INSL3/RXFP2 signalling in the development of neuroendocrine, basal ganglia and limbic circuits involved in the modulation of sensorimotor function, and their response to hormones and neuronal injury. Studies of the distribution of RXFP2 reveal enrichment of receptor at somatic and pre-synaptic sites of excitatory neurons in cortex, thalamus and basal ganglia in rat brain, with a strong association with regions that receive inputs from midbrain dopamine neurons and a strong expression in limbic and hypothalamic areas of the mouse brain [1, 2].

New immunohistochemical studies have revealed the pattern of proINSL3 and INSL3-immunostaining within the basal ganglia and motor systems of the brainstem. Central INSL3 injections produce behavioural effects in rats and mice, and the peptide is accumulated by neurons (receptor-mediated); but the nature of endogenous INSL3 signalling is unknown. This Honours project aims to determine the expression profile of INSL3 in the developing and adult brain and to assess the effect of neural damage associated with motor neuron disease and hormonal perturbations in mutant mouse strains on INSL3 expression to help determine putative roles for INSL3 in development and plasticity. In separate studies we will examine the effects of activation/inhibition of RXFP2 in sensorimotor circuits on brain activity and behaviour – such as arousal, locomotion, stereotypy and social recognition. These studies should improve our understanding of peptide control of motor function and behaviour, with broad potential implications for states such as autism, schizophrenia and degenerative diseases such as ALS.

Students will receive training in neurochemical anatomy, physiology, behaviour, and peptide pharmacology; and in techniques including animal surgery and behavioural testing; in situ hybridization and immunohistochemistry; and light/confocal microscopy and analysis.

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1. Sedaghat K et al. Neuroscience 156 (2008) 319-333.
2. Sedaghat K et al. Brain Res 1271 (2009) 83-94.

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**Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Motor Neuron Disease

Parkinson Disease

**Select Research Techniques Matching This Project**

In vivo animal models

Immunohistochemistry

DNA cloning &amp; PCR

Molecular biology

**Project Name**

**Examining the connection between U12-type mRNA splicing, development and cancer**

### **Description**

As a result of the detailed genetic and morphological characterisation of a zebrafish mutant, we have identified a gene, known as RNA-binding region containing protein 3 (rnpc3) that is indispensable for a stage in development when intestinal epithelial cells are highly proliferative. Previous studies have established that this gene encodes a protein, Rnpc3/65K involved in a specialised form of mRNA splicing. Specifically, Rnpc3 is a component of the minor class or U12-type spliceosome that catalyses the removal of a minor class of introns, called U12-type introns, from pre-mRNA molecules. U12-type introns are rare but are highly conserved in the plant and animal kingdoms. There are approximately 700 U12-type introns in the human genome (out of a total of >20,000 introns). Interestingly, these introns are not randomly distributed throughout the genome, but are found in “information processing genes”. Intriguingly, they are a feature of some tumour suppressor genes and oncogenes.

Because many of the behaviours of developing cells and tissues (eg. proliferation, cell migration and angiogenesis) are recapitulated by cancer cells, we believe that genes that play a role in intestinal development may also contribute to the development of cancer. To explore the possibility that Rnpc3 is required for the correct expression of tumour suppressor genes, we recently generated conditional and global Rnpc3 knockout mice. Using these mice, we aim to determine whether impaired U12-type splicing contributes to colon tumourigenesis.

This Honours project will entail analysis of Rnpc3 expression and function in our new mouse models. The specific aims are: (i) to describe the spatio-temporal patterns of Rnpc3 expression during normal mouse embryonic development and in adulthood and (ii) to determine whether impaired Rnpc3 activity increases cancer susceptibility in tumour-prone mutant mice.

Skills Acquisition: The project will provide opportunities to become skilled in a variety of molecular and cell biology techniques, including in-situ hybridisation, immunohistochemistry, real-time PCR and histology.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Colon Cancer

Cellular Growth & Proliferation

### **Select Research Techniques Matching This Project**

In vivo animal models

Molecular biology

Cell biology

Histology

**Project Name**

**Streptococcus pneumoniae vaccination, carriage, and immunity**

**Description**

The Gram-positive bacterium *Streptococcus pneumoniae* (the pneumococcus) is the most common cause of pneumonia and a leading cause of death in children under five years old worldwide. It is frequently carried in the nasopharynx of children. Over ninety distinct serotypes of pneumococcus have been identified. The pneumococcal conjugate vaccine PCV7 protects against seven common invasive serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) and has been widely introduced in developed countries. However, high rates of pneumoniae in developing countries and the increase in disease caused by non-vaccine serotypes worldwide highlight the need for additional research that could lead to improved surveillance, prevention, and treatment strategies. Our laboratory is interested in studying pneumococcal carriage and immunity in populations with high disease burden. This project will utilize cutting-edge microbiological and immunological techniques to examine the long-term impact of pneumococcal vaccination on the level of protective antibodies, antibody function, memory B cells, and bacterial nasopharyngeal carriage in Fijian children participating in a large phase II pneumococcal vaccine trial.

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**Pathological Disease Research Topics Matching This Project**

Infectious diseases

**Select Research Techniques Matching This Project**

Molecular biology

Cell culture

ELISA assays

**Project Name**

**Biological effects of probiotic metabolites**

### **Description**

The World Health Organisation defines probiotics as live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. The most widely studied probiotics are the Lactobacillus and Bifidobacterium species. The beneficial effects of dietary probiotics in the gastrointestinal tract are well established and include promoting mucosal immunity as well as improving the microflora balance. However, the ability of probiotic bacteria to modulate host immune responses and microbial colonisation is dependent on the species and strain used. Evidence to date suggests that these biological properties of probiotics are important in the prevention and/or treatment of diseases such as Crohn's disease, allergy and cancer. The mechanisms for this effect however are not fully understood.

One of the most extensively characterized post-translational modifications affecting chromatin organisation is histone acetylation. The acetylation status of histones is dependent upon the opposing actions of histone acetyltransferase (HAT) and histone deacetylase (HDAC) enzymes and can have widespread downstream effects on various gene transcription factor targets. Small drug molecules such as SAHA, valproic acid and butyric acid that inhibit HDAC enzymes have been shown to induce differentiation, cell cycle arrest, apoptosis, growth inhibition and cell death in cancer cell lines and are emerging as a new class of cancer chemotherapeutics. Furthermore, the effectiveness of HDAC inhibitors is currently being investigated in various models of inflammatory disease including asthma and diabetes. A major class of bioactive probiotic metabolites are short-chain fatty acids (SCFAs). These include butyric acid, a well-known known inhibitor of HDAC enzymes, and may be one mechanism for the clinical effects of probiotics. The overall aim of this BSc Honours is to investigate the cellular and molecular effects of various probiotic-derived dietary metabolites. The specific aims are to investigate cellular (e.g. cancer cell death and apoptosis; immune cell modulation) and epigenomic (e.g. histone acetylation status) responses of dietary HDAC inhibitors in comparison to the prototypical HDAC inhibitor, Trichostatin A.

Experiments will involve examining the effect of dietary probiotic metabolites on cultures of mammalian-derived lymphoid and cancer cell lines including lymphocyte proliferation, Th1/Th2 cytokine secretion, flow cytometric analysis of cellular viability (using a membrane permeability marker such as propidium iodide) and apoptosis (Annexin V), Western blot analysis (histone hyperacetylation) and specific gene activation by real-time PCR as well as the recruitment of proteins on selected genes by chromatin immunoprecipitation (ChIP) assay.

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### **Pathological Disease Research Topics Matching This Project**

Epigenetics

Allergies

Oxidative Stress

### **Select Research Techniques Matching This Project**

Cell culture

Molecular biology

Immunofluorescence

Western blot

**Project Name**

**Expression of histone deacetylase enzymes – ontogenic and phylogenetic studies**

### **Description**

Chromatin undergoes dynamic remodeling to facilitate DNA metabolic processes including transcription, replication and repair. Histone proteins organize the DNA into nucleosomes, the basic repeating units of chromatin. Nucleosomes consist of 146 base pairs of DNA tightly wrapped around a histone octamer consisting of two each of the core histones, H2A, H2B, H3 and H4. It is now well established that post-translational modifications of core histones play a major role in modeling higher-order chromatin structure and controlling gene transcription. Acetylation and deacetylation of the amino-terminal tails of lysine residues are the most well characterized post-translational histone modifications.

The opposing actions of two classes of enzymes, histone acetyltransferases (HATs) and histone deacetylases (HDACs) regulate the acetylation status of the core histones. HDAC enzymes catalyze the removal of acetyl groups from lysine residues resulting in a more compacted, transcriptionally repressed, chromatin structure. Overall, it is proposed that acetylation levels regulate gene transcription by controlling the accessibility of transcription factors to DNA.

Controlled equilibrium between histone acetylation and deacetylation is essential for normal cell growth and perturbations in histone acetylation status have been associated with various diseases. Therefore there is an interest in understanding the function and further characterizing the expression of HDAC enzymes

The aim of this project is to evaluate the expression of histone deacetylase enzymes in different vertebrate species and during mammalian development.

#### References

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### **Pathological Disease Research Topics Matching This Project**

Epigenetics

Allergies

Asthma

### **Select Research Techniques Matching This Project**

Cell culture

Molecular biology

Immunofluorescence

Western blot

**Project Name**

**Chromatin modification in chronic models of asthma**

### Description

Asthma affects more than 2 million Australians, and is the most common chronic illness affecting children. Ongoing symptoms are thought to reflect persistent airway hyperresponsiveness and progressive airway remodelling. Key clinical endpoints in asthma is a chronic inflammatory disorder with often reversible lung obstruction, but with irreversible reduction in lung function, characterized by increased airway hyperresponsiveness. Compared to airway inflammation, airway remodelling is more resistant to therapies. Therapeutic interventions targeting both components of airway hyperresponsiveness are required.

It has been shown that chromatin modifying compounds, such as histone deacetylase inhibitors, have an important influence on airway inflammation, airway remodelling and airway hyperresponsiveness in allergic airways disease. Therefore, these type compounds require exploration as potential therapies for asthma.

The aims of this BSc Honours project are:

1. To investigate the role of HDACi in the development of airway remodelling and airway hyperresponsiveness in a chronic model of allergic airways disease applied to mice.
2. To explore the mechanisms of action of HDACi in the regulation of airway remodelling and lung function, including airway hyperresponsiveness, in the mouse model.

The mouse model that will be used in this project is well-established in the laboratory. Experiments will involve establishing the chronic model of allergic airways disease, administration of the relevant histone deacetylase inhibitors. The effects of the compounds on allergic airways disease will be monitored by histology, immunohistochemistry and plethysmography. Histone acetylation will be examined by Western blots for anti-acetylated histones H3 and H4.

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### **Pathological Disease Research Topics Matching This Project**

Epigenetics

Allergies

Asthma

### **Select Research Techniques Matching This Project**

Cell culture

Molecular biology

Immunofluorescence

Western blot

**Project Name**

**Microbiota diversity and calprotectin in infant colic**

**Description**

Infant colic, characterised by excessive crying of unknown cause, affects up to 20% of babies and doubles the risk of postnatal depression. It is the most common proximal risk factor for shaken baby syndrome, and is a huge burden to health services. Despite years of research, the causes of infant colic are unclear, and its management options limited. A randomised controlled trial (n = 160 infants) of probiotic supplementation versus placebo in infants with colic will be undertaken to determine if the probiotic *Lactobacillus reuteri* can reduce infant crying and improve infant sleep, maternal mental health and family functioning in the critical first 6 months of life. As part of this trial, this honours project aims to investigate microbiota diversity and faecal calprotectin levels in these infants at baseline and at 1 month. It is hypothesized that supplementation with *Lactobacillus reuteri* will induce changes in infant gut microbiota and reduce faecal calprotectin levels, suggesting possible pathophysiological mechanisms (eg gut inflammation) in infant colic. Techniques used in this project will include Molecular Biology and ELISA.

