LOWY CANCER RESEARCH CENTRE

UNSW AUSTRALIA

CHILDREN'S CANCER INSTITUTE AUSTRALIA

STUDENT PROSPECTUS 2013

www.lowycancerresearchcentre.unsw.edu.au

A Message from Our Director

The lifeblood of a research entity like the Lowy Cancer Research Centre is its post-graduate students. They provide for a dynamic intellectual and practical environment that is crucial if new discoveries are to be made. It is with great pleasure that I welcome those of you considering your own careers in medical research and present to you the Lowy Cancer Research Centre Student Prospectus.

Childhood and adult cancer are different diseases in many ways. Childhood cancer mostly arises from an error during development of the child, while adult cancer is largely a disease of ageing. The way the cancers begin and develop and their response to treatment is very different. If we can understand the differences between childhood and adult cancer and focus on these differences then we will gain insights into both. Child and adult cancer researchers tend to ask different questions but it is becoming clearer that there are common pathways if you know where to find them. The Centre brings together childhood and adult cancer researchers to find those pathways and to understand what they mean.

Lowy Cancer Research Centre researchers have a track-record of cross-fertilisation between basic cancer research and clinical, or translational, research. This means that discoveries made in basic research are rapidly and efficiently translated to the clinic or public health arena, while the clinical experience in turn guides the basic research. The Holy Grail in medical research is translating something discovered in the lab into clinical practice to provide a better outcome for people with that disease. It is what researchers call bench-to-bedside, and it is the Centre's bench-to-bedside capability that will provide a platform for its success.

You will find the Lowy Cancer Research Centre to be a stimulating and rewarding place to undertake post-graduate studies. Feel free to contact me if you need any more information than is contained herein.

Professor Philip Hogg
Director
Lowy Cancer Research Centre

Professor Philip Hogg
Director

LOWY CANCER RESEARCH CENTRE

How to Become a Student at the Lowy Cancer Research Centre

1. Browse the information and lists of student projects in this booklet.
2. Identify an area of interest, contact a potential supervisor and arrange a suitable project. When you contact potential supervisors, please include a CV and your most recent academic transcript.
3. Submit an admissions application to the University of New South Wales (UNSW). Honours students must be accepted into an Honours program in an appropriate UNSW Faculty. PhD students should successfully fulfil the requirements for admissions through UNSW.
4. Coordinate with your supervisor to obtain clearances from the appropriate Ethics Committees.
5. Begin your research program.

Postgraduate Studies:

UNSW Graduate Research School

The UNSW Graduate Research School is the central administrative and support unit for all higher degree research students and their supervisors at UNSW. The website below will direct you to information on admissions requirements and enrolment procedures to undertake postgraduate study at UNSW together with links to scholarship application forms for both local and international students.

http://research.unsw.edu.au/units/graduate-research-school

Additional Facts for International Students:
http://www.immi.gov.au/index.htm
http://www.international.unsw.edu.au

Before beginning the admissions application process with UNSW Graduate Research School, it is also important to get in contact with your prospective school's postgraduate coordinator(s) or administrative staff to check if there are any additional steps to the process at the school's level. Your prospective supervisor(s) will also be able to help get you started.

Honours:

The standard duration of enrolment for an Honours degree is one academic year, actual dates for the honours programs you may enrol can vary, please consult the websites below for more detailed information.

When you undertake an Honours project at the Centre you will be enrolled in a UNSW Honours program. Therefore, you need to meet the UNSW Honours entry criteria. For information regarding the three Honours Programs at UNSW that students may be enrolled in, please visit the following websites:

Bachelor of Science (Medicine) Honours Program (UNSW Medicine)

http://medicalsciences.med.unsw.edu.au/students/soms-honours/overview

School of Medical Sciences Honours Program (UNSW Medicine)

http://medicalsciences.med.unsw.edu.au/SOMSWeb.nsf/page/Honours%20Current%20Students

School of Biotechnology and Biomolecular Sciences (BABS) Honours Program (Faculty of Science)

http://www.babs.unsw.edu.au/future_students/future-honours-students

Research projects at the Lowy Cancer Research Centre

In the following pages, you will find outlines of available projects and overviews of the core research interests of those laboratories within the Lowy Cancer Research Centre taking students in 2013.

If you are interested in a particular area of research at the Centre but do not find a project that appeals to you listed here we encourage you to contact these programs directly to discuss a project to best suit both you and the research program.

ADULT CANCER PROGRAM

The **Adult Cancer Program** (ACP) at the Lowy Cancer Research Centre is an exciting research program at UNSW. It brings together teams of cancer researchers from UNSW and its adjacent teaching hospitals - Prince of Wales Hospital and the Royal Hospital for Women. The collocation of the research facilities at the Lowy Cancer Research Centre with large referral hospitals provides unparalleled opportunities for cancer researchers. ACP offers a wealth of opportunities for Honours, Independent Learning Projects (ILP), Masters and PhD students.

The work over 50 full time equivalent ACP academic staff members spans the domains of basic and clinical science as well as population health research. The team leaders within ACP have all demonstrated a determined commitment to cancer research. Students in ACP have the opportunity to work alongside some of Australia's best cancer researchers. These individuals have discovered new treatments for cancer, new ways of diagnosing cancer and new causes of cancer. ACP is also the home to a number of new young researchers who have returned to Australia to set up research on exciting new areas such as stem cells and epigenetics. For students who want to help close the gap between research and clinical practice ACP offers the chance to study the real world use of cancer medicines and other therapies. ACP uniquely positions researchers alongside practicing cancer clinicians — an environment which nurtures discoveries that make a difference to cancer patients.

Opportunities for postgraduate students

Postgraduate students working in ACP will join 66 students who are currently undertaking postgraduate studies through the Prince of Wales Clinical School of UNSW Medicine. The school has a strong commitment to student training and education. Our school has an excellent record of timely student completions. We offer our students stipend scholarships, formal training opportunities and travel grants. Each year, through a competitive process we offer postgraduate research scholarships including one scholarship to new students of $22,500 per annum – for a period of two years for Masters and three years for PhD to cover student stipends and two scholarships to current students of $20,000 per annum also to cover student stipends for a period of one year. Students can also apply for grants to cover travel costs – up to maximum $5,750 during their candidature – to present at domestic and international conferences. Two of the schools highly regarded academics, A/Prof Claire Vajdic and Dr Jonathon Erlich serve in the roles of postgraduate coordinators and Caitlyn Granse is our postgraduate liaison officer. Together this team provides a strong support network which ensures that our students are well supported throughout their studies.

Peter Zazour (3rd year PhD): I completed honours with ACP (colorectal cancer) - it was an exciting and rewarding experience. It fuelled my interest in research, providing me with a supportive environment that offered a wealth of knowledge and experience through my supervisors and colleagues. I enjoyed it so much that I returned as a PhD student, where I am currently formulating and testing my own hypotheses under the mentorship of my

Interested?

If you would like to explore research opportunities with us, please contact one of our team leaders in this brochure or, if you aren't sure where to start, then speak to Caitlyn Granse c.granse@unsw.edu.au, A/Prof Claire Vajdic or myself.

For more information on applications, go to the Prince of Wales Clinical School application web page:

http://powcs.med.unsw.edu.au/powcsweb.nsf/page/howtoapply

Professor Robyn Ward
Head, Adult Cancer Program, Lowy Cancer Research Centre
Clinical Associate Dean, Prince of Wales Clinical School

Bioactive Lipid Signaling Group

Team leader: Dr Anthony Don

Our research group uses molecular biology, biochemistry, and cutting-edge mass spectrometry to investigate how a family of signalling molecules termed sphingolipids influence cancer development. The essential signalling metabolite sphingosine 1-phosphate promotes the proliferation, migration, and apoptotic resistance of cancer cells, as well as recruitment of blood vessels into the tumour. On the other hand the lipid ceramide, which is the biosynthetic precursor to sphingosine 1-phosphate, promotes cellular differentiation and apoptosis. We have found that the balance between these metabolites is significantly dysregulated in human glioma tissues. Current research looks at how this imbalance contributes to disease progression and whether we can target this property of cancer cells. We also investigate how the balance of these metabolites is altered (in the opposite direction) in the neurodegenerative condition Alzheimer's Disease, and how this may contribute to disease pathogenesis.

Dr Anthony Don

Bioactive Lipid Signalling Student Projects

Altered Ceramide/Sphingosine 1-phosphate balance in human gliomas

Supervision: Dr Anthony Don (anthonyd@unsw.edu.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

Production of the potent signalling molecule sphingosine 1-phosphate (S1P) by cancer cells is believed to promote proliferation and survival of the cells through feedback on specific extracellular receptors, as well as recruitment of vascular and lymphatic endothelial cells into the tumour microenvironment (i.e. angiogenesis and lymphangiogenesis). This metabolite is generated at the expense of its precursor ceramide, which is an important differentiation factor. We have found that the balance between these metabolites is heavily shifted in favour of S1P in human glioma tissues. In ongoing research, we are investigating how this shift in sphingolipid metabolism drives cancer progression, including how this metabolic alteration might permit cancer cells to survive in a de-differentiated state and under conditions of environmental stress (e.g. low oxygen). This project involves cell culture, gene manipulation (i.e. transfection, siRNA), monitoring of gene expression, enzyme activity assays, mass spectrometry, and testing of novel enzyme inhibitors as potential therapeutic agents.

Plasma ceramides as markers of treatment response in cancer

Supervision: Dr Anthony Don (anthonyd@unsw.edu.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

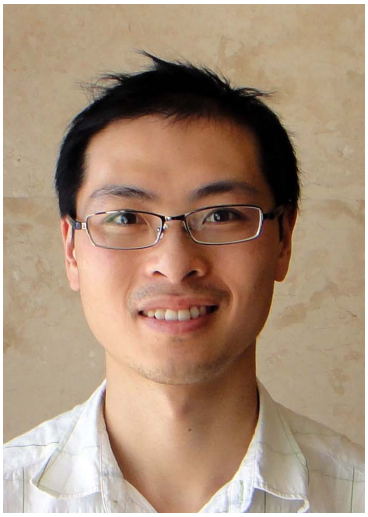
There is currently no means to monitor an individual patient's response to cancer therapy early in the treatment phase. It takes several weeks to determine if there is any response to therapy, during which time the patient may have received several rounds of a toxic therapy that is not going to succeed. The lipid ceramide is always increased in cells that are undergoing programmed cell death (apoptosis). This occurs in response to natural apoptotic stimuli, radiotherapy and a wide array of chemotherapeutics. The ceramide formed *en masse* during cancer therapy can make its way into the blood stream where it could, in theory, act as an indicator of therapeutic response. In this project we will ask whether it is theoretically possible to use plasma ceramides, generated as a result of cancer therapy, as a marker of apoptosis. The project would involve cancer cell culture, mass spectrometry, and mouse models of cancer.

Bioinformatics and Protein Mass Spectrometry Group

Team leader: Dr Jason Wong

With the proliferation of biological data over the past decade, bioinformatics has become an indispensable tool in understanding biological processes. Our research involves the application of computation methods to a broad range of problems in proteomics, genomics and molecular evolution of proteins. A major goal of our work is to bring together the enormous amount of genomic data being generated through Next - Generation Sequencing and examine how changes in the genome ultimately affect protein expression and function. In collaboration with other teams in the Lowy Cancer Research Centre, some of the cancers we work on include colorectal cancer and leukaemia.

Another active area of research in our laboratory is the application of mass spectrometry for the analysis of proteins. We are developing novel experimental techniques that will enable the study of sub-proteomes including nascent and DNA-binding proteins.



Dr Jason Wong

Bioinformatics and Protein Mass Spectrometry Student Projects

Monitoring of signal-dependent protein synthesis in leukaemic cells

Supervision: Dr Jason Wong (jason.wong@unsw.edu.au) &
Dr John Pimanda (j.pimanda@unsw.edu.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

Cells respond rapidly to environmental signals by synthesising new proteins. The selective identification of a newly synthesised proteins is often a challenge due to the inability to distinguish new and existing proteins which share the same basic amino acid make up. This project will establish a new methodology whereby azide-bearing and stable isotope labelled amino acids are metabolically incorporated into newly synthesised proteins. The introduction of azide groups into proteins will enable chemoselective tagging of newly synthesised proteins for *in vitro* visualisation and downstream enrichment. Moreover, the incorporation of stable isotopes will enable identification of these proteins by mass spectrometry. This project will investigate the use of this technique to study the affect of signal-dependent stimulus such as transcription factor over-expression or drug treatment in leukaemic cells.

Computational analysis of next-generation sequencing data to reveal genomic variations in cancer

Supervision: Dr Jason Wong (jason.wong@unsw.edu.au) &
Dr Fabio Luciani (luciani@unsw.edu.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

Genetic variations account for many phenotypic differences within and between populations and are known to be associated with predisposition to diseases in humans. In cancer, identification of somatic mutations provides an understanding of how these mutations result in the development of cancer cells. The advent of next-generation DNA sequencing technologies in recent years has revolutionised our ability to interrogate genomic variations. Using cutting edge computing facilities, this project will develop new computation approaches to rapidly and accurately identify somatic mutations in hepatocellular carcinoma and leukaemia samples from next-generation sequencing data. The project will also examine the use of identified mutations to track the evolution of cancer cells in response to drug treatment.

