CANCER RESEARCH
STUDENT PROJECTS
2017
ACCELERATING
DISCOVERY AND
TRANSLATING
RESEARCH
CONTENTS

The following pages highlight some of the projects available for future students in 2017.
Projects are arranged alphabetically by research group. The following tables of contents and project summary pages will help you find a particular project, research group or supervisor. If you are interested in a particular project, use the contact details to follow up with the listed supervisors to learn more about the project.

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Peter MacCallum Cancer Centre is a leading integrated cancer research, treatment and education centre globally. This is a place where normal days are extraordinary – as are the people we care for. Each day our team strives to provide the very best in cancer care, better treatments and potential cures for all people affected by cancer.

Globally, we are facing one of the most pivotal times in the pursuit of cancer cures, and Peter Mac stands at its forefront. Together, we aim to lead a new era of cancer prevention, care and discovery, supported by state-of-the-art facilities at our new home within the Victorian Comprehensive Cancer Centre building.

We have a 500+ laboratory and clinical research team fully integrated with our public hospital – something that is unique in cancer care in Australia.

In the words of our founder, Sir Peter MacCallum

‘Nothing but the best is good enough for the treatment of cancer.’
PROJECTS SUMMARY

ACHEN, MARC
The control of vascular remodeling in cancer by microRNAs
Supervisors: Prof. Marc Achen, Prof. Steven Stacker, Prof. Stephen Fox

BOUSSIOUTAS, ALEX
Twist as a regulator of EMT in gastric cancer and its role in invasion
Supervisors: A/Prof. Alex Boussioutas, Dr. Rita Busuttil
Discovery and validation of candidate genes involved in the progression of gastric cancer
Supervisors: A/Prof. Alex Boussioutas, Dr. Rita Busuttil
Role of the tumour microenvironment in gastric cancer
Supervisors: A/Prof. Alex Boussioutas, Dr. Rita Busuttil

BOWTELL, DAVID
Pre-Clinical Models of Cyclin E1 Amplified High-Grade Serous Ovarian Cancer
Supervisors: Prof. David Bowtell, Dr. Jessica Beach

BRITT, KARA
Developing breast cancer preventatives by mimicking parity’s protective role
Supervisor: Dr. Kara Britt
Finding a therapy for triple negative breast cancer patients
Supervisors: Dr. Kara Britt, Prof. Robin Anderson, Prof. Kelly Phillips
Reversing mammographic density to decrease breast cancer risk
Supervisors: Dr. Kara Britt, Prof. Rik Thompsonn, Prof. Michael Henderson

BROWN, KRISTEN
Identifying metabolic reprogramming events that fuel chemotherapy resistance in triple-negative breast cancer
Supervisor: Dr. Kristen Brown

CAMPBELL, IAN
Identification of genetic variation predisposing to ovarian cancer
Supervisors: Prof. Ian Campbell, A/Prof. Paul James
How does amino acid metabolism affect tumour growth?
Supervisors: Dr. Francesca Froldi, Dr. Louise Cheng
How do tumours grow at the expense of other tissues?
Supervisors: Dr. Francesca Froldi, Dr. Louise Cheng
Identification of factors which regulate neural dedifferentiation
Supervisors: Dr. Francesca Froldi, Dr. Louise Cheng

CLEMONS, NICK
Targeting redox balance in mutant p53 cancers
Supervisors: Dr. Nick Clemons, Prof. Wayne Phillips, Dr. Cuong Duong
Novel therapies to reactivate p53 function in mutant p53 cancers
Supervisors: Dr. Nick Clemons, Prof. Wayne Phillips, Dr. Cuong Duong
Developing strategies to combat chemoresistance in oesophageal cancer
Supervisor: Dr. Nick Clemons

COX, ANDREW
Fishing for metabolic clues: Role of the Hippo/Yap pathway in reprogramming metabolism to fuel tissue growth and cancer
Supervisor: Dr. Andrew Cox
Metabolic rewiring in liver cancer: Role of Nrf2 in regulating crosstalk between oxidative stress and metabolic remodeling
Supervisor: Dr. Andrew Cox

DARCY, PHIL
Enhancing the efficacy of Adoptive cellular Immunotherapy for cancer
Supervisor: A/Prof. Phil Darcy, Dr. Paul Beavis

DARIDO, CHARBELL
Investigating the requirements of pro-inflammatory signaling in skin and head & neck Squamous Cell Carcinomas
Supervisor: Dr. Charbel Darido
Identification of the cell of origin of Grhl3-deficient head and neck squamous cell carcinoma
Supervisor: Dr. Charbel Darido

DAWSON, SARAH-JANE
Circulating tumour DNA to monitor treatment response and resistance in Hepatocellular Carcinoma
Supervisor: A/Prof. Sarah-Jane Dawson