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**Pathological Disease Research Topics Matching This Project**

Immunology

**Select Research Techniques Matching This Project**

ELISA assays

Molecular biology

**Project Name**

**Investigating the roles of T regulatory cells, intestinal microbiota and early life microbial exposures in the development of allergic disease**

**Description**

The prevalence of allergic disease in Australia is among the highest in the world, and continues to increase at an alarming rate. The primary prevention of allergic disease is an important public health goal; however, we are yet to identify any preventative strategies that can significantly reduce the risk of allergic disease. The hygiene hypothesis suggests that the rapid rise in allergic conditions over the last half a century relates to reduced exposure to microbial stimuli in early life, particularly in the early postnatal periods. Acquisition of the intestinal microbiota is the most significant microbial exposure for a newborn, and plays a crucial role in regulating normal infant immune development. Children with allergic disease have altered intestinal microbiota (reduced microbial diversity and altered profile of microbiota) from the first weeks of life, suggesting that alterations in the microbiota play an important role in the development of allergic disease. However, the effects of early life microbial exposures on the intestinal microbiota and immune programming in the first year of life have not been directly examined. The Barwon Infant Study (BIS), currently underway, aims to recruit an unselected Australian birth cohort with one year follow-up in order to examine the mechanisms by which the early life environment modifies postnatal immune programming and the risk of allergic disease. This honours project will represent a sub-study of BIS, focussing on the role of T regulatory cells in the development of allergic disease, and in particular the relationship between early life microbial exposures, intestinal microbial diversity and T regulatory cell activity. Techniques used in this project will include cytokine production (cell culture, ELISA and multiplex assay), characterisation of T regulatory cell populations (flow cytometry), and characterisation of intestinal microbial diversity (DNA extraction, PCR, restriction enzyme digest).

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**Pathological Disease Research Topics Matching This Project**

Immunology

**Select Research Techniques Matching This Project**

ELISA assays

Cell culture

Flow cytometry

Molecular biology

**Project Name**

**Probiotic and Peanut Oral Immunotherapy (P-POIT) for the Treatment of Peanut Allergy**

**Description**

Food allergy is a major public health problem of childhood. 5-8% of children have food allergy, and more than 1 in 70 have peanut allergy. Peanut allergy is of particular concern as a substantial proportion of reactions are life-threatening anaphylaxis, allergy is usually lifelong, and peanut is the most common cause of death due to food anaphylaxis. A promising new treatment approach is the combined administration of a probiotic adjuvant with peanut oral immunotherapy (P-POIT). Our pilot studies show preliminary evidence of efficacy with reduced peanut specific IgE and increased peanut specific IgG4. The probiotic Lactobacillus rhamnosus GG has immunomodulatory effects that are expected to enhance the tolerogenic potential of oral immunotherapy.

This project will investigate immune mechanisms that drive tolerance acquisition. The P-POIT study offers a unique opportunity to examine this since blood and saliva samples are collected at several time points during the study from all subjects. Laboratory studies will focus on peripheral blood T-regulatory cell (Treg), T-helper 1 and T-helper 2 activity. Laboratory methods will involve flow cytometry for characterisation and enumeration of Treg subsets, gene expression analysis (RNA extraction, RT-PCR, microarray), cytokine analysis (cell culture, ELISA, multiplex). If combined treatment with probiotic and peanut OIT (P-POIT) is shown to be effective for the induction of tolerance to peanut, we will have identified a much needed cure for peanut allergy, and a proof of principle for the treatment of all food allergy. Understanding the immune mechanisms involved in the regulation of oral tolerance will represent a major advance in Allergy research.

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**Pathological Disease Research Topics Matching This Project**

Immunology

**Select Research Techniques Matching This Project**

Cell culture

ELISA assays

Flow cytometry

Molecular biology

**Project Name**

**Epigenetic modifications of the human  $\beta$ -globin locus: New therapeutic targets for haemoglobin disorders**

### **Description**

Haemoglobin disorders, such as sickle cell disease and  $\beta$ -thalassaemia are the result of mutations in the adult  $\beta$ -globin gene. When these disorders are co-inherited with hereditary persistence of fetal haemoglobin (high levels of  $\gamma$ -globin gene expression in adult life), the clinical severity of disease is much reduced. Therefore, understanding the molecular events involved in  $\gamma$ -globin gene regulation through development has been the subject of intense investigation for many years. These studies have led to a greater understanding of the role of epigenetics in globin gene expression. As a result, considerable efforts have been focused on the pharmacological induction of fetal haemoglobin using epigenetic-specific agents capable of modifying DNA methylation and histone acetylation. However, the role of individual epigenetic regulators in globin gene expression is not very well understood. This study will investigate the potential impact of epigenetic regulators on globin gene expression. We will use RNA interference (RNAi) to interrogate the expression of specific epigenetic regulators in erythroid cells that have been modified to express fluorescent reporter genes under the control of the  $\gamma$ -globin promoter. Flow cytometry, real-time PCR and western blot analysis will be used to monitor globin gene expression. Positive outcomes of such studies could pave the way for the development of better treatment strategies for sickle cell anaemia and  $\beta$ -thalassaemia patients.

Recommended reading.

- 1) Kiefer CM et al, (2008) Epigenetics of beta-globin gene regulation. Mutation Research. Dec 1;647(1-2):68-76.
- 2) Hosey et al, (2010) Crosstalk between histone modifications maintains the developmental pattern of gene expression on a tissue-specific locus. Epigenetics 5:4, 273-281.

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### **Pathological Disease Research Topics Matching This Project**

Epigenetics

Stem Cell

### **Select Research Techniques Matching This Project**

RNA silencing

Cell biology

Flow cytometry

DNA cloning & PCR

**Project Name**

**Site-specific integration of gene therapy vectors: Applications in stem cells and gene therapy**

**Description**

One of the major obstacles to successful gene therapy is the random integration into the genome of the therapeutic transgene, which is associated with insertional mutagenesis and oncogenesis. Using specific elements derived from adeno-associated virus (AAV) our research group has developed a novel strategy to enhance the delivery and site-specific integration of large DNA molecules into the human genome. We have recently used this strategy to enhance the delivery and site-specific integration of the entire 180 kb human  $\beta$ -globin locus into cultured cell lines. This project will investigate the site-specific integration of functional genomic loci into stem cells. Reporter gene expression and fluorescence in situ hybridisation will be used to monitor targeted integration and tissue-specific expression. In vitro differentiation will be used to assess the capacity of modified stem cells to differentiate along multiple lineages.

Relevant publications from our group:

1. Howden SE, Voullaire L, Vadolas J. (2008) The transient expression of mRNA coding for Rep protein from AAV facilitates targeted plasmid integration. *J Gene Med.* 2008 Jan;10(1):42-50.
2. Howden SE, Voullaire L, Warden H, Williamson R, Vadolas J. Site-specific, Rep-mediated integration of the intact beta-globin locus in the human erythroleukaemic cell line K562. *Gene Therapy* 2008 Oct;15(20):1372-83.
3. Zaibak F, Kozlovski J, Vadolas J, Sarsero JP, Williamson R, Howden SE. (2009) Integration of functional bacterial artificial chromosomes into human cord blood-derived multipotent stem cells. *Gene Ther.* Mar;16(3):404-14.
4. Hatzistavrou T, Micallef SJ, Ng ES, Vadolas J, Stanley EG, Elefanty AG. (2009) ErythRED, a hESC line enabling identification of erythroid cells. *Nat Methods.* 2009 Sep;6(9):659-62.

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**Pathological Disease Research Topics Matching This Project**

Epigenetics

Stem Cell

**Select Research Techniques Matching This Project**

Molecular biology

Cell biology

Flow cytometry

FISH

**Project Name**

**How does Thalassaemia affect resistance to bacterial pathogens?**

### **Description**

Thalassaemia is one of the most common genetic disorders affecting haemoglobin synthesis. This results in severe anaemia that must be treated with regular blood transfusions every 3-4 weeks. As a consequence of the frequent blood transfusions and excessive iron absorption, thalassaemia patients develop a state of iron overload resulting in damage and failure of the heart and/or liver. The second most frequent cause of mortality and morbidity in thalassaemia patients are infections. In particular, ferrophilic Gram-negative bacteria such as *Klebsiella pneumoniae* and *Yersinia enterocolitica*, are reported in patients undergoing iron chelation therapy. Encapsulated bacteria, such as *Streptococcus pneumoniae*, cause serious infections in splenectomized patients. A large number of immune abnormalities have also been described, mostly due to iron overload and/or long-term receipt of multiple blood transfusions. In this project, we will use a mouse model for thalassaemia to investigate the deficiencies in the immune system that predispose to increased susceptibility to infection with bacterial pathogens *S. pneumoniae*, *Salmonella typhimurium* and/or *K. pneumoniae*. The effect of immunodeficiencies in the thalassaemic mice on vaccination against these organisms will also be investigated.

The techniques that will be used include molecular biological techniques (PCR, real-time PCR, FISH), cell culture, flow cytometry, animal handling and experimentation (including dissection of organs, infection via intranasal route, intravenous injection, oral gavage), ELISA, bacterial cultures, microscopy and in vivo imaging,

Recommended reading:

- 1) Galanello, R. and Origa, R. (2010). Beta-thalassaemia. *Orphanet J Rare Dis* 5: 11.
- 2) Borgna-Pignatti C., Marsella M. and Zanforlin N. (2010). The natural history of thalassaemia intermedia. *Ann. N.Y. Acad. Sci.* (Issue: Cooley's Anemia 9th Symposium) 1202:214-220.
- 3) Vento S., Cainelli F. and Cesario F. (2006) Infections and thalassaemia. *Lancet Infect. Dis.* 6:226-233.
- 4) Jamsai D. et al. (2006) A humanized BAC transgenic/knockout mouse model for HbE/beta-thalassaemia. *Genomics* 88:309-315.
- 5) Vadolas et al. (2006) Humanized beta-thalassaemia mouse model containing the common IVSI-110 splicing mutation. *J. Biol. Chem.* 281:7399-7405.

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### **Pathological Disease Research Topics Matching This Project**

Infectious diseases

Oxidative Stress

### **Select Research Techniques Matching This Project**

In vivo animal models

Flow cytometry

Histology

Metal biology

**Project Name**

**Rapid drug screening for Parkinson's disease.**

**Description**

Current medications for Parkinson's disease only offer symptomatic relief and fail to protect remaining neurons. Reliance on mammalian models limits the rate at which new therapies can be identified and developed, as these approaches are time consuming and costly. New screening strategies are required to accelerate the development of new therapeutic options for Parkinson's disease.

During this project you will develop and utilize a unique, cost-effective and rapid screen for disease-modifying drugs for

Parkinson's disease. You will use transgenic *Caenorhabditis elegans* (a simple nematode) modified to replicate Parkinsonian brain chemistry. Initially, compounds will be screened whose effects have already been measured in mammalian models and the results compared. Furthermore, you will investigate interactions between protective compounds and candidate gene pathways to identify underlying modes of drug action.

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**Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Parkinson Disease

**Select Research Techniques Matching This Project**

In vivo animal models

Molecular biology

Metal biology

**Project Name**

**Characterizing neurotoxic oligomers of the Amyloid Beta peptide.**

**Description**

Alzheimer's disease is the most common form of dementia in the elderly and as life expectancy continues to increase the number of alzheimer's cases is predicted to reach 50 million by 2050. The exact molecular mechanism that casue Alzheimer's is not clear, however, genetic evidence and a large body of literature includes a role for the neurotoxic peptide amyloid beta (A $\beta$ ). Although A $\beta$  is clearly toxic, the form of the peptide that results in toxicity is not certain. A $\beta$  is a amyloidogenic peptide that can rapidly precipitate out of solution as a fibril. The process of going from monomeric A $\beta$  peptide to a mature fibril involves many intermediates or protofibrils. The evidence suggests that these intermediates or soluble oligomers of A $\beta$  are the neurotoxic principle. The exact nature of these toxic oligomers is not known. Understanding the exact chemical and structural nature of these oligomers is vital for drug design and diagnostic development.

The techniques that have previously been used to characterize A $\beta$  oligomers have largely have been low resolution techniques, such as SDS-PAGE. We propose to use high resolution mass spectrometric techinques to characterize the oligomeric make up of A $\beta$  species. The skills learned in this project will be directly applicable to the rapidly growing use of mass spectrometry in the neurosciences and biology.

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**Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Alzheimer Disease

**Select Research Techniques Matching This Project**

Biochemistry

Mass spectrometry

Chromatography

Protein Chemistry

**Project Name**

**Understanding the role of trace elements in Alzheimer's Disease**

### **Description**

Have you ever wondered why copper, zinc, iron, chromium, manganese and others metals are included in multivitamins? All of biology is made of five basic components; water, sugar, lipids, proteins and DNA. However, a less studied but vital portion of biology that we aim to understand are the trace elements. This project aims to understand what these metals are doing in biology and how they are involved in Alzheimer's disease.

The trace elements include the metals mentioned above. Although they exist in small amounts they are required for life. For example, if a person is anemic they are deficient in iron or potentially copper. Trace metals are involved in a diverse range of cellular functions such as transporting oxygen (iron), producing energy (copper), and regulating gene expression (zinc), just to name a few. In all of these processes the metals are bound to proteins, which work together to carry out these functions. Currently, there are few methods to study the metal status of proteins in a biological sample and most are indirect methods or require a detailed knowledge of the protein.