Wnt Signalling & Metastasis Group

Team leader: Dr Caroline Ford

Over 90% of deaths from cancer are related to the spread of the tumour to other organs (termed metastases) yet there is a current lack of drugs that target this dissemination process. The overall aim of our research is to understand the key processes in epithelial to mesenchymal transition (EMT) and cancer metastasis in order to identify targets for novel therapies. Our group focuses on an important signalling pathway involved in metastasis, the Wnt signalling pathway. We are particularly interested in investigating the regulation of a number of key proteins involved in this pathway, and understanding their role in the context of breast, ovarian and colorectal cancer.

Dr Caroline Ford

Wnt Signalling and Metastasis Student Projects

The role of the Ror2 receptor tyrosine kinase in cancer

Supervision: Dr Caroline Ford (caroline.ford@unsw.edu.au)

Suitable for: Honours Studies

Project outline:

The Wnt signalling pathway plays an important role in many human cancers, and research into regulation of the pathway has become an area of interest in recent years as a strategy to identify targets for novel drug development. Ror2 is a recently discovered receptor tyrosine kinase that appears to play a key role in regulation of downstream Wnt signalling in cancer. This project will determine the downstream effects of Ror2 on epithelial to mesenchymal transition (EMT), and metastatic potential of cancer cells. The regulation of Ror2 expression by promoter methylation and micro RNAs (miRs) will also be investigated. This project will involve protein work, cell culture, qPCR epigenetics and cell signalling analyses.

Investigating the links between Wnt signalling and EMT in triple negative breast cancer

Supervision: Dr Caroline Ford (caroline.ford@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

Breast cancer remains the leading cause of cancer in women worldwide. Despite vast improvements in detection and treatment, mortality from this disease remains high, particularly for the subset of patients referred to as “triple negative”. Triple negative breast cancer (TNB) patients lack expression of the key breast cancer drug targets, oestrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (Her2). TNB patients are often more prone to metastases and exhibit a highly “mesenchymal” expression profile.

The Wnt signalling pathway has been shown to regulate epithelial to mesenchymal transition, and this project will investigate the links between these pathways within the context of TNB. Wnt signalling is essential for crucial components of carcinogenesis and metastasis including differentiation, polarity, migration, adhesion and survival, and hence the role of Wnt signalling in human cancer is increasingly being investigated along with strategies to target pathway components. The project will investigate a number of key regulators of the Wnt pathway including members of the SFRP family and the recently discovered Wnt receptors, Ror1, Ror2 and Ryk. The project will involve cell culture, qPCR, protein work and epigenetics.

Allosteric Disulphide Group

Team leader: Professor Philip Hogg

Genes encode proteins, which are the machinery of life. All life forms make proteins that contain strong bonds between pairs of cysteine amino acids called disulphide bonds. Acquisition of disulphide bonds is an important way that proteins have evolved and are continuing to evolve. There are two basic types of disulphide bond; structural bonds which help hold proteins together and functional bonds that are involved in how proteins work.

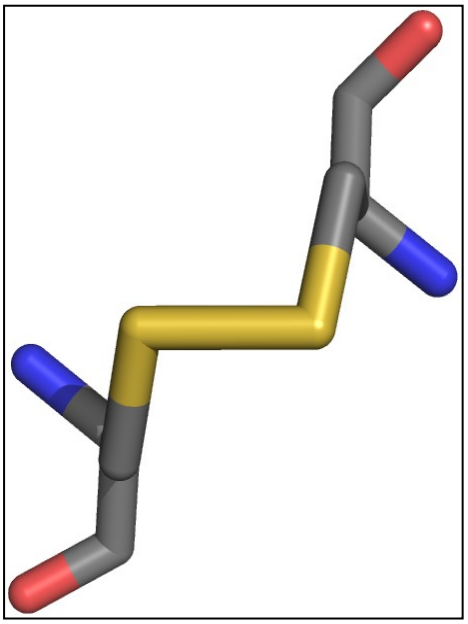
The functional disulphides are the catalytic bonds that mediate thiol/disulphide exchange in other proteins, and the allosteric bonds which have been defined and characterised by us. Allosteric disulphides are bonds that have evolved to control protein function by breaking or forming in a precise way.

Our overall research aim is to characterise control of haemostasis by allosteric disulphides. Haemostasis is the system that maintains the integrity of a closed, high-pressure circulatory system after vascular damage and haemostasis gone wrong is responsible for about half of deaths in Australia. Venous thrombosis, for instance, is the second leading cause of death in patients with cancer. We are characterising control of haemostasis by allosteric disulphides in key haemostatic proteins.

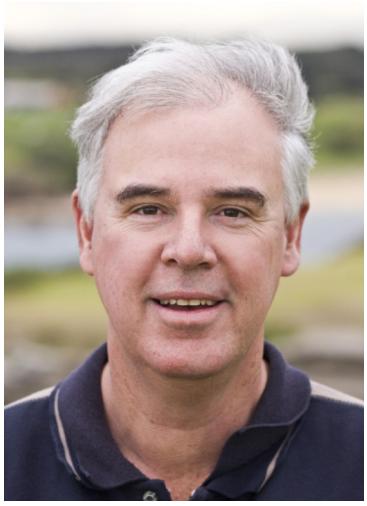
The Allosteric Disulphide Group consists of post-doctoral researchers and doctoral students with expertise from protein chemistry and cell biology to mouse models of thrombosis.

There are opportunities for Honours and PhD students in this program of research.

Contact: p.hogg@unsw.edu.au



Structure of an allosteric disulphide bond



Professor Philip Hogg

Tumour Metabolism Group

Team leaders: Dr Pierre Dilda and Professor Philip Hogg

We are developing a novel class of metabolism inhibitors for the treatment of cancer. These compounds target the power supply of tumour and tumour-supporting cells. They inactivate a mitochondrial transport protein known as adenine nucleotide translocase, which is critical for cell function.

The first generation molecule, called GSAO, has been tested in a clinical trial in adults with solid tumours and a trial of the second generation compound, called PENAO, has just begun.

We are working on new arsenical-based molecules with better anti-tumour properties than GSAO and PENAO. We are also exploring different ways of inactivating mitochondria in cancer cells.

In the clinical development of new cancer treatments, it is very important that an appropriate patient population can be identified. Choosing a patient population that is more likely to respond to the drug is vital for the success of the drug. We are discovering tumour markers that will identify patients who are more likely to benefit from treatment with GSAO and PENAO. These markers will then be used to select cancer patients in future clinical trials of these compounds.

The Tumour Metabolism Group consists of a mix of senior and junior post-doctoral researchers, research assistants and doctoral students with a broad range of expertise, from protein chemistry and cell biology to pharmacology and mouse models of cancer.

Dr Pierre Dilda

Tumour Metabolism Student Projects

Combination of the metabolism inhibitor PENAO with standard chemotherapeutics in drug—resistant cancer models

Supervision: Dr Pierre Dilda (p.dilda@unsw.edu.au) &
Prof Philip Hogg (p.hogg@unsw.edu.au)

Suitable for: ILP or Honours Studies

Project outline:

Tumours usurp the metabolic steps used by normal tissues for glucose utilisation and ATP production, which relies heavily on oxidative phosphorylation, and employ a route that includes a much greater dependency on glycolysis. This aberrant phenotype becomes more pronounced with increased tumour malignancy. While retaining the capacity for mitochondrial respiration, the ability of tumours to scavenge glucose from the surroundings and metabolise it using glycolysis is enhanced. We have developed an inhibitor of tumour cell mitochondria called PENAO. PENAO inactivates the mitochondrial transport protein, adenine nucleotide translocase, which leads to proliferation arrest and death of the cells. A clinical trial of PENAO is adults with solid tumours has just begun.

The proposed project will be to characterise the combination PENAO with various standard chemotherapeutics that have distinct molecular targets. This will performed on chemoresistant cell lines *in vitro* and in animal models of human tumours. This project will provide essential information for the future clinical development of PENAO.

Tumour Metabolism Student Projects *cont'd*

Mechanism of action of a new class of anti-cancer drug: the adamantane-type polyarsenical drugs

Supervision: Dr Pierre Dilda (p.dilda@unsw.edu.au)

Suitable for: ILP or Honours Studies

Project outline:

Arsenic(III) oxide (Trisenox) was approved by the FDA in 2000 for use in relapsed and refractory acute promyelocytic leukaemia (APL). The discovery that this drug induces complete remission in a high percentage of patients with APL has renewed interest in arsenic compounds for the treatment of various types of cancers. Arsenicin A, the first polyarsenic adamantane-type compound ever found in nature was isolated from a marine sponge. Preliminary characterisation of this compound and one of its derivatives on various drug resistant cancer cell lines demonstrated (i) a very strong anti-proliferative activity regardless of histological subtypes, (ii) a good specificity towards cancer cells, (iii) the absence of cross-resistance with platinum agents and (iv) insensitivity towards the expression of major multidrug resistance proteins.

The proposed project is to unravel the mechanism of action by which adamantane-type polyarsenical compounds selectively kill drug resistant cancer cells. This is of major significance due to the poor prognosis of drug resistant and recurrent forms of cancers.

STEM CELL GROUP

Team leader: Dr John Pimanda

We study the transcriptional regulation of genes that control the specification and subsequent development of blood and mesenchymal stem cell / progenitor cells. Our key research interest lies in identifying critical components of the hematopoietic and mesenchymal stem cell transcriptional network and their interactions with cell surface receptors and cell signaling pathways. Our goal is to determine how the disruption of the normal gene regulatory circuitry contributes to the pathogenesis of blood stem cell disorders such as leukemia and the myelodysplastic syndromes. Our long-term goal is to use this knowledge to identify and/or design better therapeutics.

Stem Cell Student Projects

Investigating the origins of pericytes and endothelial cells from a novel endogenous cardiac stem cell population during the heart development

Supervision: Dr. Vashe Chandrakanthan (v.chandrakanthan@unsw.edu.au, 02 9385 2527) &
Dr John Pimanda (jpimanda@unsw.edu.au, 02 9385 1003)

Suitable for: Honours

Project outline:

Most adult organs contain multipotent stem or progenitor cells. However, the origins of stem cells and their descendants remain largely unexplored. We helped identify a population of adult cardiac-resident stem cells that occupy a peri-vascular and adventitial niche that show broad trans-germlayer potency *in vitro* and *in vivo*. Using genetic lineage tracing techniques, these stem cells were shown to develop from the pro-epicardial region of the heart (see reference). In this project, you will investigate decedents of these stem cells and their contribution to the formation and stabilisation of the coronary vasculature in developing mouse embryos. Successful completion of this honours project could form the foundation for a future PhD thesis.

Reference:

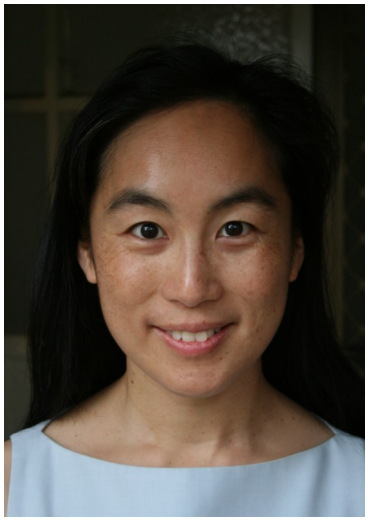
1. Chandrakanthan V*,Chong JJ*, Xaymardan M*, Asli1 N, Li J, Heffernan C, Menon MK, Ahmed I, Scarlett CJ, Rashidianfar A, Biben C, Zoellner H, Colvin EK, Pimanda JE, Biankin AV, Zhou B, Pu WJ, Prall OJ, Richard P. Harvey. Adult Cardiac-Resident MSC-like Stem Cells with A Proepicardial origin. Cell Stem Cell 2011 ;9(6):527-40. (*These authors contributed equally to this work).

Dr Vashe Chandrakanthan

Coagulation in Cancer Group

Team leader: Dr Vivien Chen

Thrombosis is the most common cause of death in the Western world as a result of stroke, myocardial infarction and venous thromboembolism. Our group is interested in the mechanisms of clot formation, the biology of platelets and coagulation proteins and how manipulation of these can be used to influence disease. We use real time intravital fluorescent microscopy to investigate the processes of platelet accumulation and coagulation initiation in the mouse circulation. Our particular focuses are on platelet apoptosis and aging, microparticles and the interaction between the tumour environment and the coagulation system. Our goal is to understand the processes that promote abnormal thrombosis, thus to be able to predict, prevent and treat thrombosis in clinical syndromes.