Trace elements such as copper, iron and zinc have been proposed to play a causal role in the aetiology of neurodegenerative diseases such as Alzheimer's disease and motor neuron disease. For example, the plaques in Alzheimer's disease brain are enriched in iron, copper and zinc. Despite the observed dyshomeostasis of metals information on how metal homeostasis is perturbed is lacking. We are currently developing new methods to directly determine the metal status of proteins from Alzheimer's disease patients tissue and fluids. This project involves using these novel techniques to determine the metal status of proteins from Alzheimer's disease brain and age matched control tissue.

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### **Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Alzheimer Disease

ALS

### **Select Research Techniques Matching This Project**

Metal biology

Biochemistry

Chromatography

Mass spectrometry

**Project Name** New dyes, New Insights: Spectroscopic detection of A $\beta$  oligomers in pathological samples

### **Description**

Alois Alzheimer first described Alzheimer's disease (AD) in 1906. Since then AD has been identified as the third leading cause of death in Australia, and there is currently no effective therapeutic for the disease. The general consensus is that soluble oligomers of A $\beta$  are the neurotoxic principle responsible for AD. We are currently working to identify and characterize oligomeric species of A $\beta$  with the aim of identifying how the toxicity in this disease occurs.

In order to effectively achieve this aim we need to develop methods for the detection of oligomeric species in pathological sections of tissue. The current amyloid dyes are extremely effective at detecting the final relatively inert amyloid plaques, but give no indication of the distribution of these oligomeric species within the tissue of interest. Thus the aim of this project is to identify dyes that bind to oligomeric forms of A $\beta$  and to characterize these dyes further in both a biophysical and histological sense.

Specifically the project will entail screening compounds for binding to A $\beta$  oligomers, followed by a characterization of what is actually binding the dye, i.e. what size is the oligomer, and how tightly is it binding the dye. Finally the most promising dyes will be examined for utility in determining the distribution of oligomeric species throughout tissue samples.

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### **Pathological Disease Research Topics Matching This Project**

Neurodegeneration

Alzheimer Disease

### **Select Research Techniques Matching This Project**

Biophysics

Biochemistry

Histology

Protein Chemistry

**Project Name**

**Analysis of molecules regulating the growth of blood vessels and lymphatics in cancer**

**Description**

The growth of blood vessels (angiogenesis) and lymphatic vessels (lymphangiogenesis) is central to the growth and spread of cancer. In the Tumour Angiogenesis Program, Peter MacCallum Cancer Centre, we have identified protein growth factors, cell surface receptors and signalling pathways that control these important processes, including members of the vascular endothelial growth factor (VEGF) family. The project will explore the regulation of these molecules in cancer and normal development, with a focus on in vivo studies using mouse genetic models of disease developed in our Program. Our Program is a leader in such in vivo models of angiogenesis and lymphangiogenesis, and we have established novel models of growth factor activation and function important for this project. The project will have a view to therapeutics designed to restrict tumour angiogenesis and lymphangiogenesis, and thereby inhibit the spread of cancer. It will have elements of translational research, and will involve the latest techniques of cell biology, molecular biology, microscopy, molecular pathology, genetics, bioinformatics and biotechnology.

Relevant references from the Tumour Angiogenesis Program:

Achen et al., Cancer Cell 7:121-127, 2005  
Francois et al., Nature 456:643-648, 2008  
Harris et al., FASEB J. 25:2615-2625, 2011  
McColl et al., FASEB J. 21:1088-1098, 2007  
McColl et al., J. Exp. Med. 198:863-868, 2003

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**Pathological Disease Research Topics Matching This Project**

Cancer

Metastasis

Cellular Growth & Proliferation

**Select Research Techniques Matching This Project**

Cell biology

Molecular biology

In vivo animal models

Histology

**Project Name**

**Role of the tumour microenvironment in gastric cancer.**

**Description**

Gastric cancer (GC) is the fourth most common cancer globally and 7th in incidence in Australia. It has a poor survival rate which can be attributed to the advanced stage at diagnosis in most patients. The molecular and cellular mechanisms underlying the development of GC are not well described.

Traditionally cancer research involved studying the cancer cell itself. More recently, there has been growing interest in studying the normal cells and molecules which surround the cancer cell. This tumour microenvironment consists of a variety of stromal cell types including cells such as fibroblasts. It is believed that the dynamic communication between tumour cells and the surrounding cell types may play a major role in cancer initiation, progression and establishment of metastatic disease. The aim of this project is to investigate tumour-stromal interactions in gastric cancer utilizing established and primary cell lines. Once the molecular pathways by which a tumour cell progresses has been elucidated it is possible that these processes could be exploited in the development of novel therapeutics.

This project will use a broad range of techniques such as live cell microscopy, cell culture techniques and siRNA to interrogate the function of gene products that influence tumour-stroma communication.

Our previous genomic experiments have provided us with a number of exciting candidate genes that may be involved in this interaction. This is novel research that may have a major benefit to our understanding of cancer and improve patient outcomes.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

Cell biology

Cell culture

Molecular biology

RNA silencing

**Project Name**

**Validation of candidate genes involved in the progression of gastric cancer**

**Description**

Gastric cancer (GC) is the fourth most common cancer globally and in many western countries is usually only diagnosed at advanced stage giving patients a 5-year survival rate of less than 20%. GC has distinct premalignant stages that have significant propensity to progress. The premalignant cascade consists of easily identifiable histological stages from chronic atrophic gastritis (ChG), intestinal metaplasia (IM) and dysplasia. The progression through these stages, particularly IM, takes years, offering a large window of opportunity to intervene. However not all patients with IM will progress and selection of patients for high-risk surveillance would reduce the burden of unnecessary screening, patient anxiety and improve outcomes due to early detection of disease.

Relatively little is known about the key genetic events leading to IM. Our laboratory is currently in the process of completing the first comprehensive analysis of IM in the world and seeks to identify candidate genes involved in the progression of IM to GC that can be used to reliably predict the progression to GC in humans by using a genomics based approach. Identification of such genes offers an opportunity to study the molecular mechanisms involved and pinpoint targets for prevention and therapy. The aim of this project is validate these candidate genes using an independent data set and then characterizing these genes using functional assays and animal models.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

Cell biology

Cell culture

Molecular biology

RNA silencing

**Project Name**

**Molecular analysis of Ovarian Clear Cell Carcinomas**

**Description**

Ovarian clear cell adenocarcinoma (OCCA) is a clinically significant subtype of ovarian cancer, accounting for ~10% of invasive ovarian cancers. OCCA have a poor response rate to standard therapy (only 11-15%), indicating the need for novel therapies. The occurrence of OCCA is associated with co-existent endometriosis and may arise from endometriotic cysts however very little is known of OCCA biology.

To understand its molecular drivers our laboratory recently performed the most extensive molecular analysis of OCCA to date. We found very consistent data associated with de-regulated cytokine signalling. A central observation was the induction of hypoxia response genes including IL6/pSTAT3/HIF as measured by microarray, biochemical studies in OCCA cell lines and immunohistochemical staining of human tumour samples. IL6 has tumour-promoting actions on both malignant and stromal cells in a range of experimental cancer models, is a downstream effector of oncogenic ras, and has been implicated in several human cancers.

This honours project will focus on investigating the functional significance of IL6 activation in ovarian cancer cell lines. Expression of HIF2a/EPAS1 is the most highly correlated gene with IL6 in OCCA tumour samples. Interestingly, the hypoxic response in renal clear cell carcinoma cells is dependent on HIF2a. This observation suggests a role for HIF2a in OCCA. Through molecular and functional techniques, the student will explore a model where strong up-regulation of IL6 expression leads to increased HIF expression, promoting a proangiogenic response and facilitation adaption of cancer cells to hypoxia.

The Bowtell lab has a very strong reputation in cancer genetics and genomics, and in fundamental studies in cancer cell biology. He/she will have the opportunity to contribute insights into one of the most clinically significant questions in ovarian cancer, platinum resistance.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

Molecular biology

Cell culture

**Project Name**

**Molecular Analysis of Platinum Resistance in Ovarian Cancer**

**Description**

Ovarian cancer is the 5th most common cancer in women, and most lethal gynaecologic malignancy. Despite aggressive surgery and platinum-based chemotherapy, the majority of women experience recurrence and ~70% will succumb to the disease. Resistance to chemotherapy, or platinum resistance, is the major barrier to long-term remissions, however the underlying molecular mechanisms are poorly understood.

We are part of the Australian Ovarian Cancer Study (AOCS), one of the largest ovarian cancer cohort studies in the world. We are also one of the two Australian projects funded through a \$27 million NHMRC grant to participate in the International Cancer Genomics Consortium (ICGC).

Our laboratory has recently performed a combined gene expression and DNA copy number change (CNC) analysis of serous ovarian cancer in a well-defined cohort of women who failed primary therapy. We identified 19q12 amplification as the most dominant amplicon associated with primary treatment failure. The 19q12 amplification is a high-level focal amplification that consistently targets a cluster of only several genes; including the cell cycle gene CCNE1; and URI, recently been associated with activation of the mTOR/S6K pathway and control of apoptosis. It is not clear, however, how these genes or other cooperating mutations may contribute to primary chemotherapy resistance. For example, dysregulation of other cell cycle machinery components needed to tolerate or enhance the consequences of amplification of Cyclin E. Molecular and functional exploration into mechanisms of platinum-resistance in ovarian cancer will form the basis of the honours project.

The student will learn key molecular biological techniques and will be exposed to large-scale human genetic studies that are making use of the emerging technologies, including microarrays and next generation sequencing. The Bowtell lab has a very strong reputation in cancer genetics and genomics, and in fundamental studies in cancer cell biology. He/she will have the opportunity to contribute insights into one of the most clinically significant questions in ovarian cancer, platinum resistance.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

Molecular biology

Cell culture

**Project Name**

**Understanding drivers of a novel molecular subtype of a high-grade serous ovarian cancer**

**Description**

Ovarian cancer is the 5-6th most common cause of cancer death in women in Western countries, with ~800 deaths per year in Australia, with high-grade serous ovarian cancers accounting for the majority of deaths (>60%). Recently, molecular subtyping of ovarian cancer has revealed four molecular categories of HG-SOC. Each molecular subtype, designated C1, C2, C4 and C5 by Tothill et al, presents with a distinct expression pattern and differing clinical outcomes.

We are part of the Australian Ovarian Cancer Study (AOCS), one of the largest ovarian cancer cohort studies in the world. We are also one of the two Australian projects funded through a \$27 million NHMRC grant to participate in the International Cancer Genomics Consortium (ICGC).

We have recently shown that the C5 subtype is associated with amplification and over-expression of MYCN, over-expression of LIN28B, repression of Let-7 family members, and over-expression of HMGA2. This work for the first time defines an oncogenic pathway specific to a molecular subtype of serous ovarian cancers, and opens a new door to patient tailored molecular therapies.

This project involves further definition of this oncogenic pathway through specific over-expression and knockdown of MYCN in ovarian cancer cell lines in vitro. The student will learn key molecular biological and tissue culture techniques. The Bowtell lab has a very strong reputation in cancer genetics and genomics, and in fundamental studies in cancer cell biology.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

Molecular biology

Cell culture

RNA silencing

**Project Name**

**Genomic analysis of early breast neoplasms**

**Description**

We have previously undertaken genomic analysis of DCIS, the immediate precursor to invasive breast carcinoma, and found that in many cases this tumour already contains a plethora of genomic events highly similar to IDC. In order to identify the earliest genomic events in the development of breast cancer, this project will analyse less advanced breast neoplasms such as atypical ductal hyperplasia (ADH). These early lesions have not been previously analysed at high resolution and are likely to contain few, but highly relevant, genomic events.

Techniques used in the project will include cutting edge technologies such as whole-exome next generation sequencing as well as microdissection of tumour material, DNA/RNA extraction, and expression microarrays. There will be a strong bioinformatics component and potentially functional assays of candidate genes in cell culture.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

**Select Research Techniques Matching This Project**

DNA cloning & PCR

Molecular biology

Microarray

**Project Name**

**Identification of highly penetrant genes in familial breast and other cancers using next-generation sequencing**

**Description**

The ability to identify disease-causing mutations in high-risk cancer families has broad implications for those affected in terms of risk assessment and management as well as treatment. A major initiative over the last year has been the application of next generation sequencing (NGS) to identify cancer predisposition genes. We are performing whole exome sequence analysis of germline DNA from multiple affected relatives from over 75 high risk non-BRCA1/non-BRCA2 breast cancer families with the aim of identifying segregating, rare, non-synonymous variants that are likely to include novel predisposing mutations. In addition, we also aim to analyse families with other cancer types including male breast cancer, colorectal cancer and papillary thyroid cancer to identify the predisposing genes.