Dr Vivien Chen

Coagulation in Cancer Student Projects

Mechanism of thromboembolism in cancer

Supervision: Dr. Vivien Chen (vivien.chen@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

We aim to understand the biology of cancer related thrombosis. This project will focus on the effect of cancer and of chemotherapy on circulating factors that enhance the coagulation system leading to thromboembolism. The project will use intravital fluorescence microscopy to visualise the interactions between cancer proteins, white blood cells and the platelet thrombus in mouse models of cancer. Through understanding the pathogenesis of thrombosis, we aim to discover biomarkers that identify patients at high risk of thrombosis, thus allowing us to target patients who maximally benefit from intervention.

Clear cell ovarian cancers have a particularly high rate of thrombosis compared with other types of ovarian cancer indicating the thrombogenic biology of this subtype is distinctive. Based on the biomarkers are being elucidated in our mouse models of thrombosis in cancer, this project will investigate a cohort of clear cell and non clear cell ovarian cancer patients known to have cancer related thrombosis, to determine if plasma based tests at diagnosis can be used to identify high risk patients.

Platelet age and thrombosis

Supervision: Dr. Vivien Chen (vivien.chen@unsw.edu.au) &
Professor Miles Davenport, CVR

Suitable for: Honours Studies

Project outline:

Platelets need to be able to activate, adhere and aggregate to successfully plug off a hole in a bleeding vessel. When highly activated, platelets also provide a surface for the assembly of coagulation factors to generate a fibrin clot. Platelet age may affect functionality and different age platelets may play different roles in haemostasis. This project investigates the role of platelet aging and the implications for the haemostatic blood clotting system. It involves direct visualising of platelets of different ages in the platelet thrombus of the mouse microcirculation, flow cytometry and platelet function studies. These findings have implications for transfusion medicine and immune platelet diseases.

Sarcoma Research Group

Team leader: Associate Professor Jia-Lin Yang

Our group focuses on translational research on sarcoma and common epithelial cancers, in identifying genes that are important in cancer initiation, development and metastasis; evaluating significance of these genetic phenotypes in prediction of patient outcome and working as targets for cancer treatment; as well as enhancing sensitivity of cancers to radio-/chemo-therapy via regulating gene expression. We have the first world report on using a calcium channel blocker to treat the special colon cancer cells with DNA mismatch repair deficiency, as well as on the treatment of cancer cells by the combination therapy of EGFR inhibitor and interferon-alpha. All these studies will have an important clinical impact on diagnosis and treatment of cancers.

Associate Professor
Jia-Lin Yang

Sarcoma Research Student Projects

Investigation of Mir34 and its promoter in a panel of cancer cell lines and tissue samples

Supervision: A/Prof. Jia-Lin Yang (j.yang@unsw.edu.au; 02 9385 9390) &
Dr. Luke Hesson (l.hesson@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

From our published literature review (see reference), we knew that MiR34 is an important p53 downstream tumour suppressor. It was reported to be dysregulated in cancers and restoration of MiR34 will have a therapeutic significance to particularly p53 mutant cancers. This study will measure MiR34 promoter epigenetic change, as well as MiR34 mutation or deletion in a panel of cancer cell lines. Further study will focus on MiR34 restoration in its dysregulated cell lines and their sensitivity to targeted therapy, chemotherapy and/or radiotherapy.

Reference: Wong M, Yu Y, Walsh WR, Yang JL. MicroRNA-34 family and treatment of cancers with mutant or wild-type p53 (Review). Int J Oncol 38: 1189-1195, 2011.

BIOSTATISTICAL GENOMICS GROUP

Team leader: Professor Susan Wilson

What are the major factors underpinning complex genetic diseases like cancer, diabetes, or Crohn's disease? To answer this question new biostatistical tools are needed, including software for mining the human genome with interactions between the genome and environment being incorporated. The focus of the Biostatistics Group is development and evaluation of statistical methods and software tools for analysis of complex genomic disease data. Application of these methods and tools will form the basis of a superior understanding of the overall process leading to disease and hence better predictions with important ramifications for new treatments and health care planning.

The fundamental focus of our research program is development and evaluation of statistical and computational methods and software tools for analysis of complex genomic, epigenomic, transcriptomic and proteomic disease data. Application of these methods and tools will form the basis of a superior understanding of the overall process leading to disease, and hence better predictions with important ramifications for new treatments and health care planning.

Projects are available for suitable PhD students in the area of development and application of novel statistical approaches to analysis of complex genomic data. Projects are tailored to the background and abilities of the individual student.

For information, contact sue.wilson@unsw.edu.au

Other
Adult Cancer
Program Groups
not offering projects in 2013

Cancer Aetiology and Prevention Group

Team leader: Associate Professor Claire Vajdic

The Cancer Aetiology and Prevention Group (CAPG) aims to better understand the causes of cancer and factors that influence outcomes after cancer diagnosis. The CAPG employs classical and innovative cancer epidemiological methods and includes large-scale studies of cancer incidence, survival and risk factors in people with immune dysfunction. It also includes studies of two complex, common and poorly understood cancers, lymphoid malignancies and cancer of unknown primary origin. The studies involve national and international collaborations that integrate cancer epidemiology with biostatistics, biological sciences, pharmacoepidemiology and health services research. The research program builds an evidence base for preventative strategies that will reduce the burden of cancer.

Colorectal Cancer Group

Team leader: Dr Luke Hesson

Colorectal cancer (bowel cancer) is the second most common cancer in Australia, as well as the most common cause of death from cancer in this country. For the past 19 years, Prof Robyn Ward has led this multidisciplinary group of laboratory scientists, oncologists and pathologists, known as the Molecular and Cellular Oncology group (MCO). The goal of the group has been to better understand the genetic and epigenetic mechanisms that drive the development of colorectal cancer, and to translate that new understanding into ways of improving outcomes for people with cancer.

In the past few years, under the leadership of Dr Luke Hesson, the group has focussed much of its efforts on the precursor lesions of bowel cancer, and in particular a distinctive subtype known as laterally spreading tumours (LSTs). Understanding these earliest stages of tumour development will be important in both the early detection of colorectal cancer, and ultimately its prevention.

Medical Epigenetics Group

Team leader: Dr Megan Hitchins

This group focuses on unusual “epigenetic” mechanisms that predispose to young-onset cancer. Most familial cancers occur due to the inheritance of a mutation within the genetic code of a cancer-protection gene. Some patients are mutation-negative, but instead, their gene has been switched off by the accumulation of a repressive chemical at the start of the gene, namely methylation. Termed an “epimutation” this cancer-causing mechanism shows unusual patterns of inheritance. In addition, mutations in front of the gene can similarly attract methylation. The aim of this group are to determine the role and inheritance of various types of epimutation in cancer.

Ovarian Cancer Group

Team leader: Professor Neville Hacker AM

Ovarian cancer is the gynaecological malignancy with the highest mortality world-wide. 75% of patients get diagnosed in advanced stage disease as symptoms are rare to detect this cancer at an early stage. Our research focus is on the detection of ovarian cancer at an early stage using blood-based molecular markers on to therefore identify more effective methods of early diagnosis. Our group has numerous national and international collaborations, particularly in Russia, USA and Switzerland.

Whilst our research focus is on ovarian cancer biomarkers, we are also conducting research into other gynaecological cancers, particularly ovarian/uterine carcinosarcomas (MMMT), squamous cell carcinomas of the cervix and vulval melanomas.

CENTRE FOR VASCULAR RESEARCH

The Centre for Vascular Research (CVR) has an outstanding reputation internationally as a centre for excellence in vascular biology.

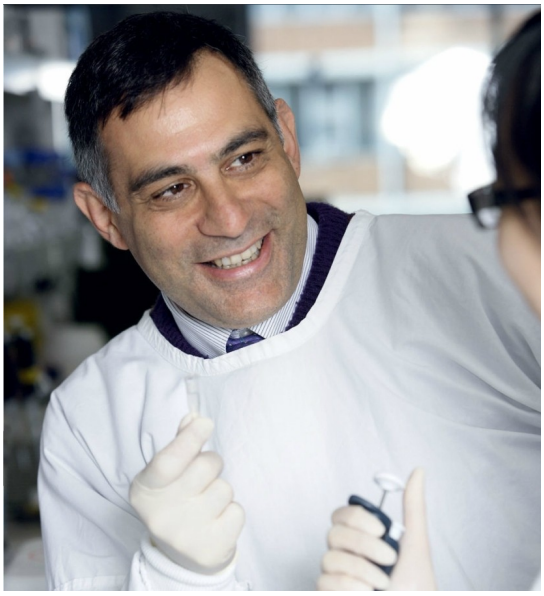
One of Australia's leading biomedical research centres. CVR is a multidisciplinary group with wide-ranging research interests in the expanding field of vascular biology spanning investigations of the causes and treatment of cancer, angiogenesis and new blood vessel formation, macrophage biology, platelet and megakaryocyte biology, complex systems biology, cell membrane biology, cardiovascular genetics, vascular redox processes, transcription and gene targeting.

CVR's mission is to better understand fundamental mechanisms in the cell and molecular biology of the vascular system, and the pathogenesis of vascular disease, and to develop new treatments to combat vascular disorders where unmet needs exist.

CVR comprises over 120 research personnel, led by 11 independent group leaders and 3 laboratory leaders. The majority of research within CVR is conducted in the Lowy Cancer Research Centre. CVR also has vibrant collaborative links with its 4 nodes in locations outside UNSW, including the University of Sydney (NSW), Australian National University (ACT), Monash University (Victoria) and La Trobe University (Victoria).

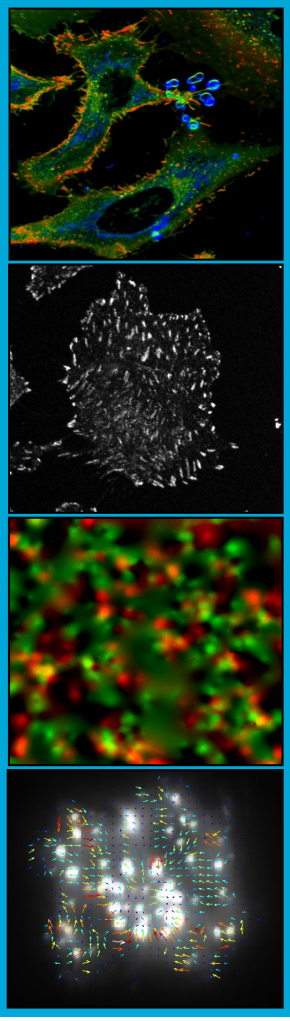
Postgraduate students are key to the success of CVR. In addition to strong supervision, CVR offers scholarship top ups to those with APA or equivalent scholarships, and for those without scholarships, stipends are offered on a case-by-case basis. If you're considering an Hons, Masters or PhD project, and are looking for a dynamic research environment at the cutting edge, please do not hesitate to contact us.

Professor Levon Khachigian
Director
Centre for Vascular Research
http://www.cvr.net.au



Cellular Membrane Biology Group

Professor Katharina Gaus



Group leader: Professor Katharina Gaus

Our research aims to understand how signalling processes in mammalian cells are organised in time and space. This is important for many fundamental cellular processes such as T cell activation and cell migration that become deregulated in disease. We have developed unique fluorescence microscopy imaging techniques that have made the Biomedical Imaging Facility (BMIF) a world-leading facility. Our imaging tools range from live cell imaging to super-resolution and single molecule imaging. We are looking for motivated students to join our interdisciplinary team that ranges from cellular immunology and biology to molecular biology, biophotonics, surface chemistry and quantitative image analysis.

Cellular Membrane Biology Student Projects

Fluorescent proteins for super-resolution microscopy

In 2008, the prestigious journal *Nature Methods* named super-resolution fluorescence microscopy Method of the Year. In the same year, Roger Tsien received the Nobel Prize in Chemistry for the identification and development of green fluorescent protein, GFP. This project combines the two with the aim to test and establish new fluorescent proteins for super-resolution fluorescent microscope.

2-colour super-resolution imaging to characterise T cell signalling vesicles

We have recently discovered signalling vesicles in T cells (Williamson et al. *Nature Immunology* 2011) and wish to characterise them further to have they function in T cell activation. The vesicles are ~100 nm in diameter and can therefore not be accurately imaged with conventional fluorescence microscopy approach. This project aims to establish 2-colour super-resolution microscopy using stimulated emission depletion (STED) and apply this approach to T cells.

Why do fat cells not walk: live cell imaging of migrating T cells

It is known that obese patients often have a compromised immune system because of the deregulation in T cell activation responses. We have recently observed that cholesterol-loaded T cells migrated poorly and T cells enriched in an oxysterol completely fail to migrate. Using live cell imaging, this project aims to elucidate why sterol-modified T cells have impaired chemotaxis. The project also involves biochemical assays (Western blotting, FACS) to measure expression levels of chemokine receptors and other proteins.

Curvature-dependent membrane organisation

One fundamental aspect in cell biology is how proteins know where to go inside the cell. Membrane targeting sequences of proteins are well characterised but even within a membrane, proteins are not homogenously distributed. The project examines whether specific proteins are targeted to areas of high membrane curvature such as membrane invaginations or protrusions. For this, fluorescent beads are immobilised on a glass coverslip and artificial and cell membranes 'plated' on top. Quantitative microscopy will be used to assess lipid and protein re-organisation.

There are opportunities for Honours and PhD students in this program of research.

Scholarships are available.

Contact: k.gaus@unsw.edu.au

Molecular Machines Group

Team leader: Dr Till Böcking

Molecular chaperones are molecular motors that drive a variety of intracellular assembly and disassembly processes to catalyse protein folding, prevent aggregation and facilitate the recycling of the components of macromolecular complexes. These functions are vital to cellular homeostasis and chaperone malfunction underlies a range of cardiovascular diseases, neurodegenerative disorders and cancers. However, the molecular mechanisms of these processes and how they can be targeted pharmacologically are not well understood.

Our research focuses on elucidating how molecular chaperones mediate fundamental cellular processes using cutting-edge microscopy in conjunction with cell biological and biochemical approaches. We have recently demonstrated a fluorescence imaging approach to record movies of these ATP-driven molecular motors as they carry out their diverse tasks (Nature Structural and Molecular Biology 2011, vol. 18, pp. 295-301). Importantly, we can observe the dynamics of the processes at the single-molecule level. In this way we can observe transient intermediates that are invisible with traditional techniques. The Molecular Machines Group is an interdisciplinary team of biologists, chemists and physicists with extensive expertise in single-molecule and live cell imaging and access to a suite of state-of-the-art microscopes in the Biomedical Imaging Facility.

There are opportunities for Honours and PhD students in this program of research.

Contact: till.boecking@unsw.edu.au

Dr Till Böcking

Complex Systems in Biology Group

Professor Miles Davenport

Group leader: Professor Miles Davenport

Although many acute infectious diseases are now effectively controlled by vaccination, we currently lack vaccines for many chronic infectious agents. These infections are of particular importance in the developing world, where hundreds of millions of people each year are affected by chronic infections such as HIV, tuberculosis and malaria. The Complex Systems in Biology group aims to understand the basic dynamics and pathogenesis of these infections, how the immune system interacts with them, and ultimately how we can control them. To achieve this we apply computational and mathematical approaches to understanding and predicting the complex interactions between host and pathogen. These interactions range from the molecular level (how immune molecules such as the T cell receptor interact with viral molecules), through to the dynamics of infection within individual hosts, and finally to the level of the host and pathogen population. The group brings together medical biologists, bioinformaticians, physicists, mathematicians, engineers and computer scientists to tackle these fundamental questions. The laboratory has a wide range of collaborations with experimentalists working in different areas of infection and immunity. The group's key research areas are:

- HIV infection and immunity
- The role of the T cell receptor repertoire in immune responses
- Dynamics of infection and immunity
- Malaria immunity and pathogenesis

There are opportunities for PhD students with a strong background in mathematics, physics, bioinformatics or another quantitative discipline in this program of research.

Contact: m.davenport@unsw.edu.au

COMPUTATIONAL BIOLOGY GROUP

Team leader: Dr Vanessa Venturi

The health, social, and economic impact of infectious diseases on the Australian and global populations is enormous. A major obstacle to the development of treatments for and vaccines against some infections is our limited understanding of the immune responses to these infections. Our research aims to better understand the complexities of the recognition and control of infectious diseases by the immune system using computational biology approaches. Advances in technology over the past decade enable more in-depth studies of biological systems through the generation of an enormous volume of experimental data, the analysis and interpretation of which requires a computational biology approach. Thus, there is a growing need for computational biology in immunological and virological studies.

One of our main research interests is the T cell receptor repertoire. Cytotoxic T cells play an important role in immune responses to infection by recognising pathogen peptides presented at the surface of infected cells and killing pathogen-infected cells. Effective T cell recognition and immune control of infection depends upon the availability of a diverse and well-balanced repertoire of T cell receptors. Our research involves the application of innovative bioinformatics/computational approaches to the analysis and interpretation of T cell receptor sequence data obtained by experimental collaborators using either traditional and/or next generation sequencing techniques. We are particularly interested in studying the factors that shape the T cell repertoire, the role of the T cell repertoire in the recognition and control of infection, and the evolution of the T cell repertoire with age and during persistent infection.

There are opportunities for PhD students in this program of research.

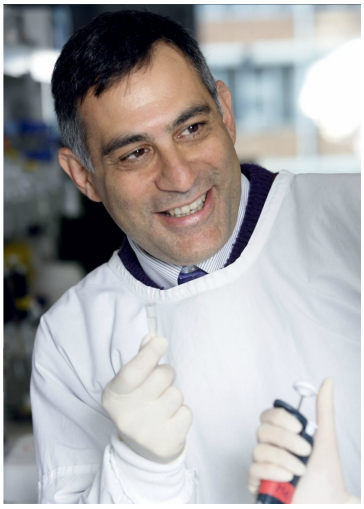
Contact: v.venturi@unsw.edu.au

Dr Vanessa Venturi

TRANSCRIPTION AND GENE TARGETING GROUP

Group leader: Professor Levon Khachigian

Cardiovascular disease and cancer remain the most prevalent causes of morbidity and mortality. The pathogenesis of these and a myriad of related diseases is underpinned by molecular and cellular changes in our blood vessels. Our research is uncovering key networks of transcriptional control and inducible gene-regulatory circuits that lead to vascular disease. The group is also developing new experimental drugs that have the potential to treat a diverse range of health problems, from cancer and inflammation through to eye and heart disease.



Professor Levon Khachigian

This involves strategic collaborations with a range of clinical specialists, academics and drug development consultants. Novel drugs developed in the Khachigian lab are currently undergoing clinical trials in cancer patients in Sydney. The lab provides an exemplary environment of bench-to-bedside "translational" research.

Projects in the Khachigian laboratory are available in 2 general areas:

- To better understand how harmful genes are controlled in vascular cells. This arm investigates signalling and transcriptional mechanisms of pro-inflammatory cytokine-dependent gene expression, post-translational mechanisms that modify protein behaviour, proteinase control, the isolation and characterisation of new genes induced or repressed by vascular cell injury, and the molecular control of vascular cell migration and proliferation. The group has considerable expertise in animal models of neointima formation, angiogenesis, tumour growth, myocardial ischemia, and inflammation
- To develop new vascular therapeutic agents. The lab is harnessing the outcomes of its fundamental research by pioneering the development of novel "anti-gene-", "gene-therapeutic" and small molecule pharmacological strategies targeting key regulatory genes in a myriad of vascular disorders. For example, the Khachigian laboratory has developed DNA-based drugs targeting c-Jun as potent, and safe, inhibitors of skin cancer (*Science Translational Medicine* 2012;4(139):139ra82), which are now under evaluation in clinical trials in cancer patients

Transcription and Gene Targeting Student Projects

Greater understanding of signalling and transcriptional mechanisms underlying proliferative vascular disease

Supervision: Prof Levon Khachigian &
Drs Jianmei Li, Estella Sanchez-Guerrero, Fernando Santiago

Suitable for: Honours or PhD Studies

Project outline:

Smooth muscle cell (SMC) hyperplasia is the underlying cause of proliferative vascular conditions such as restenosis and bypass graft failure. The roles played by transcription factors in these repair processes are only partly defined. Transcription factors are important molecular conduits that integrate acute changes in the vascular environment with changes in gene expression and thickening of the blood vessel wall. Our laboratory has targeted key transcription factors to control SMC proliferation in new interventional strategies in vascular disease. This project will provide new mechanistic insight on the roles played by key transcriptional players and pathways in the reparative response to vascular injury. Examples include Egr-1, c-Fos, RZR-alpha, YY1 and c-Jun. Recent publications in this area include Malabanan.. Khachigian *Am J Pathol* 2012;180:2590-7, Zhang.. Khachigian *Am J Physiol Cell Physiol* 2012;302:C1590-8; Sanchez-Guerrero.. Khachigian *PLoS ONE* 2012;7(7):e39811.

Transcription and Gene Targeting Student Projects *cont'd*

Novel immune mechanisms mediating the antitumor activity of DNAzymes

Supervision: Prof Levon Khachigian &
Prof Gary Halliday (USyd)

Suitable for: Honours or PhD Studies

First-in-human clinical trials of DNA-based drugs, called DNAzymes, have recently been completed in cancer patients in Sydney. We have been developing DNAzymes as a novel class of therapeutic agent. Underpinning these trials, we found that Dz13 inhibited tumour growth in both immunodeficient and immunocompetent syngeneic mice and reduced lung nodule formation in a model of metastasis (Cai.. Khachigian *Science Translational Medicine* 2012;4(139):139ra82). Interestingly we also found that the capacity of DNAzymes to cause regression of tumour growth is blocked by antibodies to T-lymphocytes. This project aims to better understand the process whereby DNAzyme activates adaptive immunity to cause tumour decay. It will involve a range of techniques in immunology, cancer and vascular biology. These studies will be performed alongside a new larger clinical trial of DNAzymes in cancer patients.

Development of small molecule inhibitors of AP-1 as novel treatments for vascular disease: angiogenesis, inflammation, restenosis, heart attack

Supervision: Prof Levon Khachigian &
Drs Lionel Lourenco-Dias, Lucinda McRobb, Mei-Chun Yeh

Suitable for: Honours or PhD Studies

We have recently developed a series of small molecule inhibitors of a range of immediate-early genes through a large systematic screen of >100,000 compounds. These will be tested in a variety of *in vitro* and *in vivo* models of human vascular disease, including cancer, atherosclerosis, post-angioplasty restenosis and rheumatoid arthritis. Eventually these inhibitors will be used as novel therapeutics in patients. This project will provide invaluable experience in cutting-edge molecular and cellular techniques, and exposure to a range of animal models in cardiovascular biology and cancer, together with associated imaging and diagnostic techniques.

***PhD scholarships, and top ups to those already with APAs are available.**

Please send your CV to L.Khachigian@unsw.edu.au as soon as possible

Molecular Signalling Group

Group leader: Mary Kavurma

The Molecular Signalling Group are uncovering new pathways leading to diabetes, atherosclerosis and cardiovascular disease. Our studies will lead to better strategies in designing new therapies for incapacitating and life-threatening vascular disorders

Molecular Signalling Student Projects

TRAIL in advanced cardiovascular disease and related disorders

Supervision: Dr Mary Kavurma (m.kavurma@unsw.edu.au)

Suitable for: PhD Studies

Project outline:

TRAIL (Tumour necrosis factor-related apoptosis-inducing ligand) was first discovered as a molecule that selectively controls apoptosis of cancer cells. My lab has identified a new function for TRAIL that mediates abnormal vascular smooth muscle cell (VSMC) growth leading to arterial thickening and cardiovascular disease (CVD). In addition my lab has recently identified a role for TRAIL in the development of diabetes. The role of TRAIL as an apoptosis-inducing or growth-regulatory factor, or its importance in CVD and related pathologies is unclear.

Dr Mary Kavurma

There are a number of projects, suitable for PhD studies, available in the lab:

- The transcriptional regulation of TRAIL and TRAIL receptors (e.g. DcR1 and OPG)
- Role of diabetes in TRAIL-deficient animal model
- Role of TRAIL in metabolic syndrome, including obesity
- Role of TRAIL in CVD progression and regression
- Role of TRAIL in neovascularisation

Using multiple TRAIL deficient animals, we can provide new insight into how proliferation and other important processes related to growth function (e.g. death) are regulated by TRAIL and its receptors. Understanding these pathways has promising potential to lead to novel approaches for the prevention and/or treatment of diabetes, CVD and related pathologies.

Redox Cell Signalling Group

Group leader: Dr Shane Thomas

The Redox Cell Signalling Group has two primary areas of interest:

- Understanding the molecular mechanisms by which oxidative stress causes cardiovascular disease
- Investigating an enzyme important in controlling the immune system during cancer

Redox Signalling Student Projects

Oxidative stress and cardiovascular disease

Supervision: Dr Shane Thomas (shane.thomas@unsw.edu.au, 02 9385 2582) & Dr Martin Rees (m.rees@unsw.edu.au, 02 9385 1478)

Suitable for: Honours or PhD Studies

Project outline:

In cardiovascular disease, endothelial cells, which form the barrier between the flowing blood and the artery wall, become "dysfunctional". Endothelial dysfunction can increase the risk of heart attack and stroke for a cardiovascular disease patient. Growing evidence indicates that a protein that the immune system normally uses to destroy infectious microbes can cause such endothelial dysfunction. This protein, called myeloperoxidase (MPO), accumulates in the diseased arteries of cardiovascular disease patients, just below the endothelial cell layer where it promotes oxidative stress. We are studying how the oxidative stress reactions catalysed by MPO cause endothelial dysfunction, hypertension and cardiac fibrosis. We are also working towards the discovery of novel drugs capable of preventing the deleterious actions of MPO during cardiovascular disease, leading to improved vascular function. The general techniques involved include tissue culture, biochemistry/molecular biology, microscopy and cardiovascular physiology.