This project will perform and analyse NGS data to identify candidate gene variants identified and validate these variants in the family in which the variant was found including segregation analysis. After validation, the gene will be further analysed for mutations in other families and individuals with the same cancer type. For breast cancer this latter validation may be undertaken using a boutique exon capture and NGS of 200 additional breast cancer families. Techniques used will include DNA sequencing (NGS and Sanger), PCR, high resolution melting and potentially assays of gene transcription or function.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

**Select Research Techniques Matching This Project**

Next generation sequencing

DNA sequencing

DNA cloning & PCR

**Project Name**

**Mucinous ovarian carcinoma is a distinct ovarian subtype requiring alternative chemotherapeutic regimes**

**Description**

Mucinous ovarian carcinoma (MOC) differs in appearance and behavior from the other common epithelial ovarian cancer subtypes. MOC is frequently confused with metastases from organs such as the appendix, but it is not known if this resemblance extends to similarities in genetic alterations. Advanced MOC does not respond well to conventional ovarian cancer chemotherapies, indicating that there is a need for more subtype-specific therapies. We hypothesize that genomic aberrations found in MOC will be similar to those in mucinous cancers from other organs. Consequently, MOC may be better treated with chemotherapeutics that show success with other mucinous tumours.

This project will obtain genomic data from primary MOC and compare this with data from metastases to the ovary from extra-ovarian sites (initially presenting as ovarian), appendiceal tumours, diffuse gastric tumours, mucinous colorectal tumours and pancreatic tumours. Techniques used will include copy number and expression arrays and next-generation sequencing. Cell lines representative of MOC will be used to compare treatments with typical ovarian chemotherapies such as cisplatin with therapies more commonly used in other cancer types such as colorectal cancers.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

Cell culture

DNA cloning & PCR

RNA Microarray

Molecular biology

**Project Name**

**Manipulating metal ions as a novel approach to cancer treatment**

**Description**

Elevated copper in both malignant tissue and serum is emerging as a hallmark of cancer, having been established in a range of cancer types including breast, ovarian, cervical, lung, stomach, prostate and leukemia. We are developing a therapeutic approach aimed at exploiting elevated copper in cancer cells, which involves the use of copper specific ionophores. An ionophore transports specific metal(s) into cells often allowing them to become bioavailable. We have recently discovered that prostate cancer cells have a remarkable elevation in intracellular copper and are consequently sensitive to copper-ionophore treatment. We have demonstrated that the copper-ionophore clioquinol can selectively target and destroy cancerous prostate cells without harming normal prostate cells (for more information go to <http://www.ncbi.nlm.nih.gov/pubmed/21426304>). Considering that copper is critically involved in multiple facets of cancer development and progression and that copper accumulation is emerging as a hallmark of cancer, an exciting opportunity exists to develop a therapeutic strategy that might be applicable to a variety of cancer types.

Our project brings together the fields of cancer research and copper biology, to interrogate and develop copper-targeted treatments for prostate cancer. Specifically, we aim to (1) determine at what stage in prostate cancer development intracellular copper accumulates, (2) when during prostate cancer development cells become sensitive to copper-ionophore treatment, (3) how prostate cancer development affects cellular copper homeostasis and (4) to evaluate the therapeutic efficacy of copper-ionophores in the treatment of human prostate cancer using preclinical mouse models. We are looking for motivated and enthusiastic students to help achieve some of these aims. Students will carry out research in a broad field of disciplines ranging from, molecular biology, biochemistry, cell biology, animal models and metallomics.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Oxidative Stress

**Select Research Techniques Matching This Project**

Cell biology

Molecular biology

Metal biology

Biochemistry

**Project Name**

**Understanding Barrett's oesophagus and oesophageal adenocarcinoma.**

**Description**

Over the past thirty years there has been a dramatic increase in the incidence and prevalence of oesophageal adenocarcinoma, a cancer with particularly high mortality. The reason for the increase is not clear but is thought to reflect an increase in the occurrence of its recognised precursor lesion, Barrett's oesophagus. Barrett's oesophagus is a metaplastic abnormality in which the normal stratified squamous epithelium of the oesophagus is replaced by an intestinal-type columnar epithelium. The risk of adenocarcinoma in patients with Barrett's oesophagus is approximately 30-125-fold greater than that in the general population. The origin of Barrett's oesophagus is a matter of conjecture. There is compelling etiological evidence that gastro-oesophageal reflux disease is a major contributing factor but the actual molecular and cellular mechanism(s) underlying the phenotypic change are not clear. Furthermore, it is unclear what the key molecular drivers of progression from Barrett's to cancer are, which has contributed to the clinical problem of indentifying those patients with Barrett's oesophagus that are most at risk of progression to cancer. Our group has developed novel in vivo and in vitro models that allow the 3-D reconstitution of the oesophageal epithelium from mouse or human tissue and cell lines. Projects are available for Honours or PhD students to use these models to investigate the molecular and cellular mechanisms underlying the development of Barrett's oesophagus and/or the progression of Barrett's oesophagus to adenocarcinoma.

Possible projects include:

- Determining the signalling pathways involved in the transition of the normal squamous oesophageal epithelium to Barrett's intestinal-like epithelium.
- Investigating the effect of the stromal microenvironment in Barrett's carcinogenesis
- Investigating Aurora A kinase inhibition in combination with chemotherapy as a novel treatment for oesophageal adenocarcinoma
- Elucidating a role for miniSox9, a novel splice variant of Sox9, in Barrett's carcinogenesis

Understanding the biology underlying this condition will ultimately help us to design effective strategies for the management and treatment of Barrett's oesophagus and to predict, and/or prevent, progression to oesophageal adenocarcinoma.

- Phillips WA, Lord RV, Nancarrow DJ, Watson DI, Whiteman DC. Barrett's Oesophagus. J Gastenterol Hepatol 2011 26(4): 639-48
- Wang DH, Clemons NJ, Miyashita T, Dupuy AJ, Zhang W, Szczepny A, Corcoran-Schwartz IM, Wilburn DL, Montgomery EA, Wang JS, Jenkins NA, Copeland NA, Harmon JW, Phillips WA, Watkins DN. Aberrant epithelial-mesenchymal Hedgehog signaling characterizes Barrett's metaplasia. Gastroenterology 2010 138(5): 1820-22.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

**Select Research Techniques Matching This Project**

Cell biology

In vivo animal models

Molecular biology

RNA silencing

**Project Name**

**Providing “Help” For Effective Cancer Immunotherapy**

**Description**

Adoptive immunotherapy involving transfer of tumour-specific T cells into patients has shown remarkable anti-tumour effects and has led to remission of disease in a proportion of patients with metastatic melanoma. To broaden this approach against other malignancies, genetic modification of T cells with single-chain (scFv) chimeric receptors that specifically target tumour associated antigen has emerged as a promising approach (1,2). To date, evidence in patients and in immunocompromised mouse models have shown a correlation between effective anti-tumour responses and increased transfer of CD4+ T cell helper cells. However, the question of whether increased transfer of gene-modified CD4+ T cells may cause associated pathology has not been properly assessed. The proposed study on offer will employ novel tools involving transgenic mice which express target antigen on both normal tissue and tumour cells. These models more closely reflect the patient setting. Studies will be undertaken to genetically modify enriched CD8+ and CD4+ T cell populations with anti-tumour scFv receptors and evaluate both the anti-tumour efficacy and potential pathology to normal tissue following adoptive transfer of CD8+ and CD4+ T cells at varying ratios. The results of this project will have direct implications for enhancing this type of therapy for cancer patients.

The project will involve a number of molecular and biochemical methods including flow cytometry, ELISA, cytokine and proliferation assays. The student will also become competent in tissue culture (retroviral transduction of T cells and tumour cells) and handling of mice. We are looking for a highly motivated student who is interested in developing effective treatments for cancer.

**References**

- 1 Morgan RA, Dudley ME, Wunderlich JR, et al. Cancer regression in patients after transfer of genetically engineered lymphocytes. Science 2006;314:126-9.
- 2 Kershaw MH, Teng MW, Smyth MJ, Darcy PK. Supernatural T cells: genetic modification of T cells for cancer therapy. Nat Rev Immunol 2005;5:928-40.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Immunotherapy

**Select Research Techniques Matching This Project**

Cell culture

Flow cytometry

ELISA assays

In vivo animal models

**Project Name**

**18F-FPHCys as a reliable imaging biomarker to monitor early efficacy of PI3K/mTOR targeted cancer therapies by Positron Emission Tomography (PET)**

### **Description**

Abnormal cell signalling contributes to the progression of many cancers. The development of anticancer drugs that specifically targets the PI3K/mTOR signalling has dramatically improved the way cancer patients are treated. However, PI3K/mTOR targeted therapy is not always successful, even when the tumours harbour the malfunctioning proteins. Consequently, non-responding patients are often treated unnecessarily when they would otherwise respond to alternative therapies.

Currently, multiple biopsies are the only way drug efficacy can be determined at the molecular level. This is often impractical for some patients due to the inaccessibility of the tumour. Positron Emission Tomography (PET) allows serial non-invasive imaging of the tumour and has the potential to identify early molecular changes induced by treatment. However, there are currently no reliable imaging biomarkers available to monitor PI3K/mTOR targeting treatment by PET. Recently, we identified a new amino acid analogue of methionine, 18F-FPHCys, with excellent potential for imaging solid tumours. Tumours are 18F-FPHCys-avid due to their high expression of LAT1 amino acid transporter compared to normal tissues. We have observed that blocking PI3K/mTOR pathway significantly decreased tumour cell accumulation of 18F-FPHCys indicating a strong relationship between PI3K/mTOR signalling and LAT1-dependent 18F-FPHCys uptake.

The overall objective of this research project is to investigate the potential of 18F-FPHCys-PET as a reliable imaging tool for the detection of early molecular responses to PI3K/mTOR treatment in cancer. This project is suitable for Honours students and will make use of various techniques including cell culture, protein and molecular techniques (protein immunoblotting, immunohistochemistry, real time quantitative PCR, use of siRNA technology) as well as in vivo PET imaging.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Cellular Growth & Proliferation

### **Select Research Techniques Matching This Project**

In vivo animal models

Cell culture

RNA silencing

Western blot

**Project Name**

**Assessment of CHK inhibitor therapeutics in Leukaemia**

**Description**

Several specific inhibitors of the cell cycle checkpoint kinase CHK1 are currently in clinical trials. These drugs were originally developed for use in combination with DNA damaging agents such as conventional chemotherapeutic agents or irradiation. Our recent studies have demonstrated that CHK inhibitors are effective as single agent therapeutics in MYC-driven lymphoma 1.

Recent studies suggest that CHK1 is a potential target for therapy in a subset of Acute Myeloid Leukaemia (AML) 2. This project will assess the efficacy of a few highly potent CHK1 inhibitor drugs in leukaemia using in vitro drug response assays on human AML cell lines. The results of these projects will determine the potential benefit of CHK1 inhibitor drugs in the treatment of AML as single agents and in combination with cytotoxic drugs.

1. Ferrao et al Oncogene 2011 adv online pub doi:10.1038/onc.2011.358 [Epub ahead of print]
2. Cavelier et al Cancer Res 2009 69(22):8652-61

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**Pathological Disease Research Topics Matching This Project**

**Select Research Techniques Matching This Project**

Cell culture

Cell death

Flow cytometry

Western blot

**Project Name**

**Hijacking growth factor receptor signalling in cancer**

### **Description**

Background: Aberrant receptor tyrosine kinase (RTK) signalling leads to the activation of a plethora of downstream signalling pathways (such as the MAPK and PI3K pathways) involved in growth, proliferation, migration, invasion and angiogenesis, all of which are important factors in the development and progression of cancer. One mechanism proposed to contribute to the dysregulation of this signalling is a phenomenon called G protein-coupled receptor (GPCR) RTK transactivation, where GPCR signalling mechanisms ‘hijack’ well-known cellular signalling machinery to drive various cellular outcomes distal of the RTK (reviewed by Fischer et al., 2003). In collaboration with Prof. Walter Thomas (University of Queensland), our lab has an interest in the transactivation of the epidermal growth factor receptor (EGFR) by signalling through the well-known renin-angiotensin system type I receptor (AT1R), a GPCR (reviewed by George, Thomas and Hannan, 2010). This is known to occur in selected cell types, and while the exact mechanism remains unclear, current theories suggest Gq/11-dependent metalloproteases, such as members of the ADAM family of proteins (e.g. ADAM10, 12 and 17) are activated after stimulation of the receptor with angiotensin II (AngII), causing the shedding of EGF ligands, which activate the EGFR and promote cellular growth (Thomas et al., 2002, reviewed by Smith et al., 2004). We have developed a stable cellular model of AngII-mediated EGFR transactivation, and we have used this to perform a high-throughput functional genomic screen (using RNAi technologies) through the Victorian Centre for Functional Genomics (VCFG) to determine the molecular mechanisms underlying EGFR transactivation. We have identified a number of potential candidate genes involved in transactivation that we are currently investigating.