Immune control and cancer

Supervision: Dr Shane Thomas (shane.thomas@unsw.edu.au, 02 9385 2582)

Suitable for: Honours or PhD Studies

Project outline:

A protein called indoleamine 2,3-dioxygenase (IDO) is important in controlling the immune system under normal and disease conditions, including cancer, inflammation, infectious disease and autoimmunity. This protein acts to suppress the immune system and during cancer is employed by certain tumour cells to protect them against the patient's immune system. Our studies focus on under-standing how the expression and activity of this protein is controlled in human immune and cancer cells and in the discovery and testing of potent, small molecule inhibitors of IDO that have the potential as a new class of immunotherapeutic, anti-cancer drugs. The general techniques involved include tissue culture, protein biochemistry, molecular biology, immunology and pharmacology.

Dr Shane Thomas

CHILDREN'S CANCER INSTITUTE AUSTRALIA

CHILDREN'S CANCER INSTITUTE AUSTRALIA

Children's Cancer Institute Australia's (CCIA) vision is to save the life of *every* child with cancer and eliminate their suffering through world-class medical research. Established in May 1976 by a dedicated group of doctors and parents of children with cancer, CCIA is Australia's only independent medical research institute totally dedicated to childhood cancer and this organisation is at the forefront of global medical research efforts that have seen survival rates for childhood cancer improve to over 70%.

Seven out of ten is not good enough for us at CCIA or for the families of children with cancer. The sole focus of the research team at CCIA is to improve outcomes for children with cancer through outstanding medical research. The Institute has established an international reputation for driving new research knowledge generated in the laboratory through to the clinic.

At CCIA, our people are our greatest asset and we are strongly committed to encouraging and fostering the next generation of research leaders through our research students. We are committed to providing a work environment and culture conducive to productivity and creativity and ensuring the development of our students.

Student opportunities at CCIA are listed in the following pages, if you are interested in exploring these further please get in touch with the listed supervisor or our Careers and Strategy Officer, Dr Amanda Philp (education@ccia.unsw.edu.au).

Professor Michelle Haber AM
Executive Director
Children's Cancer Institute Australia

Student Support at CCIA

Our students bring great energy and enthusiasm, providing fresh ideas and perspectives to tackle the complex challenges faced in childhood cancer research today. As a student, you will be guided and mentored by a dynamic team of world class researchers who have strong collaborative links with research and clinical teams throughout the world. In addition to this you will have access to a comprehensive professional development program run by a dedicated team focussed on career development at CCIA, state-of-the-art equipment and facilities, professional support staff, access to a full range of laboratory services and opportunities for overseas travel to present at conferences and work with collaborators and the support of your peers through the CCIA Student Association that runs activities throughout the year, including an annual student retreat.

CCIA Postgraduate Supplementary Award

CCIA offers a Supplementary Award of $6000 per annum for up to 3 years to students who have been awarded a competitive scholarship. This will be awarded to students where the scholarship is equivalent to an Australian Postgraduate Award or University Postgraduate Award.

CCIA Postgraduate Excellence Award

These tax-free, competitive awards will be offered to a value of up to $10,000 AUD per annum and are offered to students demonstrating exceptionally high potential who have succeeded in attracting a primary competitive scholarship such as an APA. This Excellence Award is in addition to the $6000 top-up supplementary award.

CCIA Honours Scholarship

We offer 2 honours year scholarships of $5,000 tax free annually. Selection is based on academic achievement throughout the undergraduate degree, interest in cancer research, personal qualities, as well as other evidence as may be deemed relevant to future success in the area of biomedical research. Scholarships are awarded for one year and are not deferrable. Applications for honours year scholarships will be open in June each year and close in early-November.

CCIA Summer Studentships

These scholarships are provided to outstanding undergraduate science students during the summer university break. Summer scholarships are a great way for students to get involved in real-life cancer research.

For further information and application forms for our Honours Scholarships and the Summer Student Program please visit the student pages on our website at www.ccia.org.au or contact Dr Amanda Philp, Careers and Strategy Officer education@ccia.unsw.edu.au

Cancer Cell Development Group

Group leader: Dr Karen MacKenzie

Our research is focused on understanding how normal cells evolve into cancer cells. This knowledge is essential for the development of more effective, less toxic anticancer drugs. In particular, we are investigating the defects that promote continued cell replication of malignant cells. The unlimited replicative ability (immortality) of malignant cells is a fundamental property of most, if not all, advanced stage childhood cancers and leukaemias. In contrast, most normal cells undergo a strictly programmed number of cell divisions. We aim not only to define how the mechanisms that program cell replication become defective, but also to demonstrate the best approach to restore these programs in cancer cells.

Dr Karen MacKenzie

OBJECTIVES

- To characterise the mechanisms that promote the unlimited replication (immortality) of cancer
- To identify means of restoring programs that regulate cell replication in malignant cells
- To determine whether therapeutic approaches that target the pathways that promote immortality will be detrimental to normal blood cells

Cancer Cell Development Student Projects

Discovering drugs that halt the replication of immortal cancer cells

Supervision: Dr Karen MacKenzie (k.mackenzie@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

One characteristic that is common to most, if not all, cancers is that they are immortal. While cancer cells are capable of unlimited replication, the replication of normal cells is programmed and strictly limited. Thus drugs that specifically target the biochemical pathways that promote immortalisation are expected to halt the replication of cancer cells without effecting normal cells and healthy organs. The Cancer Cell Development Group have confirmed the therapeutic potential of targeting immortalisation pathways by showing that silencing genes that are involved in this process inhibit the replication of pre-malignant and tumour-derived cells, but has no effect on normal cells. These results provide a very sound precedent for conducting experiments to identify a compound that will mimic the effects of silencing immortalising genes. This project will involve a high throughput screen of scores of thousands of clinically relevant compounds to identify compounds that will potently and specifically halt the replication of immortal cancer cells. The drug screening will be performed in the Drug Discovery Centre for Childhood Cancer at CCIA. Since immortality is a fundamental property of virtually all cancers, compounds identified in our screen will have therapeutic relevance to a broad-spectrum of childhood malignancies.

Cancer Cell Development Student Projects *cont'd*

Targeting telomerase components in premalignant and tumorigenic mesenchymal cells

Supervision: Dr Karen MacKenzie (k.mackenzie@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

Outcomes for cancer patients will be dramatically improved by new therapies that specifically target cancer cells, and are non-toxic to normal tissue. Toward this goal, it is essential to understand how the regulation and function of biochemical pathways involved in cancer development differ between malignant cells and their normal counterparts. Data recently generated in our laboratory show that depletion of certain telomerase components halts the replication of premalignant and tumour-forming cells, while having no apparent adverse effect on the survival or replication of normal cells. The central objective of ongoing experiments in our laboratory is to understand the mechanistic basis for the potent and specific effects of ablating telomerase components in normal and malignant cells. This project will make use of microarray gene expression data generated by our Group to investigate the expression and function of candidate genes that are regulated by siRNA-mediated depletion of telomerase components in normal, premalignant and tumorigenic cells. Once the gene expression changes are validated in this model, experiments will be undertaken to test the function of representative candidate genes by suppressing their expression The project is using an *in vitro* model of mesenchymal tumorigenesis developed and extensively characterised in our laboratory. Results from these investigations will provide insight into the mechanism by which the silencing specific components of the telomerase holoenzyme elicits potent and specific anti-proliferative effects on cancer cells. Ultimately this information may be applied in the development of therapeutics that specifically target cancer cells without causing toxicity to normal tissues.

Drug discovery for the treatment of bone marrow failure syndromes

Supervision: Dr Karen MacKenzie (k.mackenzie@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

Telomeres are chromosomal-end structures that function to protect against chromosomal erosion, fusion and recombination. Short, dysfunctional telomeres are causally involved in inherited bone marrow failure syndromes (BMFS) that are prone to karyotypic evolution and development of aggressive acute leukaemias and other malignancies. There is currently no effective pharmacologic treatment for these disorders and patient survival after transplantation is poor. Identification of compounds that bolster the activity of the telomere-maintenance enzyme, telomerase, will provide a vital treatment option for children with these syndromes, who will (almost certainly) otherwise succumb to the disease.

This project will be performed in collaboration with Dr Greg Arndt in the Drug Discovery Centre for Childhood Cancer. The project will involve the construction and testing of a plasmid-based vector that will be applied in a high throughput screen to identify lead compounds that bolster telomerase enzyme activity. Compounds identified in this screen will provide an urgently needed alternative for the treatment of children with BMFS and other degenerative conditions. These investigations will synergise with the collaborative efforts of the Kids Cancer Alliance, which will establish a national centre for diagnostic testing of telomere length and telomerase mutations in children (and adults) with haematologic disease.

Cancer Cell Development Student Projects *cont'd*

Modelling Ewing's Sarcoma for studies of molecular targeted therapeutics

Supervision: Dr Karen MacKenzie (k.mackenzie@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

Ewing's Sarcoma is an aggressive malignancy that arises in mesenchymal tissue and is distinguished by specific chromosomal translocations - most commonly fusions between the EWS gene and ETS family transcription factors. These malignancies are generally diagnosed in children and young adults between the ages of 10 and 24 years. They often present as metastatic disease requiring surgery in conjunction with multidrug chemotherapy and/or radiation. The long-term prognosis for patients with metastatic disease is poor, with survival rates currently less than 30%. New targeted therapies are urgently needed in order to improve treatment outcomes and mitigate the side effects that are often inflicted by the currently employed treatment regimes. In this project, a new model of Ewings Sarcoma will be established by overexpression of EWS-ETS fusion genes in human mesenchymal cells in conjunction with other genes known to contribute to the development of human sarcomas. The malignant properties of the transduced cells will be assayed in a series of *in vitro* and *in vivo* tests. The reagents that will be developed and characterised through these investigations will provide a platform for the discovery and pre-clinical testing of new targeted therapies that be applied to improve the treatment of young people diagnosed with these malignancies.

Halting the replication of immortal neuroblastoma cells

Supervision: Dr Karen MacKenzie (k.mackenzie@unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

The enzyme telomerase is expressed in 80-90% of cancers, including neuroblastoma, which is the most common extracranial solid tumour that affects children. Telomerase functions to maintain the integrity of chromosomal-end structures (telomeres) and is central to the immortalisation process, which is an essential step in carcinogenesis. Core components of the telomerase holoenzyme include a reverse transcriptase (TERT), an RNA component (TERC) that functions as a template for the synthesis of telomere repeats and the protein dyskerin, which binds and stabilises TERC. As cellular immortality is a fundamental property of cancer-initiating cells, the molecular mechanisms that are responsible for the activation of telomerase are ideal for targeted anti-cancer therapeutics. Hence the objective of this Student project will be to delineate mechanisms that are involved in the activation of telomerase in neuroblastoma cells. The results will provide insight to effective ways of targeting telomerase and reversing the immortal phenotype of neuroblastoma cells.

Experimental Therapeutics Program

Program Head: Professor Michelle Haber AM

Research in the Experimental Therapeutics Program is directed at identifying critical genes or proteins that contribute to the unregulated growth and malignant behaviour of cancer cells. By identifying these 'molecular targets', we can work towards developing new cancer therapies based on blocking or modifying the action of these molecules, either using existing anti-cancer drugs or by developing novel anti-cancer agents.

OBJECTIVES

- To understand the role of the MYCN oncogene and the related c-myc gene in regulating the behaviour of multidrug transporter genes in childhood and adult cancers
- To understand how the MRP1 and MRP 4 multidrug transporter genes are involved in mediating neuroblastoma development and progression
- To develop and optimise clinically relevant small-molecule inhibitors of the MYCN and c-myc oncogenes, and MRP 1 and MRP 4 genes
- To develop a safer more effective treatment for neuroblastoma, involving inhibition of the ODC1 gene by DFMO combined with modern combination chemotherapy
- To establish a new laboratory model of metastatic neuroblastoma to study genes that promote tumour spread and to identify new treatment approaches to block that spread

Professor Michelle Haber AM

Experimental Therapeutics Student Projects

The role of ABC transporters in adult cancers driven by the Myc Oncogene

Supervision: Dr Michelle Henderson (mhenderson@ccia.unsw.edu.au)
Prof Michelle Haber &
Prof Murray Norris

Suitable for: Honours or PhD Studies

Project outline:

Our research has previously shown that the levels of expression of three members of the ABCC/MRP family of transporters are strongly predictive of poor outcome in the childhood cancer neuroblastoma. The combined expression of these three genes represents possibly the strongest prognostic indicator yet discovered for this disease. We have shown that these genes appear to be controlled by Myc oncogene family members and, specifically in neuroblastoma, by the MYCN oncogene, amplification of which is a strong indicator of poor patient outcome. While c-Myc is known to be amplified and/or over-expressed in a number of adult cancers including those of the ovary, prostate, breast, colon and lung, as well as melanoma, the prognostic significance of c-Myc aberrations in these cancers is not well established. The relationship between c-Myc over-expression and expression of ABCC/MRP transporter genes is also unknown. The first aim of this project is to examine c-Myc and ABCC/MRP gene expression in these tumour types and to correlate the expression levels with clinical outcome. The second aim of the work will be to explore the function of these genes in adult tumours, utilising appropriate cell line and mouse models, with a view to identifying new therapeutic avenues.