Project: To investigate this mechanism in cancer in more detail, we will screen human cancer cell lines for expression of the AT1R using real-time qRT-PCR, and test their propensity to transactivate RTKs (such as EGFR). We will also introduce the receptor into cancer cells using retroviral delivery and determine whether overexpression of the AT1R increases the likelihood of cells to transactivate RTKs, and whether this has any downstream cellular effects (e.g. increased cellular growth). We will also clone the constitutively active mutant AT1R (N111G) receptor into a retroviral vector and stably introduce this receptor into untransformed, partially transformed or fully transformed human cell lines to determine the effect of the activated receptor on cellular growth and proliferation, migration and invasion in an array of different assays. If time permits, we will also investigate the role of a number of the candidate genes (identified in the siRNA screen) in cancer cells and their effects on AT1R-EGFR transactivation and cellular behaviour.

References:

Fischer et al (2003) Biochem Soc Trans 31(Pt 6):1203-8.

George, Thomas and Hannan (2010) Nature Rev Cancer 10(11):745-59.

Smith et al (2004) Cell Mol Life Sci 61(21): 2695-703.

Thomas et al (2002) Circ Research 90(2):135-42.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Cardiovascular Disease

### **Select Research Techniques Matching This Project**

Cell culture

Western blot

Molecular biology

RNA silencing

**Project Name**

**Functional and genetic characterisation of ovarian oncogenes**

**Description**

Ovarian cancer is a disease characterised by complex genomic rearrangements including high-level copy number amplifications but the majority of the genes in these regions that drive ovarian cancer remain unidentified. Cataloguing these target genes will provide useful insights into disease etiology and may provide an opportunity to develop novel diagnostic and therapeutic interventions. We have recently undertaken a high-throughput siRNA knockdown screen of 300 candidate genes located in recurrent regions of high-level gene amplification and have identified a number of promising candidate oncogenes. This project will select a subset of these genes for further characterisation, including validation of the effect of knockdown, screening tumours for mutations using custom exon capture and NGS, stable shRNA gene knockdown in cell culture for various in vitro and in vivo assays, the effects of small molecule inhibitors and immunohistochemistry.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

Cell culture

Molecular biology

RNA silencing

**Project Name**

**The Hippo pathway, Regeneration and Cancer**

### **Description**

In the Cell Growth and Proliferation laboratory we are interested in how tissue growth is controlled during development and regeneration. We are also interested in how deregulation of signalling pathways that control tissue growth contributes to the genesis of human cancer. We utilise the model organism, *Drosophila melanogaster* (vinegar fly), and mammalian cell culture to discover and investigate genes involved in tissue growth and cancer. Our approach is to identify genes involved in cancerous-like growth in flies and then use human and mouse models to determine whether the human counterparts of these fly cancer genes have a role in human cancer. Approximately 70% of human disease genes are conserved in flies, making it an excellent model for these studies.

One newly identified signaling pathway that our laboratory helped to discover and actively studies is the Salvador-Warts-Hippo (Hippo) pathway, which controls organ size during development (reviewed in references 3 and 9). This pathway controls organ size by restricting cells from growing and dividing excessively, properties central to the formation of cancer. The Hippo pathway is conserved in humans and several studies from our laboratory and others have implicated this pathway in the genesis of human cancer (e.g. reference 2). By studying various aspects of this pathway we aim to understand how organ size is correctly specified during development and tissue regeneration, and how deregulation of this pathway contributes to human cancer.

#### **BROAD RESEARCH AIMS:**

- To understand how the Hippo pathway controls the size of developing, and regenerating, organs.
- To understand how Hippo pathway deregulation contributes to the genesis of human cancers.

We currently have several projects based around these aims which we would like to discuss with students.

References from our laboratory relevant to the project:

1. F. Grusche et al. (2011) *Dev Biol.* 350, 255-266.
2. X. Zhang et al. (2011). *Oncogene.* 30, 2810-2822.
3. F. Grusche et al. (2010). *Curr Biol.* 20, R574-582.
4. C. Milton et al. (2010). *Development.* 137, 735-43.
5. X. Zhang et al. (2009). *Cancer Res.* 69, 6033-6041.
6. K.F. Harvey and N. Tapon (2007). *Nat Rev Cancer.* 7, 182-191.
7. F.C. Bennett and K.F. Harvey (2006). *Curr Biol.* 16, 2101-2110.
8. K.F. Harvey et al. (2003). *Cell* 114, 457-467.
9. N. Tapon et al. (2002). *Cell* 110, 467-478.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Stem Cell

Cellular Growth & Proliferation

### **Select Research Techniques Matching This Project**

In vivo animal models

Cell biology

Biochemistry

Molecular biology

**Project Name**

**Role Of Immunomodulators In The Development & Progression Of Osteosarcoma In Vivo**

**Description**

The Sarcoma Genetics and Genomics laboratory studies tumours of soft tissue and bone. Osteosarcoma is the most common cancer of bone. These tumours are highly metastatic and often metastasise to lung via the hematogenous route. Treatment involves aggressive surgery with intensive adjuvant chemotherapy. Although these measures have improved prognosis, a third of those diagnosed will die from this disease. Understanding how osteosarcoma arises and persists will enable the development of targeted therapies. The skeleton and the immune system share a number of cytokines and transcription factors and therefore may mutually influence each other; the study of these cells and their interactions has been termed osteoimmunology. In this project we will investigate the interaction between the immune system and bone cancer in an in vivo mouse model of osteosarcoma. The project will use broad range techniques including mouse models of cancer, histology, cell culture, flow cytometry, and molecular profiling.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Immunotherapy

**Select Research Techniques Matching This Project**

In vivo animal models

Cell biology

Flow cytometry

Cell culture

**Project Name**

**Using Cancer To Fight Cancer**

### **Description**

After decades of cancer research, one thing is certain – cancer is tough! It can develop resistance to chemotherapy and radiotherapy, and its pervasive nature can make a mockery of our best attempts at surgical removal. Cancer can also evade our most powerful immune therapies through a number of mechanisms that include stealth and potent suppression of immunity.

Given the resilience and versatility of cancer, in this project we wish to test the concept that the best way to fight cancer might be with another cancer. To test this idea, we wish to produce a kind of leukemia that we can manipulate to possess many cancer fighting abilities, while retaining absolute control over its growth and malignant properties. We might imagine that such leukocytes endowed with the abilities to localize to tumors, execute cytotoxicity and overcome immune inhibition, while retaining the cancer-associated attributes of persistence and resistance to death might beat cancer cells at their own game.

Currently, T cells can be genetically modified to recognize and respond to cancer cells in a limited way, and adoptive transfer of these T cells can inhibit small tumors in mice. However, larger widespread disease is refractory to this form of immunotherapy. Factors that contribute to the failure of adoptive immunotherapy include a poor ability of T cells to localize to tumors, together with inhibition of T cell activity at the tumor site and a failure to persist in large numbers. Genes exist that can be used to remedy these problems, but our ability to get enough genes into mouse primary T cells to satisfy all these requirements is limited by the low ability of mouse T cells to grow in vitro. Therefore, immortalizing mouse T cells would give us the opportunity to insert many genes and test their ability to defeat cancer.

Immortalization will be achieved using oncogenes in a tetracycline-inducible genetic vector system. A series of oncogenes including *tert*, *hras* and *sv40gp6* will be sequentially inserted into mouse T cells until they attain continuous growth in media containing tetracycline. These cells will then be gene modified to express molecules enabling responses to tumor cells and resistance to inhibition etc. The ability of these molecules to enable T cells to respond against cancer cells in vitro and in mice will then be determined in the presence and absence of tetracycline. As an added safety measure, a suicide gene can be inserted into the T cell line to enable elimination of those cells in vivo if tetracycline removal is insufficient to control the artificial leukemia.

This project will use molecular biology and a range of immunological assays to determine the anti-tumor activity of gene-modified immune cells in mouse models of cancer.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Immunotherapy

Breast Cancer

### **Select Research Techniques Matching This Project**

Molecular biology

Cell culture

ELISA assays

Flow cytometry

**Project Name**

**Therapeutic targeting of the PI3K pathway in endometrial and ovarian cancer.**

### **Description**

The oncogenic PI3K/mTOR pathway is commonly deregulated in human cancers and novel therapies targeting this pathway is an exciting focus of many clinical trials. We are interested in using genetically engineered mouse models to understand how PI3K pathway mutations contribute to tumourigenesis; and then utilizing such tumour models in pre-clinical evaluation of novel therapeutics.

Endometrial and ovarian cancer commonly exhibit mutations in multiple PI3K pathway genes, including the oncogene PIK3CA and tumour suppressor PTEN, making these tumour types potentially susceptible to PI3K pathway inhibitors. As such, endometrial cancer patients are currently being treated in human clinical trials using mTOR inhibitors. Our lab is currently in various stages of development of both endometrial and ovarian cancer mouse models via tissue specific genetic manipulation of these PI3K pathway components.

An honours project will 1) explore the role of PI3K pathway mutations in the development of disease in one of these gynecological cancer models and/or 2) evaluate the in vivo consequences of PI3K pathway inhibition using novel targeted therapeutics in tumour-bearing mice. These in vivo experiments may be complemented with in vitro cell culture analysis of drug efficacy in human cancer cell lines – analyzing drug responses such as perturbation of pathway signaling, cell cycle, cell death or senescence.

During this project, the student will develop skills for the analysis of mouse models of cancer and the preclinical evaluation of targeted therapies, including animal handling/dissection techniques and ex vivo analysis of mutant tissues and/or tumours, immunohistochemistry, western blotting and microscopy; and in vitro cell culture and drug response analysis.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Cellular Growth & Proliferation

### **Select Research Techniques Matching This Project**

In vivo animal models

Cell biology

Immunohistochemistry

Cell culture

**Project Name**

**Investigating The Tumour/Stroma Microenvironment In Breast Cancer**

**Description**

Breast cancer is the most common cancer in women, with approximately one in ten women developing this disease during their lifetime. The metastatic spread of the tumour to distant organs is the most common cause of morbidity in breast cancer patients, and treatment options for metastatic disease are limited. Our research focuses on understanding the progression of breast cancers, especially the interaction of tumour cells with surrounding cells that make up the tumour microenvironment. These cells include infiltrating immune and mesenchymal cell lineages, that play a role in hypoxia and neo-angiogenesis (development of new blood vessels) and the process of metastasis to distant organs. We are developing new approaches to translate this knowledge into novel treatment options for breast cancer patients. To achieve these aims, we have generated novel knockout and transgenic breast cancer mouse models, which we are using in conjunction with state-of-the-art techniques including imaging, FACS, microarray, and drug development. This project will investigate the interaction of tumour cells with their surrounding stroma, and how this interaction enables the tumour to grow and eventually metastasise. Understanding the relationship of tumour cells with the surrounding stroma in the tumour microenvironment is crucial in order to therapeutically target tumour progression. Apart from tumour cells, the tumour microenvironment is comprised of several different cells types, including endothelial cells (involved in new blood vessel formation), fibroblasts (involved in wound healing and fibrotic responses) and immune cells (involved in immune surveillance). Using isolated cell lines and co-culture experiments, cytokine and growth factor secretion will be assessed by the student and observations verified by qPCR, ELISA and IHC on both individual cell lines and tumour samples. This approach will shed light on the communication between tumour cells and their surrounding, non-tumour cell lineages.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

Western blot

ELISA assays

Flow cytometry

**Project Name**

**The identity, role and function of immune cells at sites of metastasis in breast cancer**

### **Description**

Immune cells are key mediators of anti-tumour and pro-tumour functions at both the primary and metastatic sites of breast cancer. While the role of monocyte derived cells at the primary site of breast cancer is slowly being understood, there is very little known about the role and composition of immune cells at metastatic sites. We have generated a unique breast cancer model, utilizing fluorescently marked immune and tumours cells, to assess the immune cell infiltrate at metastatic sites in breast cancer. We found that immune cell infiltration into metastatic sites is directed and orchestrated by the primary tumours, and results in a permissive environment at secondary sites for metastatic outgrowth.

In this project, bone marrow chimeras and orthotopic breast cancer mouse models will be used to determine the composition and function of the immune cell infiltrate at the metastatic site. Using FACS and Immunohistology, the immune cell lineages will be investigated in great detail. Isolated immune cells, which are induced by tumours to populate the metastatic site, will be assessed for their cytokine production. Furthermore, the frequency of metastasis will be assessed in experiments where the immune cell lineages which populate the metastatic site have been ablated. These experiments will provide an insight into the metastatic progression of breast cancer and will be the first of their kind. Ultimately the goal is to understand the identity, role and function of immune cells at the metastatic site and explore the potential to use this information to reduce metastatic tumour burden in breast cancer patients. Students will have access to unique reagents and mice, and will acquire skills in mouse tumour model experimentation, immune cell isolation, multi-colour flow cytometry, IHC, and other basic cellular immunology techniques.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

Metastasis

### **Select Research Techniques Matching This Project**

Flow cytometry

In vivo animal models

Immunohistochemistry

Hypoxia techniques

**Project Name**

**Establishing a humanized mouse model of cancer**

**Description**

Research into the causes and treatment of cancer ideally requires pre-clinical animal models that closely recapitulate human disease. Our laboratory specializes in blood cancers with a focus on multiple myeloma (MM) and chronic lymphocytic leukemia (CLL), which are malignancies of the bone marrow. There are no accurate models of human MM and CLL in mice as most models use mouse cancer cells. For the few models that use human MM or CLL cells, these are transplanted into immune-deficient mice that lack an immune system to prevent graft rejection. However this is not ideal as these models do not have an active immune system. Recently, a world wide groundbreaking study described a ‘humanized’ mouse model whereby human stem cells are injected intrahepatically into newborn immune-deficient mice to establish a functional human immune system. Our lab aims to take this further by establishing humanized mouse models using stem cells from MM or CLL patients. Once these mice are adults, we aim to transplant in MM or CLL cells (from the same patients where the stem cells were derived), thus creating a world’s first patient-derived humanized mouse model. These models harboring both a functional human immune system and cancer will become exceptionally powerful tools to study cancer biology and therapy. The aims of this exciting Honours project are two-fold: 1) to optimize the humanized mouse model, and 2) to establish the first humanized MM and/or CLL model.

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**Pathological Disease Research Topics Matching This Project**

Immunology

Leukemia

**Select Research Techniques Matching This Project**

Cell biology

Flow cytometry

Histology

In vivo animal models

**Project Name**

**Investigating The Mechanisms Of Immune Escape By Breast Cancer Cells**

**Description**

Over 80% of patients who die from their breast cancer succumb due to the development of metastatic disease. The mechanisms of breast cancer spread to bone are largely unknown. Our recent studies using a unique model of breast cancer have revealed that cancer cells growing in bone suppress an immune defence pathway called the Type I interferon pathway, and that restoration of this pathway blocks cancer spread.

Our studies provide evidence that breast cancer cells have the ability to modulate the immune response to avoid being recognised and eliminated. This allows breast tumour cells to survive in bone and grow into lethal tumours that are currently untreatable. We are looking to extend these studies. This project aims to identify the immune responses that are activated in response to this pathway and if restoration of such responses is critical in blocking the spread of breast cancer to bone.

Through both national and international collaborations, we have access to rare models of breast cancer and the tools required to study the role of Type I IFNs at an internationally competitive level. A broad range of techniques will be utilised for this PhD project, including histological analysis, flow cytometry, confocal and light microscopy, real time PCR, molecular cloning, cell culture, animal models of breast cancer, in vitro and in vivo metastasis assays.

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**Pathological Disease Research Topics Matching This Project**

Cancer

**Select Research Techniques Matching This Project**

In vivo animal models

Cell culture

Immunohistochemistry

Molecular biology

**Project Name**

**How do PIK3CA mutations cause cancer?**

### **Description**

The phosphoinositide 3-kinase (PI3K)/Akt signalling pathway controls a range of fundamental cellular processes which, when de-regulated, are considered hallmarks of cancer. While it is now well established that somatic mutations in PIK3CA, the gene coding for the p110 $\alpha$  catalytic subunit of PI3K, are one of the most common, and thus potentially one of the most important, genetic abnormalities in many human tumours. However, it remains unclear how these mutations drive tumourigenesis.

We have recently generated a novel mutant mouse with which to study the role of PIK3CA mutation in vivo and in vitro. This mouse has been designed with a Cre recombinase (Cre)-inducible knock-in of the most common tumour-associated PI3K mutation, PIK3CAH1047R. Our strategy of making the knock-in inducible with Cre allows us to target the expression of the mutant to specific tissues using mice expressing Cre under the control of appropriate tissue-specific promoters. We can also knock-in the mutation into cells growing in culture allowing us to examine the effects of PIK3CAH1047R mutation in vitro under defined conditions.

Two potential projects are being offered.

(1) PIK3CAH1047R in oesophageal cancer. The student will isolate oesophageal epithelial cells from our PIK3CAH1047R mouse and use our novel 3D in vivo culture systems to examine the effect of PIK3CAH1047R expression in the growth and differentiation of the oesophageal epithelium and the development of cancer. This project would be particularly suitable for BSc(Hons) or MD students.

(2) PIK3CAH1047R in breast cancer. The student will isolate mammary epithelial cells from our PIK3CAH1047R mouse and use these to examine the signaling pathways by which PIK3CAH1047R induces tumourigenesis and regulates the growth and differentiation of mammary epithelial cells. This project would be suitable for PhD, MD or BSc(Hons) studies.

For more information about these projects contact:

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

### **Select Research Techniques Matching This Project**

Cell biology

In vivo animal models

Molecular biology

Cell culture

**Project Name**

**Mechanisms and therapy of breast cancer metastasis to brain**

**Description**

Breast cancer affects 1 in 10 women in Australia and is fatal once it has spread to and compromised the function of distant organs such as the brain. However, the molecular mechanisms regulating metastasis to brain remain largely unknown, due in part to the lack of clinically relevant animal models in which to study disease progression. Moreover, despite improved detection methods and the introduction of novel targeted therapies against systemic disease extending the life of patients, the lack of effectiveness of these treatments against brain metastasis has led to an increase in the incidence of advanced breast cancer patients developing aggressive brain metastases.

We have now developed and characterised a unique and clinically relevant mouse model of spontaneous breast cancer metastasis to brain. The model is ideally suited to identify and investigate the function of brain metastasis genes in vivo and to test novel therapies against this devastating disease. Thus, the overall objective of this research project will be to characterise the function of selected genes in metastasis to brain and to test the efficacy of various inhibitors alone or in combination with radiation against brain-metastatic breast tumour cells, both in vitro and in vivo. The project is suitable for both Honours and PhD students and will make use of a variety of techniques ranging from basic cell culture and in vitro functional assays (proliferation, migration, invasion, survival) to molecular techniques and in vivo therapies in animals.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

Metastasis

**Select Research Techniques Matching This Project**

Cell biology

Molecular biology

Histology

In vivo animal models

**Project Name**

**Targeting tumour-stroma interactions to treat breast cancer metastasis to bone**

**Description**

Our laboratory focuses on the identification and characterisation of genes involved in the spread (metastasis) of breast tumours to specific organs. By far, the most commonly affected organ in advanced breast cancer patients is bone, leading to severe and debilitating skeletal complications. While recent work has led to the development of more effective therapies against bone metastases, a particular subtype of aggressive breast tumours called triple negative (TN) remains largely resistant to treatment. Therefore, targeting factors present in the bone environment that support the growth of TN tumours rather than directly targeting tumour cells has been proposed as an alternative/complementary strategy to prevent or delay the development of TN bone metastases in advanced breast cancer patients. To test this, the project will make use of a unique mouse model of TN breast cancer that aggressively metastasises to bone to investigate the effectiveness of therapies targeting various stromal factors thought to contribute to bone metastasis including the extracellular matrix protein laminin-511 and two soluble factors secreted by bone cells, transforming growth factor- $\beta$  and Gas6. The project is suitable for both Honours and PhD students and will make use of a variety of techniques ranging from basic cell culture, in vitro functional assays (proliferation, migration, invasion, survival), immunohistochemistry, fluorescence imaging, molecular techniques and the use of inhibitors for in vivo therapy in animals.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

In vivo animal models

Molecular biology

Immunohistochemistry

**Project Name**

**The Upstream Binding Factor Ubf Regulates Genome Stability**

### Description

Background: RNA Polymerase I (Pol I) transcribes the 200 copies of ribosomal DNA (rDNA) to produce the 45S precursor of the 18S, 5.8S and 28S ribosomal RNAs (rRNAs), which together with the 5S rRNA form the RNA backbone of the ribosome. Initiation of rDNA transcription requires the binding of the Selectivity Factor (SL1) and the Upstream Binding Factor (UBF), which together form the preinitiation complex at the rDNA promoter, facilitating the recruitment of Pol I.

In addition to transcription initiation, UBF plays an equally important role in regulating promoter escape, transcription elongation and maintenance of the open chromatin structure required for transcription. Interestingly, depletion of UBF does not affect the rate of rDNA transcription – a 70-80% reduction in UBF equates to a modest 15% reduction in rRNA synthesis (Sanij, et al. 2008). Despite the relatively unchanged transcriptional output, cells eventually enter cell cycle arrest and exhibit chromosomal aberrations, nucleolar disorganization and senescence, suggesting that UBF has additional non-nucleolar functions within the cell that, when perturbed, lead to defects in cell cycle progression. Chromatin Immunoprecipitation (ChIP) sequencing was performed to identify novel UBF target genes and the results demonstrated UBF enrichment at 2212 genomic regions within 10kb of known Polymerase II (Pol II) transcription start sites (TSS). To determine if UBF might directly regulate transcription of the identified genes, we performed expression array analysis in control and UBF depleted cells. Gene ontology analysis was performed to identify the molecular functions of genes whose expression significantly changed following UBF knockdown and were also bound by UBF within 200 bp of their TSS. The analysis demonstrated significant overrepresentation of genes belonging nucleosome organization and DNA packaging, chromatin assembly and regulation of transcription, chromatin condensation and G2-M cell cycle progression, and DNA repair. In addition, we have detected increased relocalisation of UBF from the nucleoli into the nucleoplasm following inhibition of Pol I activity, which correlates with increased UBF enrichment at a subset of these Pol II genes. We therefore hypothesize that UBF plays a global role in the regulation of chromatin through positive transcriptional regulation of histones, histone assembly factors and DNA repair genes.

This project will address the following specific Aims:

Aim 1: to define the molecular mechanism by which UBF modulates Pol II target gene expression and determine how UBF is selectively recruited to specific Pol II transcribed loci.

Aim 2: to explore the biological relevance of UBF's role in Pol II gene transcription by addressing the hypothesis that UBF is a dual Pol I and Pol II transcription factor which functions to allow cells to sense changes in Pol I transcription and to adapt appropriately through inducing global modifications in chromatin.

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### **Pathological Disease Research Topics Matching This Project**

Epigenetics

Cellular Growth & Proliferation

Leukemia

### **Select Research Techniques Matching This Project**

Cell biology

Molecular biology

DNA cloning & PCR

Immunofluorescence

**Project Name**

**Using functional genomics approaches to identify genes that regulate breast carcinoma invasion and metastasis**

**Description**

The Functional Genomics Facility at the Peter Mac provides the infrastructure, resources and expertise to perform genome-scale RNA interference screens. We offer both shRNA and siRNA strategies to knockdown gene expression to researchers Australia-wide. Such access places us in the unique and exciting position of enabling and discussing cutting edge gene discovery projects from diverse scientific backgrounds on a daily basis. The facility also has a research interest in the mechanisms regulating breast carcinoma invasion and metastasis and this project would be directly involved with Assoc Prof Robin Anderson's metastasis laboratory. We are interested in speaking with people who share an interest in fundamental gene discovery, particularly in relation to breast cancer. We have well established cell-based and animal tumour models in which genes promoting invasion and metastasis can be tested functionally and their mechanism of action explored. Projects related to identifying novel gene targets that may regulate the cytoskeletal changes associated with acquisition of cell motility, invasion and ultimately metastasis are on offer.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

Metastasis

**Select Research Techniques Matching This Project**

RNA silencing

Cell biology

Immunofluorescence

Cell culture

**Project Name**

**Characterisation of molecules involved in lymphatic vessel function**

**Description**

We have performed a genome-wide siRNA screen to identify molecules involved in the formation of lymphatic vessels in tumors and other pathological settings. These screens have selected genes on the basis of their capacity to affect the migration and tube formation ability of primary human lymphatic endothelial cells using high throughput in vitro assays.

By using a combination of in vitro assays and bioinformatics analysis of molecular networks and signalling pathways we have identified a short list of gene candidates for more detailed analysis.