Experimental Therapeutics Student Projects *Cont'd*

Dr Jamie Fletcher

Genes underlying bone marrow metastasis in neuroblastoma

Supervision: Dr Jamie Fletcher (jfletcher@ccia.unsw.edu.au) &
Prof Michelle Haber (mhaber@ccia.unsw.edu.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

The overwhelming majority of tumour-related deaths are attributable to metastases. Different tumour types infiltrate and colonise different organs, however little is currently known about the genes underlying these abilities.

The paediatric tumour neuroblastoma arises in the sympathetic nervous system and frequently metastasises to the bone and bone marrow. In mouse models, xenografted human neuroblastoma cells also grow in these sites. Re-isolation of tumour cells from mouse bone marrow can enrich for cells with enhanced ability to grow at this site. These cells often grow more aggressively in bone marrow upon xenografting into secondary recipients. Comparative gene expression analysis of these populations can identify candidate genes governing enhanced ability to grow in bone marrow. These genes are potential therapeutic targets for patients with metastatic disease.

Aims:

- Produce tumour cell populations with enhanced ability to colonise bone marrow using vivo selection
- Identify candidate genes contributing to efficient bone marrow colonisation
- Validate these genes using databases, mouse models and cell culture systems

Techniques: Human neuroblastoma cell xenografts in immunodeficient mice, cell culture, whole-genome expression analysis, real-time PCR analysis and other *in vitro* techniques

Characterisation and inhibition of tumour-stroma interaction in neuroblastoma

Supervision: Dr Jamie Fletcher (jfletcher@ccia.unsw.edu.au) &
Prof Michelle Haber (mhaber@ccia.unsw.edu.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

Children with the solid tumour neuroblastoma often have metastatic disease in the bone and bone marrow that is resistant to chemotherapy. The bone marrow microenvironment is likely to play an important role in drug insensitivity and subsequent relapse and these interactions are an attractive target for therapeutic intervention.

Paracrine loops established between stromal and tumour cells are recognised to contribute to proliferation and drug resistance in tumours, and similar loops have recently been demonstrated for neuroblastoma. Molecular analysis of tumour and stromal cells as both mono- and co-cultures can facilitate the characterisation of these interactions. Furthermore, high throughput screening can be used to identify small molecule inhibitors to disrupt these interactions or to target weaknesses arising from them.

Aims:

- To characterise the interaction between bone marrow stromal cells and neuroblastoma cells using gene expression analysis and other molecular profiling techniques
- To identify small molecule inhibitors of the tumour-stroma interaction using recently developed bioluminescence based high-throughput screening techniques

Techniques: Cell culture, bioluminescence assays, whole-genome expression analysis, high-throughput small molecule inhibitor screening and real-time PCR analysis.

Experimental Therapeutics Student Projects *cont'd*

Identification and development of MRP4 inhibitors

Supervision: Dr Jamie Fletcher (jfletcher@ccia.unsw.edu.au) &
Dr Michelle Henderson (MHenderson@ccia.org.au)

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline:

The multidrug transporter, MRP4 (ABCC4) is a potential therapeutic target in neuroblastoma as:

- MRP4 knockdown inhibits neuroblastoma cell growth *in vitro*
- MRP4 is expressed at high levels in poor-outcome neuroblastoma and effluxes drugs currently used in neuroblastoma therapy
- MRP4 deficiency increases the bioavailability of its substrate drugs

Aims

- To characterise novel MRP4 inhibitors in cell culture and mouse neuroblastoma models
- To understand the role of MRP4 in neuroblastoma cell proliferation

Techniques: Cell culture, xenograft and genetic mouse neuroblastoma models, high-throughput small molecule inhibitor screening, real-time PCR analysis and other *in vitro* techniques.

Dr Michelle Henderson

ABC transporters and cholesterol homeostasis: potential therapeutic targets in ovarian cancer

Supervision: Dr Michelle Henderson (MHenderson@ccia.org.au)

Suitable for: ILP, Masters, Honours or PhD Studies

Project outline:

With five-year survival rates below 30% for women with advanced disease, epithelial ovarian cancer is one of the most deadly malignancies and survival rates have not improved over recent decades. A better understanding of the factors contributing to malignancy will facilitate more informed treatment decisions and ultimately highlight new therapeutic avenues. We have found a strong association between clinical outcome and expression of ATP-binding cassette (ABC) transporter genes of the ABCA sub-family, which have functions in lipid biosynthesis, trafficking and homeostasis. In light of the importance of cholesterol, bioactive lipids and the inflammatory microenvironment in several cancers, this is an important area for further investigation. This project will test the hypothesis that ABCA transporter proteins contribute to the malignant phenotype of ovarian cancer cells.

Aims

- Determine the effect of ABCA transporter modulation on cell proliferation, migration or drug response in ovarian cancer cells
- Examine the contribution of ABCA transporters to tumour-stromal cell interactions in ovarian cancer
- Identify the transported substrates which influence the malignant phenotype of ovarian cancer

The proposed studies will determine how these transporters contribute to highly malignant ovarian cancer. Identification of their precise roles would highlight potential interventions for improved treatment.

Histone Modification Group

Group Leader: Dr Tao Liu

Research in the Histone Modification Group focuses on the interplay among Myc oncoproteins, histone deacetylases (HDACs) and histone demethylases during tumour initiation and progression, the mechanism through which histone deacetylases and histone demethylases result in transcriptional repression of tumour suppressor genes, and the anticancer efficacy of histone deacetylase inhibitors and histone demethylase inhibitors.

Dr Tao Liu

OBJECTIVES

- To investigate the role of the interplay among Myc oncoproteins, HDACs and histone demethylases in modulating gene transcription, the initiation and progression of neuroblastoma in children and pancreatic cancer in adults
- To determine the anticancer efficacy of novel inhibitors of the class III histone deacetylase SIRT1 against neuroblastoma
- To determine the role of histone demethylases in Myc-induced transcriptional modulation and tumourigenesis and the role of histone demethylase inhibitors in cancer therapy

Histone Modification Group Student Projects

Histone demethylases and histone methyltransferases in modulating gene transcription, tumour initiation, progression and metastasis

Supervision: Dr Tao Liu (TLiu@ccia.org.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

One of the most important advances in cancer research in the last 5 years is the identification of histone demethylases and histone methyltransferases as critical players in gene transcription, tumour initiation, progression and metastasis. In collaboration with researchers at University of North Carolina, Baylor College of Medicine (USA) and Nagoya City University (Japan), we are investigating histone demethylases and histone methyltransferases in modulating gene transcription, tumour initiation, progression and metastasis, as well as examining the use of histone demethylase inhibitors and histone methyltransferase inhibitors as novel anti-cancer agents in human cancer cell lines and in animal models of human cancers.

Techniques: Cell culture, siRNA and plasmid transfection, cell proliferation, apoptosis, migration, invasion and metastasis assays, RNA, DNA and protein extraction, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, molecular cloning, immunohistochemistry, immunocytochemistry, animal work, Affymetrix microarray and protein expression.

Identification of novel proteins critical for Myc oncoprotein stabilisation/ degradation

Supervision: Dr Tao Liu (TLiu@ccia.org.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

Myc oncoproteins including N-Myc and c-Myc are over-expressed in approximately 50% of tumour tissues from the general population of cancer patients. One of the most important aspects of Myc oncogenesis is the stabilisation/degradation of Myc oncoproteins. In the last 2 years, we have identified two novel pathways through which Myc oncoproteins are stabilised/degraded. These novel pathways provide novel targets for cancer therapy, and we are currently investigating proteins critical for the pathways and their roles as novel anti-cancer targets.

Techniques: Cell culture, siRNA and plasmid transfection, cell proliferation and apoptosis assays, RNA, DNA and protein extraction, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, luciferase assay, ubiquitination assay and protein expression.

Histone Modification Group Student Projects *cont'd*

The role of histone deacetylases in Myc oncogenesis and histone deacetylase inhibitors in cancer therapy

Supervision: Dr Tao Liu (TLiu@ccia.org.au)

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline:

Histone deacetylases (HDACs) repress the transcription of tumour suppressor genes and are involved in the initiation and progression of a variety of human cancers. Myc oncoproteins are over-expressed in approximately 50% of tumour tissues from the general population of cancer patients. We have found that Myc oncoproteins directly recruit HDACs to target gene promoters, leading to transcriptional repression of tumour suppressor genes and malignant transformation, and that therapeutic treatment with HDAC inhibitors reverses the effect of Myc oncoproteins in tumour-bearing transgenic mice.

In this project, we will further explore the interaction between HDAC and Myc oncoproteins, identify other components of the HDAC-Myc protein complex, and establish the role of HDAC inhibitors as effective agents for the prevention and treatment of Myc oncoprotein-induced cancers.

Techniques: cell culture, siRNA and plasmid transfection, cell proliferation and apoptosis assays, RNA, DNA and protein extraction, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, molecular cloning, immunohistochemistry, immunocytochemistry, animal work, Affymetrix microarray and protein expression.

The critical roles of long noncoding RNAs in tumourigenesis and as targets for cancer therapy

Supervision: Dr Tao Liu (TLiu@ccia.org.au)

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline:

Myc oncoproteins Long intergenic noncoding RNAs (lincRNAs), which range in size from two hundred to tens of thousands of bases, comprise a distinct class of newly discovered noncoding RNAs. Although >3,000 human lincRNAs have been annotated and predicted by bioinformatics analysis, <1% of these have been experimentally characterised. Recent studies suggest that lincRNAs regulate gene transcription, tumour initiation, progression and metastasis. We have made the novel finding that gene amplification of a lincRNA is essential for the transcription of a critical oncogene, and is essential for neuroblastoma cell proliferation. We are currently investigating how the lincRNA modulates gene transcription of oncogenes and how to target the lincRNA for cancer therapy.

Techniques: RNA extraction, bioinformatics analysis of RNA sequencing data, cell culture, siRNA and plasmid transfection, cell proliferation and apoptosis assays, RT-PCR, immunoblot, immunoprecipitation, chromatin immunoprecipitation, molecular cloning, animal work, Affymetrix microarray and protein expression.

Leukaemia Biology Program

Program Head: Associate Professor Richard Lock

The Leukaemia Biology Program maintains a focus on investigating how childhood leukaemia develops resistance to conventional chemotherapeutic drugs, how new drugs can be rapidly tested and prioritised for clinical trials and how novel targets can be identified to develop a new generation of more effective and specific drugs to treat leukaemia.

Associate Professor Richard Lock

OBJECTIVES

- To gain a greater understanding of drug resistance mechanisms in relapsed paediatric acute lymphoblastic leukaemia (ALL), and design and test strategies to reverse resistance in preclinical experimental models
- To use preclinical models to prioritise new drugs for clinical trials in children with aggressive and chemoresistant leukaemia
- To identify new molecular targets that can be exploited for the development of a new generation of drugs that will specifically target leukaemia cells and spare the normal cells of the body

Leukaemia Biology Student Projects

Targeting leukaemic stem cells in paediatric leukaemia

Supervision: A/Prof Richard Lock (rlock@ccia.org.au)

Suitable for: Honours or PhD Studies

Project outline:

Seminal research carried out in the adult acute myelogenous leukaemia (AML) field has shown that minor populations of leukaemia-initiating cells, or leukaemic stem cells (LSCs), are able to initiate and maintain the disease in laboratory models. Moreover, the relative resistance of LSCs to chemotherapeutic drugs may be responsible for post-treatment relapse in patients. A detailed understanding of the cell and molecular biological characteristics of LSCs would facilitate the identification of novel targets for the development of new drugs that more specifically target leukaemia cells, thereby reducing many of the toxic side-effects associated with chemotherapy treatment. In contrast with adult AML, LSCs in paediatric AML are relatively poorly characterised. The PhD project will aim to identify LSCs in paediatric AML, compare their cell and molecular biological characteristics with those of normal haematopoietic stems cells, and test novel therapies designed to specifically target leukaemic and not normal haematopoietic cells.

Mechanisms of glucocorticoid resistance in acute lymphoblastic leukaemia

Supervision: A/Prof Richard Lock (rlock@ccia.org.au)

Suitable for: Honours or PhD Studies

Project outline:

Despite dramatic improvements in therapy, ALL remains one of the most common causes of death from disease in children, and a significant number of patients relapse and succumb to their disease. Glucocorticoids are an essential component of drug treatment regimens in paediatric ALL, and mechanisms of resistance are poorly understood. Several Honours/PhD projects are available on the central theme of glucocorticoid resistance, all of which will use a variety of cell and molecular biology techniques and a clinically relevant xenograft model of paediatric ALL. The projects are as follows:

- Investigate mechanisms of epigenetic silencing of candidate pro-apoptotic genes in glucocorticoid-resistant ALL and develop strategies to reactivate silenced genes;
- Optimise high throughput screens to identify and characterise small-molecules that reverse glucocorticoid resistance;
- Carry out genome-wide analyses for the identification of glucocorticoid receptor target genes using ChIP-chip and/or ChIP-SEQ techniques.