This Honours project will involve the detailed characterisation of one of these selected genes, using a combination of molecular and cell biological techniques. The project will initially involve the validation of the effects seen by siRNA knockdown of the specific gene in primary lymphatic endothelial cells, and will be confirmed at the protein level using specific antibody probes. An expression pattern for this gene and protein will be generated using RT-PCR and immunohistochemical techniques on both normal and pathological tissue (in collaboration with Prof. Stephen Fox, PMCC). In vivo animal models will be used to determine the role of these genes in the process of lymphangiogenesis in the context of tumor biology and tissue repair.

The project will provide a basis for determining key molecules which control lymphatic endothelial cell function in the context of human pathology and provide potential therapeutic and diagnostic targets.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Metastasis

Cellular Growth & Proliferation

**Select Research Techniques Matching This Project**

Cell biology

Molecular biology

Immunohistochemistry

In vivo animal models

**Project Name**

**How does Latet affect infectious and autoimmune disease pathology?**

**Description**

Accumulating evidence indicates that immune responses to microbial infection play an important role in the pathogenesis of autoimmune diseases. A major question is: How do immune responses to infection affect one's risk for developing autoimmune disease? Our group has identified a novel gene, termed Latet, for which sequence variation is associated with autoimmune disease in mice. While expression of this gene is upregulated in activated immune cells, its actual molecular function has not been previously described (hence, we have temporarily given it the name Latet, which is Latin for 'to be unknown'). The goal of this project is to determine Latet's role in immune-related disease pathology. To facilitate this work we have established a mouse strain that is Latet-deficient (ie conditional knockout) and exhibits altered immune responses associated with autoimmune disease. The aims of this Honours project are: 1) identify which immune cells express Latet, 2) determine how immune responses are altered in Latet-knockout mice, and 3) characterize various infectious and autoimmune disease pathologies in Latet-knockout mice. This project will utilize a range of methods including: DNA/RNA isolation, genotyping, real-time PCR techniques, cell culture, in vitro and in vivo cytokine and cell proliferation assays, FACS analysis of immune cells, and tissue histology.

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**Pathological Disease Research Topics Matching This Project**

Immunology

Immunotherapy

Diabetes

**Select Research Techniques Matching This Project**

Molecular biology

Flow cytometry

Cell culture

ELISA assays

**Project Name**

**Sleeping Beauty mutagenesis - discovering new genes underlying disease pathology**

### **Description**

While not possible in humans, various genetic techniques can be used to identify genes that when mutated prevent or cause disease pathology. Our group has recently established the Sleeping Beauty transposon mutagenesis system in the nonobese diabetic (NOD) mouse strain. NOD mice spontaneously develop autoimmunity with leukocytic infiltration of various tissues, including pancreatic islets, salivary glands and the thyroid. Anti-nuclear antibodies are also detectable at relatively low levels in the peripheral blood of NOD mice. Due to this pathology, NOD mice are widely used as a model for type 1 diabetes, Sjogren's syndrome, and thyroiditis. Moreover, experimental encephalomyelitis and lupus can be induced in NOD mice. The Sleeping Beauty transposon is a mobile DNA element that can be activated to 'jump' around the mouse genome and disrupt genes by landing within them. We have used a unique Sleeping Beauty transposon containing a fluorescent marker that results in mice that 'glow' if the transposon has jumped into a gene. The goal of this Honours project is to use the Sleeping Beauty transposon to identify genes that when disrupted by a transposon prevent or exacerbate disease pathology in the NOD mouse. The specific aims are: 1) identify transposon-disrupted genes in fluorescent NOD mice; 2) determine how transposon insertions affect the function of disrupted genes; 3) characterize transposon-mutant NOD mice for various disease pathologies. This project will utilize a range of methods including:

DNA/RNA isolation, genotyping, real-time PCR techniques, cell culture, in vitro and in vivo cytokine and cell proliferation assays, FACS analysis of immune cells, and tissue histology.

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### **Pathological Disease Research Topics Matching This Project**

Immunology

Immunotherapy

Diabetes

### **Select Research Techniques Matching This Project**

Molecular biology

Flow cytometry

Cell culture

ELISA assays

**Project Name**

**Identification of osteoblast lineage cells by fluorescence-activated cell sorting in normal and cancerous states.**

### **Description**

Osteoblasts are bone-forming cells. There is a well-recognised hierarchy of osteoblast-lineage cells, with the most immature cell being the mesenchymal stem cell and the most mature cell being the osteocyte. Studies of osteoblast lineage cells have been hampered by the lack of methods by which to purify cells at different stages of osteoblast differentiation.

Fluorescence activated cell sorting (FACS) has been used widely in the field of blood cell research and has markedly enhanced our understanding of the blood cell system. More recently, attempts have been made to isolate out different osteoblast lineage cells using FACS. Currently 3 different populations of osteoblast lineage cells can be isolated, but are likely still heterogeneous in nature.

The aims of this project are to further improve on existing FACS methods to isolate different osteoblast lineage cells. These methods will also be useful in further characterizing the nature of the osteoblastic cell that gives rise to the osteoblast cancer, osteosarcoma.

These studies will involve fluorescence activated cell sorting (FACS) and a range of different techniques used in bone biology, including in vitro cultures, analysis of bone parameters using microCT and histomorphometry, immunohistochemistry, molecular biology (quantitative real-time PCR), mouse model of osteosarcoma.

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### **Pathological Disease Research Topics Matching This Project**

Cancer

Stem Cell

### **Select Research Techniques Matching This Project**

Immunofluorescence

Flow cytometry

Cell biology

In vivo animal models

**Project Name**

**Identification of the niche that regulates quiescence in acute lymphoblastic leukaemia cells.**

**Description**

Acute lymphoblastic leukaemia (ALL) is the most common form of childhood cancer. Many patients relapse with the disease after their treatment and the majority die after relapse. Studies from Dr Bendall's laboratory have identified a small population of ALL cells that are resistant to chemotherapy, hence are the likely cancer cells that cause the relapse of the disease after cancer treatment. These ALL cells are quiescent (do not divide very often) which can also help to protect them against chemotherapy. The bone marrow is known to contain many different cell types that include developing blood cells and non-blood cells (cells of the bone lineage, vasculature and fat) all of which help to regulate blood cell production. We propose that these quiescent ALL cells reside in a particular place in the bone marrow, (which we term the quiescent ALL niche) which provides them with signals that enable them to resist chemotherapy. By understanding more about the nature of this quiescent ALL niche we might be able to better treat ALL patients by disrupting the quiescent ALL cells from their niche. This project therefore aims to characterize the quiescent ALL niche in a model of human ALL, including its response to cancer therapy.

These studies will involve a range of different techniques used in blood and bone biology. It will predominantly focus on immunohistochemistry methods but will also include mouse models of BM transplantation and chemotherapy, fluorescence activated cell sorting (FACS), and some molecular biology.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Stem Cell

**Select Research Techniques Matching This Project**

Immunofluorescence

Flow cytometry

Cell biology

In vivo animal models

**Project Name**

**The involvement of Hoxa1 in blood cell diseases.**

**Description**

Myelodysplastic syndromes (MDS) cover a range of blood cell diseases that affect red blood cell and platelet production. A significant proportion of these blood cell diseases can also progress to leukaemia. Currently, very little is understood in how MDS occurs, and as a result, treatment options for patients with MDS are limited- there is no current cure.

We have developed a mouse model that has all of the signs of MDS- the mice develop low red blood cell and platelet counts and a proportion of these mice also develop leukaemia. These mice have a deregulated pathway of one of the Hox genes, Hoxa1. The aims of this Honours project is to further understand how deregulation of Hoxa1 impairs red cell and platelet production. By understanding further how Hoxa1 contributes to MDS and leukaemia we might be able to find better treatments for patients with MDS.

These studies will involve a range of different techniques used in blood cell biology. It will predominantly focus on immunohistochemistry methods but will also include mouse models of BM transplantation and leukaemia, fluorescence activated cell sorting (FACS), and some molecular biology.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Stem Cell

**Select Research Techniques Matching This Project**

Immunofluorescence

Flow cytometry

Cell biology

In vivo animal models

**Project Name**

**Impact of TNFalpha in the bone marrow microenvironment in normal and stressed situations.**

**Description**

The bone marrow microenvironment consists of many different cell types, including bone, adipocytes, endothelial cells and blood-forming cells. We have found that cancer therapies cause dramatic changes to the bone marrow microenvironment, some of which (bone loss) are irreversible. Tumour necrosis factor alpha (TNFa) is a cytokine involved in inflammation. We have found that TNFa is markedly upregulated in mice at early time points after common cancer therapies, and propose that this contributes significantly to side-effects observed after these therapies (reduced blood counts, irreversible bone loss and other alterations to cells in the bone marrow (BM)).

The aims of this Honours project are to further characterise the role that TNFa plays in the BM microenvironment in normal and stressed situations (after cytotoxic therapies). We will characterize the bone marrow microenvironment and blood cell phenotypes of TNFa knockout mice and determine the impact of TNFa in the changes that occur at early time points post-cancer therapies.

These studies will involve a range of different techniques used in HSC and bone biology, including mouse models of BM transplantation and chemotherapy, fluorescence activated cell sorting (FACS), analysis of bone parameters using microCT and histomorphometry, immunohistochemistry, some molecular biology.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Stem Cell

**Select Research Techniques Matching This Project**

Immunofluorescence

Flow cytometry

Cell biology

In vivo animal models

**Project Name**

**The role of Oncostatin M in rheumatoid arthritis and osteoarthritis**

**Description**

Osteoarthritis (OA) and rheumatoid arthritis (RA) are characterised by inflammation, destruction of joint cartilage, and either accrual of bone (OA) or destruction of bone (RA). Our research goal is to identify specific mechanisms that contribute to joint degeneration within RA- and OA-affected joints. Oncostatin M (OSM) is a cytokine that may contribute to OA and RA joint degeneration. We have evidence to suggest that OSM, acting via its specific receptor OSMR, contributes to joint degeneration in OA and RA. This project seeks to: 1) use mouse models of RA and OA to determine the effect of deficiency in OSMR expression on inflammation, arthritis severity and bone remodelling within the arthritic joint; 2) identify cell specific effects of OSM/OSMR signalling on genes known to contribute to inflammation and joint destruction in OA and RA.

To achieve these goals students will use a combination of in vivo and in vitro approaches including: mouse models of osteoarthritis and rheumatoid arthritis, histologic analyses, micro-CT, bone histomorphometry, immunohistochemistry, in situ hybridisation, in vitro cell culture, gene expression analyses (qPCR), analyses for activation of cellular signalling.

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**Pathological Disease Research Topics Matching This Project**

Inflammation

**Select Research Techniques Matching This Project**

In vivo animal models

Histology

Cell culture

Molecular biology

**Project Name**

**RECOGNITION OF H2-M3 BY LY49 AND SUBSEQUENT REGULATION OF NK CELL RESPONSES**

**Description**

Natural Killer (NK) cells clearly contribute to immune responses to cancer and viruses. Unlike adaptive immune lymphocytes such as B and T cells, the receptor repertoire of NK cells is independent of rearrangement and requires another form of regulation to mediate specificity. Each NK cell expresses a range of stimulatory or inhibitory receptors, which allows them to target cells with increased or decreased ligand expression. The regulation of NK cell responses is balanced by interactions that transmit signals mediating activation or inhibition. Under normal conditions NK cells are repressed through the recognition of MHC class I by inhibitory Ly49 molecules. Among this family, Ly49A is enigmatic in that it is expressed in mice where the MHC is not recognised.

We have described a novel pathway of NK cell regulation through Ly49A recognition of the non-classical MHC class I molecule H2-M3. Our results demonstrate that the absence of H2-M3 prevents licensing in C57BL/6J mice, which results in NK cell hypo responsiveness and manifests as increases in tumour burden. In contrast, blockade of H2-M3 in mice with a recognised Ly49A ligand results in increased NK cell activation and a reduction in tumour burden.

We are seeking an honours student to pursue a role for other Ly49 molecules in the recognition of H2-M3. This project will entail cloning and expression of plasmids, animal handling, tissue culture of primary cells and cell lines as well as Flow Cytometry.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Immunotherapy

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

Flow cytometry

In vivo animal models

Clonogenic assays

**Project Name**

**FUNCTIONAL CHARACTERIZATION OF THE SCRIBBLE POLARITY NETWORK IN PROSTATE CANCER METASTASIS**

**Description**

Cell polarity refers to the asymmetry of cells within a tissue and is a fundamental property of all mammalian cells. Loss of cell polarity (the orientation of cells within a tissue) is one of the hallmarks of epithelial cancer, and is correlated with more aggressive and invasive cancers. However how loss of cell polarity occurs and how it contributes at the molecular level to tumour formation remains poorly understood.

Metastatic spread of tumours is the major cause of cancer related morbidity in patients. We have recently shown that the tumour suppressive functions of the cell polarity gene Scribble are highly conserved in mammalian epithelial tissues. Indeed, Our analysis of mice genetically engineered to mutate Scribble in prostate tissue have indicated that Scribble disruption can promote loss of cell polarity, hyperplasia and in combination with oncogene activation prostate cancer in the mouse. Disruption of Scribble also correlates with poor outcome in prostate cancer patients. Whether disruption of human Scribble can contribute to tumour metastasis however is not known.

This project aims to examine using in vitro and in vivo transplantation models the role Scribble and associated proteins may play in prostate cancer metastasis. A better understanding of this pathway and how loss of tissue architecture can occur and impact on cancer progression will lead to the discovery of novel prognostic factors, novel chemotherapeutic targets and fundamental insights in to epithelial tumour biology and cancer progression.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

In vivo animal models

RNA Microarray

Molecular biology

**Project Name**

**THE ROLE OF POLARITY REGULATORS IN MELANOMA**

**Description**

Cell polarity refers to the asymmetry of cells within a tissue and is a fundamental property of all mammalian cells. Loss of cell polarity (the orientation of cells within a tissue) is one of the hallmarks of epithelial cancer, and is correlated with more aggressive and invasive cancers. However how loss of cell polarity occurs and how it contributes at the molecular level to tumour formation remains poorly understood.

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This project aims to examine using in vitro and in vivo transplantation models the role Scribble and associated proteins may play in prostate cancer metastasis. A better understanding of this pathway and how loss of tissue architecture can occur and impact on cancer progression will lead to the discovery of novel prognostic factors, novel chemotherapeutic targets and fundamental insights in to epithelial tumour biology and cancer progression.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

In vivo animal models

DNA cloning & PCR

Molecular biology

**Project Name**

**STRUCTURAL AND BIOCHEMICAL CHARACTERIZATION OF POLARITY COMPLEXES IN CANCER**

**Description**

Every cell in our body has an intrinsic orientation (or polarity) that is controlled by a universal set of genes known as polarity genes. Loss of this orientation is a defining early feature in cancers, and has been linked to cancer spread or metastasis. Our team has previously identified the gene Scribble as a new human polarity gene that controls cell orientation and tumour growth. Scribble works in concert with the two other proteins called Discs Large (Dlg) and Lethal giant larvae (Lgl) to define the polarity of a cell. Using mouse models and samples from tumour patients we have shown that Scribble acts as a suppressor of tumours. In particular, we have shown that lowering levels of Scribble in normal cells increases the risk of cancer by disorganizing the tissue and by increasing the speed at which cells grow within the tissue.

We now need to establish how Scribble and its partners contribute to tumour formation and metastasis and clarify their molecular mechanism of action, to enable targeting of these proteins for therapeutic purposes. This projects aims to gain deeper insight into the nature of the physical interactions that allow Scribble and its partners to perform its function using combination of biochemical, yeast-two-hybrid, proteomics and functional assays. Structural and biochemical information will be validated for their functional relevance in our well established mouse and cellular models, and therefore rapidly translated into biological information directly relevant to human cancer patients and their outcome. We believe that studies investigating the mechanism of how this complex is formed may lead to the discovery of new prognosis factors and new chemotherapeutic targets, as well as a better understanding of cancer biology and cancer progression.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

In vivo animal models

RNA Microarray

Molecular biology

**Project Name**

**DEVELOPMENT OF A NOVEL SCREENING TEST TO ASSESS INDIVIDUAL RADIOSENSITIVITY OF RADIOTHERAPY PATIENTS**

**Description**

A few percent of patients experience abnormally severe side-effects of radiotherapy, due to innate (genetically determined) radiosensitivity (RS). If such patients could be identified, this would enable radiation oncologists to prescribe customized radiotherapy schedules, with increased prospects of cure.

The importance of this clinical problem has prompted numerous attempts to develop effective assays by using blood and other normal tissues from radiotherapy patients. However until recently, these have been unsuccessful, largely due to limitations of methodology, such as sensitivity, reproducibility, reliability and a long time delay (2-3 weeks) to obtain the results. Also, previous assays required that the cells were “transformed” so they could proliferate indefinitely, and this procedure itself changes their RS.

An important feature of this project is the rapid “readout” of the  $\gamma$ -H2AX assay, which enables use of untransformed primary cells. The assay is based on a very early event in the response of cells to radiation-induced DNA damage, namely phosphorylation of histone H2AX to form  $\gamma$ -H2AX. Fluorescent foci are detectable in cells by immunofluorescence using labelled anti- $\gamma$ -H2AX antibodies, within minutes after irradiation. We are using primary lymphocytes and plucked hair follicles, which are subsequently irradiated and then assayed. In the context of validation, there is the access to a retrospective collection of ex-RT patients at PeterMac, who experienced abnormally severe side-effects, together with matched controls. The database of ex-RT patients was assembled by Dr Trevor Leong, a radiation oncologist. The first stage of the project involves testing the ex-RT patients, and comparison of the assay results with the extent of clinically reported radiation-induced side effects.

This project involves collaborators at Peter Mac (Prof. Stephen Fox and Assoc. Prof. Trevor Leong)

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**Pathological Disease Research Topics Matching This Project**

Cancer

Radiotherapy

Radiotherapy

**Select Research Techniques Matching This Project**

DNA cloning & PCR

ELISA assays

Cell biology

Molecular biology

**Project Name**

**THE ROLE OF SIGNALING AND POLARITY PROTEINS IN ASYMMETRIC CELL DIVISION OF T LYMPHOCYTES**

**Description**

Our laboratory studies the role of signaling and polarity proteins in T lymphocyte biology. Polarity - or the compartmentalisation of proteins within a cell - is critical for T lymphocyte functions such as migration, immunological synapse formation and cytotoxic activity during an immune response. More recently, we demonstrated that asymmetric cell division of T lymphocytes in response to antigen presentation may be used to generate effector and memory T lymphocytes (Chang et al. Science, 2007) - a process regulated by polarity proteins in other cell types. This observation provides a potential mechanism for generating the diversity of T lymphocytes required for an effective immune response, and suggests that a conserved mechanism based on asymmetric cell division also exists in immune cells.

An Honours project is available to investigate the role of polarity proteins and the cell surface receptor, CD46, in the regulation of asymmetric cell division of T lymphocytes. CD46 is a receptor for a number of pathogens, including measles virus, and signaling through CD46 can affect T lymphocyte polarity, function and fate in human T and NK cells (Oliaro et al. PNAS, 2006). CD46 has previously been shown to interact with members of the polarity network, and pathogens that bind to CD46 may utilise this to alter T lymphocyte responses. The project will focus on how polarity proteins control asymmetric cell division, whether signaling through CD46 affects this process, and what the consequences are for T lymphocyte fate and function.

The project will involve some animal experimentation, immunological techniques such as tissue culture and flow cytometry, and both fixed and live imaging of cells using our state of the art microscopy facilities.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Immunotherapy

Leukemia

**Select Research Techniques Matching This Project**

Immunofluorescence

Molecular biology

Biochemistry

Cell biology

**Project Name**

**A FUNCTIONAL GENOMIC SCREEN TO IDENTIFY GENES THAT REGULATE BREAST CANCER METASTASIS**

**Description**

The development of metastatic disease is the major cause of death in patients with breast cancer. The overall aim of our research is to understand the molecular regulation of metastasis and to develop improved therapies for patients with advanced disease.

The aim of this project is to identify genes that prevent the development of metastatic disease following growth of the primary tumour in the mammary gland. To achieve this aim, we are using a genome-wide library of shRNA sequences cloned into lentiviral vectors. These are used to infect a population of tumour cells such that each tumour cell, on average, expresses one shRNA species and hence the expression of one gene is knocked down. We then inject this population of cells into mice to see if loss of one gene now permits the tumour to metastasise to distant sites. By recovery of the metastatic nodule, we can sequence the shRNA insert and identify the gene whose loss allowed metastasis to occur.

The project will involve further screening of mice to find metastatic nodules caused by infection with the lentiviral vector, identification of the shRNA insert and hence the gene, followed by functional analysis of the role of this gene in metastasis.

The project will involve cell culture, molecular biology, tumour growth and metastasis analysis in mice.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

Cell biology

RNA Microarray

Molecular biology

**Project Name**

**REGULATION OF BREAST CANCER METASTASIS BY NON-CODING RNA**

**Description**

The development of metastatic disease is the major cause of death in patients with breast cancer. The overall aim of our research is to understand the molecular regulation of metastasis and to develop improved therapies for patients with advanced disease.

Many genes in the human or mouse genome do not encode proteins, but make RNA sequences that have profound effects on cells and organisms. They are known to regulate the expression of many protein-encoding genes. We have identified several long non-coding RNA (lncRNA) species that are differentially expressed in tumours that can metastasise to distant organs compared to those that remain localised in the breast. The aim of this project is to investigate the functional significance of one of these lncRNA that we find to be expressed at very different levels in aggressive tumours.

The project will involve cell culture, molecular biology, tumour growth and metastasis analysis in mice.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Breast Cancer

Metastasis

**Select Research Techniques Matching This Project**

Cell culture

Cell biology

RNA Microarray

Molecular biology

**Project Name**

**CHARACTERIZATION OF NORMAL MELANOCYTE DEVELOPMENT**

**Description**

This project will adapt classical stem cell biology techniques developed in other solid organ systems (Nature 439:84) to the study of normal melanocyte development. Using sophisticated mouse models, melanocytes at different stages of development will be conditionally tagged, isolated and functionally characterized. The oncogenic effects of various genetic and environmental stimuli on melanocyte lineage subpopulations will then be studied, and strategies explored to prevent oncogenesis in different contexts. Complementary studies of human melanocyte development will also be performed.

The techniques used will include working with mouse models, cell culture, flow cytometry and cell sorting, microarray-based gene expression studies, and quantitative PCR.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Melanoma

Melanoma

**Select Research Techniques Matching This Project**

Cell culture

In vivo animal models

DNA cloning & PCR

Molecular biology

**Project Name**

**IDENTIFICATION OF DETERMINANTS OF MELANOMA PROGRESSION**

**Description**

This project will use a novel human melanoma tumourigenesis assay (Nature 456:593) to study how melanomas progress once they have formed. This assay offers a unique opportunity to study human cancer biology, genetics and epigenetics at the clonal level. By comparing the malignant and molecular properties of sister clonal tumours, this approach enables direct correlation of tumour phenotype and genotype/epigenotype in a way that is likely to reveal those molecular aberrations that are functionally relevant to malignant progression and potentially target-able by modern therapeutic approaches. Multiple projects within this framework are planned, involving a wide range of techniques: working with fresh human tumour specimens and analyzing clinical data, mouse handling and surgery, immunostaining and flow cytometry, and molecular studies such as SNP genotyping, DNA methylation analysis, NextGen sequencing and functional genomics.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Melanoma

Melanoma

**Select Research Techniques Matching This Project**

Cell culture

In vivo animal models

Clonogenic assays

Molecular biology

**Project Name**

**REGULATION AND FUNCTION OF PERFORIN, A KEY EFFECTOR MOLECULE OF CYTOTOXIC LYMPHOCYTES**

**Description**

Perforin is a pore-forming toxin expressed in cytotoxic lymphocytes, a subtype of immune cells, which recognise and destroy virus-infected or cancerous cells.

Functional perforin is essential for the killing activity of cytotoxic lymphocytes and, more generally, for maintaining immune homeostasis. We have demonstrated that the loss of PRF function due to detrimental bi-allelic mutations in the perforin gene leads to a catastrophic immunoregulatory disorder, Familial Haemophagocytic Lymphohistiocytosis (FHL) [1]. At the same time, partial perforin deficiency appeared to be a strong predisposition factor for haematological malignancies in early adolescence [2]. Our biochemical studies have revealed the structural basis for perforin membrane binding [3] and oligomerisation [4], which were further supported by the structural studies of perforin monomer and the entire pore [5]. We have also identified a unique intracellular transport mechanism that protects cytotoxic lymphocytes as they shuttle the toxic perforin protein through the secretory pathway to the cell surface [6].

While these studies have led to some of the major advances in the field, they also raised new important questions, which we are now in position to address.

A prospective student will be a part of a successful multidisciplinary research team of immunologists, biochemists, cell biologists, geneticists and clinical scientists.

We offer the following projects:

1. Structure-function analysis of perforin,
2. Genetic regulation of perforin in cancer patients,
3. Molecular basis of granule exocytosis in cytotoxic lymphocytes.

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**Pathological Disease Research Topics Matching This Project**

Cancer

Cellular Growth & Proliferation

Immunotherapy

**Select Research Techniques Matching This Project**

Cell biology

In vivo animal models

DNA cloning & PCR

Cell death