Leukaemia Biology Student Projects *cont'd*

New treatments for high risk acute leukaemia in children

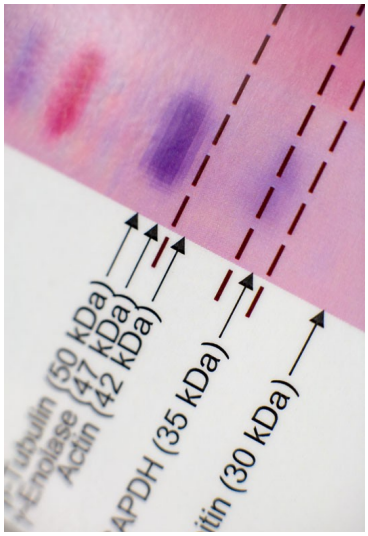
Supervision: A/Prof Richard Lock (rlock@ccia.org.au)

Suitable for: Honours or PhD Studies

Project outline:

Despite dramatic improvements in the survival of children with acute ALL over the past 40 years, relapsed ALL remains one of the most common causes of death from disease in children. A more rare form of acute leukaemia in children, AML is even less curable than ALL. Therefore, new treatments for relapsed or high-risk disease are urgently required. The Leukaemia Biology Program is involved in national and international preclinical drug testing programs to prioritise new drugs for clinical trials in children with relapsed or refractory leukaemia. Several Honours and PhD projects are available within the Program to further study novel drugs that have shown significant activity against our paediatric ALL experimental models, and to identify new drugs with potential activity in ALL and AML. Potential projects investigating novel drugs could involve studying:

- Molecular determinants of *in vivo* sensitivity or resistance;
- Their molecular mechanism of action against leukaemia cells;
- Whether they preferentially target leukaemia cells and not normal cells of the body; and
- How best to combine them with established therapy.



Molecular Carcinogenesis Program

Program Head: Professor Glenn Marshall

The overall strategy of the Molecular Carcinogenesis Program is to dissect the mechanisms of cancer initiation and progression and use this information to develop more powerful treatments and prevention strategies for childhood cancer.

Professor Glenn Marshall

OBJECTIVES

- To better understand the molecular basis of embryonal cancer initiation
- To evaluate p53 signal activators as postnatal rest deletion therapy
- To identify mechanisms of histone modification that contribute to carcinogenesis
- To better understand factors that promote the action of Myc oncoproteins in cancer cells
- To define molecular factors which increase retinoid sensitivity in cancer cells

Molecular Carcinogenesis Student Projects

Ubiquitin mediated proteolysis as a mechanism of treatment sensitivity in leukaemia.

Supervision: Dr Alena Malyukova (AMalyukova@ccia.org.au)

Suitable for: Honours or PhD Studies

The chromosomal translocation, which fuses the TEL and AML1 genes is the most common structural chromosomal alteration in paediatric cancer and occurs in approximately 25% of acute lymphoblastic leukaemia (ALL) cases. However, TEL-AML1 translocation alone is insufficient to develop ALL. This suggests that additional and complementary genetic changes are required. Moreover, epidemiological evidence now supports the view that secondary genetic changes possibly occurs in the context of an abnormal immune response to infection. Research into the nature of mutations that can cooperate with TEL-AML1 to cause ALL has yielded interesting results. In particular, it appears that the most common mutation found in the cells with TEL-AML1 translocation is a deletion of the second allele of TEL that occurs in approximately 70 % of cases. In addition, it has also been proposed that deletion or mutation of Paired-Box-Containing Gene 5 (PAX5) participates with TEL-AML1 in the induction of ALL but again this has not been experimentally verified. Using a specially developed laboratory model of leukaemia, we aim to introduce the TEL-AML1 translocation into normal bone marrow cells, and then inactivate other genes like TEL or PAX5 to see if together they cause normal bone marrow cells to be transformed into leukaemia cells.

Dr Alena Malyukova

OBJECTIVES

- To identify cooperating cellular mutations which promote ALL development in the context of TEL-AML1 expression
- To identify inflammatory cytokines involved in the transformation of a TEL-AML1–driven preleukaemic clone to ALL

Molecular Carcinogenesis Student Projects *cont'd*

Identification of novel therapies that target precursor cells in MycN-initiated embryonal cancers

Supervision: Dr Belamy Cheung (bcheung@ccia.org.au) &
Dr Carol Au (CAu@ccia.unsw.edu.au)

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline:

Neuroblastoma and medulloblastoma are childhood cancers of the peripheral and central nervous system. These tumours arise from embryonal precursor cells that have pathologically persisted beyond birth. Treatment of embryonal childhood cancers remains a clinical challenge and additional research is needed to discover more effective therapies.

MycN is a proto-oncogene that is involved in the initiation and pathogenesis of neuroblastoma and medulloblastoma. Our laboratory has generated a unique precursor cell line that overexpresses MycN. Using these cells, we have performed high throughput screening of chemical compounds and identified several 'hit' compounds that may selectively overcome the MycN survival signals. The specific aims of this project will be:

- To identify compounds that are effective against MycN-expressing precursor cells, but non-toxic to normal cells.
- To characterise the molecular pathways targeted by these compounds, focusing on the p53 tumour suppressor signal.

Dr Belamy Cheung

Understanding the role of oxidants and oxidative stress in mediating the anti-cancer action of histone deacetylase inhibitors

Supervision: Dr Aldwin Suryo Rahmanto (ASuryo@ccia.unsw.edu.au) &
Dr Belamy Cheung (bcheung@ccia.org.au)

Suitable for: Honours or Masters Studies

Project outline:

Cancer cells have the ability to turn off particular genes for their own advantage, and this can help them to grow and to resist drug treatment. Drugs known as histone deacetylase inhibitors (HDI) are becoming very important in cancer as they can switch some of these genes back on. Recently however, it has been shown that HDIs also stimulate the production of highly reactive molecules within the cancer cell that lead to the cancer cell being damaged. The aims of this project are to define how these reactive molecules are being produced and to test whether they can be harnessed in combination with other drugs to kill cancer cells more effectively. The project will involve tissue culture and variety of cutting-edge molecular biology techniques such gene manipulation by transfection, real-time PCR, Western blotting, and Flow cytometry.

Dr Aldwin Suryomanto

Molecular Carcinogenesis Student Projects *cont'd*

Retinoid Therapeutics

Project Leader: Dr Belamy Cheung

Increasing the effectiveness of retinoid anticancer therapy for embryonal cancer

Supervision: Dr Belamy Cheung (bcheung@ccia.org.au)

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline:

Retinoids are an important component of therapy for the commonest cancer of early childhood, neuroblastoma, while considerable pre-clinical evidence has led to a current US trial assessing effectiveness of 13-*cis*-retinoic acid in the most common brain tumour of children, medulloblastoma. However half of all advanced neuroblastoma patients treated with 13-cis-retinoic acid still relapse and die, indicating the need for more effective retinoid therapy. We have evidence of marked synergy between a novel synthetic retinoid and the histone deacetylase inhibitor with far greater potency than 13-*cis*-retinoic acid. To identify the specific genes and pathways activated by the novel combination treatment, we have performed a global gene expression microarray analysis on neuroblastoma cells treated with the combination therapy; this data set has provided a short-list of statistically significant genes which may serve as biomarkers for patients who will best benefit from the therapy. We will further study the relative importance of specific genes and pathways to the drug response, and define the mechanism of therapeutic synergy demonstrated by the combination therapy.

Dr Daniel Carter

Mechanisms of MYCN mediated death resistance in Neuroblastoma initiation

Supervision: Dr Daniel Carter (DCarter@ccia.unsw.edu.au) &
Dr Belamy Cheung (bcheung@ccia.org.au)

Suitable for: ILP, Honours, Masters or PhD Studies

Project outline:

Neuroblastoma (NB) begins in embryonal cells that have pathologically persisted beyond birth as remnant or rest cells. These pre-cancerous cells have an inability to undergo programmed cell death (PCD) in response to developmental cues. Our data suggests that the MYCN oncogene is crucial in governing this ability to resist PCD in NB rest cells.

Currently we have a primary rest cell culture model that demonstrates MYCN death resistance against deprivation of developmental cytokine, nerve growth factor (NGF). To investigate the mechanisms of MYCN mediated death resistance, we will conduct a global gene expression analysis on pre-cancerous rest cells upon NGF deprivation. Using this dataset, the proposed project will involve identification and characterisation of novel MYCN driven tumourigenesis factors. Candidate genes will be chosen that satisfy a number of requirements, including applicability to preventative or treatment oriented therapeutic approaches.

Molecular Diagnostics Program

Program Head: Professor Murray Norris

The Molecular Diagnostics Program uses molecular genetic technology and small molecule drug screening approaches as a means of improving the diagnosis and treatment of children with malignant disease.

To isolate potential new pharmaceutical agents that target cancer-associated genes, we have been employing high-throughput screening of small molecule chemical libraries. Our research has identified a number of small molecule inhibitors of these targets in childhood neuroblastoma, as well as in infants with leukaemia. Both these groups of children have particularly poor survival rates compared with children with other tumour types.

The development of inhibitors of defined molecular targets – such as the MYCN and MLL oncoproteins and the MRP1 and MRP4 multidrug transporters – provides the opportunity to devise therapies that are more specific in their action and effective at low concentrations, and have an irreversible effect on cancer cells.

OBJECTIVES

- To develop molecular targeted therapies for childhood neuroblastoma based on specific small-molecule inhibitors of key target genes
- To develop clinically relevant chemical small molecules that specifically inhibit leukaemia cells with an abnormal MLL gene
- To use large scale mutagenesis screens to identify novel genes and co-factors involved in MycN-driven neuroblastoma

Professor Murray Norris

Molecular Diagnostics Student Projects

Novel Therapies for high-risk leukaemia in children

Supervision: Dr Michelle Henderson (MHenderson@ccia.org.au) &
Prof Murray Norris

Suitable for: Honours or PhD Studies

Project outline:

While survival rates for children with acute lymphoblastic leukaemia (ALL) overall are approaching 80%, for those who present with this disease as infants, prognosis is dismal despite intensified treatment. Consequently there is a need to develop therapeutic agents with better specificity towards this disease.

Most cases of infant ALL have chromosomal translocations resulting in rearrangement of the MLL gene on chromosome 11q23. This project involves small molecule drug screening to identify compounds with activity against MLL-rearranged leukaemia. We have identified several 'hit' compounds which kill leukaemia cells that harbour a MLL translocation, while having minimal effect on other leukaemia cell types. These 'hits' will be assessed and characterised to determine their potential clinical utility.

This will involve:

- Cytotoxicity assays using a diverse panel of cell lines to determine the specificity of the compounds for MLL-rearranged leukaemia
- Testing efficacy of the compounds on infant leukaemia samples using a xenograft model
- Elucidating mechanism of action of the MLL-specific compounds

These studies will not only assist in developing new potential therapeutic agents for high-risk leukaemia, but should also shed light on the mechanisms of MLL-driven leukaemogenesis.

Molecular Diagnostics Student Projects *cont'd*

Dr Michelle Henderson

Mechanism of relapse in acute lymphoblastic leukaemia

Supervision: Dr Michelle Henderson (MHenderson@ccia.org.au) & Prof Murray Norris

Suitable for: Honours or PhD Studies

Project outline:

Despite significant improvements in treatment regimes, relapse remains a barrier to survival in approximately 20% of children suffering from acute lymphoblastic leukaemia. Relapse occurs as a result of small numbers of leukaemia cells that survive treatment and continue to proliferate, eventually causing disease reappearance. This project involves the use of an *in vivo* model to study the leukaemia cells responsible for relapse and has three broad aims:

- To compare clonal gene rearrangements of patient leukaemic bone marrow samples obtained at diagnosis and relapse in order to identify clonal markers specific to the cell populations present at diagnosis and relapse
- To use these clonal markers in the NOD/SCID mouse xenograft model to follow the ability of individual leukaemia sub-clones to grow and proliferate in the presence and absence of various chemotherapeutic agents *in vivo*
- To compare the gene expression profiles of individual leukaemia sub-clones as a means of identifying cellular pathways that contribute to relapse and which may represent novel therapeutic targets.

These studies will enable identification of the unique properties of leukaemic cells responsible for disease maintenance and will further characterise the NOD/SCID model as a system for evaluation of novel therapies against ALL.

Cancer and Stem Cell Biology

Identification and validation of novel therapeutic targets for lung cancer stem cells

Supervision: Dr Jenny Y. Wang (JWang@ccia.unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

The discovery of rare cancer cells with stem-cell features, first in leukaemia and later in solid tumours, including lung cancer, has emerged as an important area in cancer research. These 'stemness' cancer cells, termed 'cancer stem cells' or tumour-initiating cells, initiate and drive the process of tumourigenesis. In addition to their stem-like capacity to self-renew, cancer stem cells also possess characteristics making tumours resistant to standard chemotherapy treatment. Thus, targeted elimination of these cells is believed to be key for achieving a complete remission. By using genome-wide gene expression analysis and advanced stem-cell technologies, this project aims to identify genetic and epigenetic pathways that control the malignant transformation of normal lung cells into cancer stem cells, and to validate these pathways as potential targets for therapeutic intervention in lung cancer.

Molecular Diagnostics Student Projects *cont'd*

Cancer and Stem Cell Biology *cont'd*

Development of new therapeutic strategies for elimination of AML stem cells by disrupting critical signalling pathways

Supervision: Dr Jenny Y. Wang (JWang@ccia.unsw.edu.au)

Suitable for: Honours or PhD Studies

Project outline:

One of the most exciting concepts being explored in cancer research today is the idea of cancer stem cells. The first evidence of the existence of such cells was documented in acute myeloid leukaemia where only a small subset of cancer cells with stem cell features were capable of initiating leukaemia in mice. In addition to their stem-like ability to self-renew and differentiate, leukemic stem cells (LSC) also possess characteristics making leukaemia resistant to standard anti-cancer therapies. Thus, targeting LSC is an essential step in the development of novel effective agents. We have established disease models and techniques for detailed LSC functional studies and identified critical signalling pathways that drive LSC development (Nature 2006; Science 2010). This project aims to develop new effective therapeutic agents to selectively eliminate LSC through direct targeting of these key signalling pathways while leaving normal stem cells unharmed.

Dr Jenny Wang

Epigenetic regulation of leukaemic stem cells - to develop effective epigenetic therapeutic approach to AML

Supervision: Dr Jenny Y. Wang (JWang@ccia.unsw.edu.au)
Dr Owen Sprod

Suitable for: Honours or PhD Studies

Project outline:

For decades, cancer has been considered a genetic disease that is caused by abnormal changes in an individual's DNA sequence. But today, a more complex picture has emerged. Recent studies have shown that some cancers are caused by epigenetic changes that can 'turn on' disease cells or 'shut off' tumour-suppressor genes. Unlike genetic mutations that are currently not reversible, epigenetic changes can potentially be reversed by pharmacological interventions that make them excellent targets for anti-cancer therapies. However, development of effective targeted epigenetic therapy is still in its infancy because a comprehensive understanding of the epigenetic mechanisms controlling cancer cell malignancies is still lacking. The aim of this project is to identify critical epigenetic regulators required for leukemic stem cell development, and to develop effective epigenetic therapeutic approaches for specific targeting and eradication of leukaemic stem cells in AML.

Dr Owen Sprod

Skills learned throughout these projects:

Establishing primary mouse cell lines with fusion oncoproteins, purification of normal and cancer stem cells, stem cell transplantation, drug treatment of cancer cells and mouse models, histone modification analysis, genome-wide localisation and gene expression analysis, flow cytometry, cell culture techniques, and other technologies related to cancer stem cell studies and epigenetic regulation of cancer cells.

Significance:

Successful completion of these projects will generate new insights into cancer stem cell biology, identify novel therapeutic targets, and provide pre-clinical validation of therapeutic potential. These studies therefore have the potential to lead directly to the development of novel therapeutic strategies that directly and selectively target cancer stem cells.

Molecular Epidemiology Group

Group Leader : Dr Lesley Ashton

The overall goals of the Molecular Epidemiology Group are to better understand the causes of childhood cancer and to characterise the incidence and risk of long-term outcomes in children successfully treated for cancer.

OBJECTIVES

- To characterise gene variants and environmental exposures that influence the risk of childhood cancers
- To identify gene variants that influence the long-term health of people treated for cancer during childhood
- To determine gene variations that can modify the effectiveness of anti-cancer drugs used to treat childhood cancer
- To characterise the likelihood of developing a second cancer following haematopoietic stem cell transplantation and establish causes of premature death in this group

Dr Lesley Ashton

Molecular Epidemiology Student Projects

Determining gene variations that modify the long-term health outcomes of survivors of childhood cancer**

Supervision: Dr Lesley Ashton (LAshton@ccia.org.au)

Suitable for: PhD Studies

Project outline:

Survivors of childhood cancer are at an increased risk of a broad spectrum of treatment–related outcomes, such as early death, second cancers, cardiovascular disease, and pulmonary complications. Molecular and epidemiological evidence suggests an underlying genetic basis for the variable therapeutic responses to anticancer agents observed in children with cancer. Such genetic variation is also likely to contribute to the long-term sequelae observed in survivors of childhood cancer.

This NSW population based cohort study will examine how specific gene variants modify the impact of the long-term health effects of cancer therapy received during childhood. More than 1,000 childhood cancer survivors treated over the last 3 decades will be included in the study. The project will use data and biological specimens collected over the past 8 years. The aim of the project is to determine how genetic variations modify the long-term health effects of cancer therapy. The project will focus on five long-term health outcomes in survivors and will include; second malignant neoplasms, avascular necrosis, myocardial infarction, ischaemic stroke, and congestive heart failure

****Note: This project has a laboratory component.**

TUMOUR BIOLOGY AND TARGETING PROGRAM

Program Head : Professor Maria Kavallaris

There remains much work to be done to improve the survival rates of children with cancer. The Tumour Biology and Targeting Program is focused on developing ways to target drug resistant cancer and to develop new, less toxic forms of treatment.

OBJECTIVES

- To target the cytoskeleton in cancer cells to make them more sensitive to chemotherapy and to decrease the formation of tumours
- To examine the role of the cytoskeleton in tumour blood vessel formation so new treatments can be developed
- To determine how cancer cells develop resistance to chemotherapy and develop more effective treatments
- To map the protein pathways involved in Aurora kinase inhibitor drug action, so new targets for cancer therapy can be identified and developed
- To develop and evaluate nanotechnology strategies to deliver low toxicity therapeutics to target cytoskeletal and other key molecules in cancer cells

Professor Maria Kavallaris

Tumour Biology and Targeting Student Projects

Targeting of Aurora A inhibitors in childhood acute lymphoblastic leukaemia

Supervision: Prof Maria Kavallaris (MKavallaris@ccia.org.au)

Suitable for: Honours Studies

Project outline:

Antimitotic agents, such as the tubulin-binding drugs vincristine and vinblastine that block cell division are highly effective in the treatment of leukaemia and lymphoma. Despite the success of these agents, the development of drug resistance can be a major clinical problem. The need to find alternate therapies to block cell division has led to the discovery of Aurora kinase A inhibitors. How these potent inhibitors alter specific signalling pathways to cause cancer cell death and how disease specific variations in protein networks will influence efficacy in patients is poorly understood. We hypothesise that the activity of Aurora A inhibitors in leukaemia cells is influenced by the pattern of expression of proteins in Aurora A dependent signalling pathways.

The aim of this project is to establish the mechanism of action of Aurora A inhibitors by identifying critical proteins and signalling pathways associated with response to Aurora A inhibitors.

Tumour Biology and Targeting Student Projects *cont'd*

Dr Josh McCarroll

Identifying protein networks regulated by βIII-tubulin

Supervision: Prof Maria Kavallaris (MKavallaris@ccia.org.au) &
Dr Josh McCarroll (JMaccaroll@ccia.org.au)

Suitable for: Honours or PhD Studies

Project outline:

Lung cancer is the most common cancer and despite advances in treatments, overall 5 year survival rates for advanced disease are dismal. βIII-tubulin is a neuronal-specific cytoskeletal protein that is associated with aggressive tumours and drug resistance in a range of cancer types including non-small cell lung cancer (NSCLC), ovarian, and breast cancers.

We demonstrated for the first time that targeting the microtubule protein βIII-tubulin using siRNA sensitises NSCLC cells to different classes of chemotherapeutic agents such as the tubulin-binding (TBA) and DNA damaging agents (Gan et al Cancer Research 2007). Recent studies have correlated high βIII-tubulin levels with poorly differentiated tumours and increased metastases (reviewed in Kavallaris Nat Rev Cancer 2010). Despite strong correlative evidence implicating a role for βIII-tubulin in tumourigenesis, its role in tumour formation and aggression has not been addressed.

Strong preliminary data from our laboratory clearly shows that suppression of βIII-tubulin expression significantly reduces NSCLC cell anchorage independent growth and tumour formation. Recent proteomic studies on βIII-tubulin and its effect on differential protein expression have been performed in our laboratory and proteins involved in tumour growth and survival have been identified. We hypothesise that βIII-tubulin is regulating key protein networks lung cancer cells that are influencing tumourigenesis.

The aim of this project is to functionally validate the role of nuclear and cytoplasmic proteins regulated by βIII-tubulin in lung cancer using gene silencing and expression studies.

Determining the role of the cytoskeleton protein βIII-tubulin in tumour formation

Supervision: Prof Maria Kavallaris (MKavallaris@ccia.org.au) &
Dr Josh McCarroll (JMaccaroll@ccia.org.au)

Suitable for: Honours or PhD Studies

Project outline:

Lung cancer is the most common cancer and despite advances in treatments, overall 5 year survival rates for advanced disease remain dismal. βIII-tubulin is a neuronal-specific cytoskeletal protein that is associated with aggressive tumours and drug resistance in a range of cancer types including non-small cell lung cancer (NSCLC), ovarian, and breast cancers.

We demonstrated for the first time that targeting the microtubule protein βIII-tubulin using siRNA sensitises NSCLC cells to different classes of chemotherapeutic agents such as the tubulin-binding (TBA) and DNA damaging agents (Gan et al Cancer Research 2007). Recent studies have correlated high βIII-tubulin levels with poorly differentiated tumours and increased metastases (reviewed in Kavallaris Nat Rev Cancer 2010). Despite strong correlative evidence implicating a role for βIII-tubulin in tumourigenesis, its role in tumour formation and aggression has not been addressed.

Strong preliminary data from our laboratory clearly shows that suppression of βIII-tubulin expression significantly reduces NSCLC cell anchorage independent growth and tumour formation. We hypothesise that βIII-tubulin is involved in tumourigenesis of cancers that aberrantly express this protein.

The aim of this project is to functionally characterise βIII-tubulin in NSCLC tumourigenesis in a mouse model of altered βIII-tubulin expression.

Tumour Biology and Targeting Student Projects *cont'd*

Defining the role of beta-adrenergic receptors in neuroblastoma

Supervision: Dr Eddy Pasquier (EPasquier@ccia.org.au) &
Prof Maria Kavallaris (MKavallaris@ccia.org.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

The neuroendocrine system has recently emerged as a critical factor in cancer progression, angiogenesis and metastasis. Accumulating pre-clinical and clinical evidence suggests that β-adrenergic receptors (βARs) in particular could represent a major therapeutic target in the fight against cancer. The mechanisms involved remain however poorly understood. This project aims at defining the role of βARs in neuroblastoma, a highly vascular and often metastatic tumour representing one of the deadliest forms of childhood cancer. RNAi gene silencing technology will be used to specifically knockdown the expression of βARs in neuroblastoma cells. The role of βARs in neuroblastoma cell proliferation, motility and invasion will then be determined using state-of-art cell biology techniques including live cell imaging. Cytotoxicity assays will also be employed to study the influence of βARs on drug sensitivity. Overall, this research project will provide major insights into the role of βARs in neuroblastoma progression, metastasis and response to treatment.

Lung Cancer Stem Cells: Target identification for nanomedicine development

Supervision: Prof Maria Kavallaris (MKavallaris@ccia.org.au) &
Dr Jenny Y. Wang (JWang@ccia.unsw.edu.au)

Suitable for: Honours, Masters or PhD Studies

Project outline:

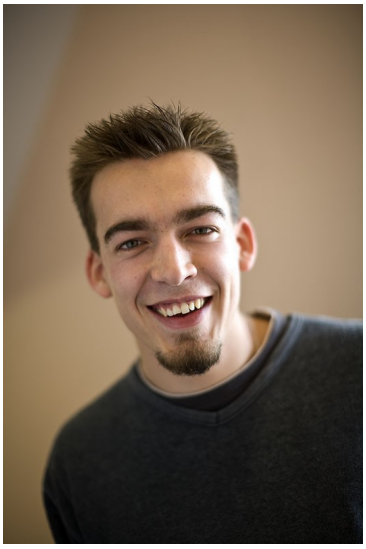
Lung cancer is the most common cancer and despite advances in treatments, overall 5 year survival rates for advanced disease are dismal. Most of the cells in a tumour have limited ability to grow and divide and can differentiate into cells that make up the bulk of the tumour. A small population of cells within some tumours have the ability to self-renew and proliferate and are thus able to maintain the tumour. These cells are also referred to as cancer stem cells or tumour-initiating cells. This population of cells within the tumour are intrinsically resistant to therapy and difficult to destroy. Identifying ways to target cancer stem cells may lead to more effective ways to treat difficult to treat cancers such as advanced non-small cell lung cancer.

Aim:

To isolate cancer stem cells from a mouse model of non-small cell lung cancer in order to identify unique genes and proteins differentially expressed in these cells relative to normal cells. Once identified, unique genes and proteins will be validated in human cells and their role in the growth and survival of lung cancer stem cells determined. Genes critical to the survival of the cancer stem cells will be prioritised for therapeutic targeting.

Significance and outcomes:

The identification of target genes and proteins in cancer stem cells will allow us to develop gene targeted therapy to destroy lung cancer stem cells using nanoparticle delivery. This research has broader implications for the identification and future targeting of cancer cells in other types of cancers.



Dr Eddy Pasquier

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