ELLIS, SARAH
How loss of the polarity protein, Par3, alters intracellular signaling pathways to drive Acute Myeloid Leukemia
Supervisors: A/Prof. Sarah Ellis, A/Prof Phil Darcy
Investigating the intracellular pathways impacted by loss of the scaffolding protein, Scribble
Supervisors: A/Prof. Sarah Ellis, A/Prof Phil Darcy

FELLOWES, ANDREW
Clinical Trials Database Design and Implementation
Supervisors: Dr. Andrew Fellowes, Mr. Anthony Bell, Mr Ken Doig, Mr Gareth Reid.
Molecular Pathology Workflow Metrics Data Visualisation
Supervisors: Dr. Andrew Fellowes, Mr. Anthony Bell, Mr Christopher Welsh, Mr Gareth Reid.
PROJECTS SUMMARY

GORRINGE, KYLIE
Analysis of USP9X in low grade ovarian serous carcinoma
Supervisors: Dr. Kylie Gorringle, Prof. Ian Campbell, Dr. Dane Cheasley
Personalised risk evaluation in DCIS
Supervisors: Dr. Kylie Gorringle, Prof. Ian Campbell.

HARVEY, KIERAN
Control of tissue growth and cancer by the Hippo pathway
Supervisors: Dr. Joep Vissers, A/Prof. Kieran Harvey
A novel personalised medicine approach for the treatment of the asbestos-related cancer, malignant mesothelioma
Supervisors: Dr. Joep Vissers, A/Prof. Kieran Harvey

HAUPT, YGAL
Exploration of novel approaches to anti-cancer treatment: manipulation of mutant p53
Supervisors: Dr. Sue Haupt, Prof. Ygal Haupt
Restoration of tumour suppression by using the ubiquitin proteasomal system as an anti-cancer approach.
Supervisor: Prof. Ygal Haupt
Exploring novel regulators of mutant p53 using computational analyses
Supervisor: Prof. Ygal Haupt

HICKS, ROD
Understanding intra-patient disease heterogeneity in human melanoma
Supervisor: Dr. Richard Tothill
Understanding the mechanisms of biologically targeted radiation on neuroendocrine tumours and the host immune system
Supervisors: Dr. Richard Tothill, Dr. Carleen Cullinane, Prof. Rod Hicks

JOHNSON, RICKY
Investigating the role of CRLF2/JAK2 Signaling in high-risk B-cell Acute Lymphoblastic Leukemia (B-ALL)
Supervisor: Prof. Ricky Johnstone

KATS, LEV
Development of targeted therapy for acute myeloid leukaemia with mutations in isocitrate dehydrogenase
Supervisor: Dr. Lev Kats

LOI, SHERENE
Understanding host anti-tumour immunity in preclinical models of breast cancer: mechanisms evading the immune system
Supervisors: A/Prof. Sherene Loi, A/Prof Phil Darcy
Understanding host anti-tumour immunity in preclinical models of breast cancer: biological interactions and mechanisms of PIK3CA mutations
Supervisors: A/Prof. Sherene Loi, Prof Wayne Phillips, Dr. Joyce Teo
Development of new therapeutic approaches for the treatment of Breast Cancer patients: Projects 1 and 2
Supervisors: Dr. Mariam Mansour, A/Prof. Sherene Loi

McARTHUR, GRANT
Impact of targeted therapy on the melanoma immune microenvironment
Supervisors: Dr. Karen Sheppard, Prof. Grant McArthur
Functional genomics of BRAF driven glycolysis in BRAFV600 melanoma
Supervisors: Dr. Lorey Smith, Prof. Grant McArthur
Targeting CDK4 in melanoma
Supervisors: Dr. Karen Sheppard, Prof. Grant McArthur

NEESON, PAUL
Exploring the immune context of human cancer
Supervisor: Dr. Paul Neeson
Exploring chimeric antigen receptor T cells
Supervisor: Dr. Paul Neeson
Exploring multiple myeloma immunotherapy
Supervisor: Dr. Paul Neeson

OLIARO, JANE
The role of DOCK8 in immune cell biology
Supervisor: Dr. Jane Oliaro
The role of co-signalling receptors in cytotoxic lymphocyte activity during infection and cancer
Supervisor: Dr. Jane Oliaro

PAPENFUSS, TONY
Impact of targeted therapy on the melanoma immune microenvironment
Supervisor: Prof. Tony Papenfuss
Mechanistic and Functional Drivers of Cancer Neochromosomes
Supervisor: Prof. Tony Papenfuss

PEARSON, RICK
Impact of targeted therapy on the melanoma immune microenvironment
Supervisors: Dr. Jian Kang, Prof. Rick Pearson
AKT driven senescence and cancer
Supervisors: Dr. Keefe Chan, Prof. Rick Pearson
Biochemical and molecular dissection of the mechanisms controlling ribosome biogenesis by the PI3K/AKT/mTORC1 network
Supervisors: Dr. Elaine Sanij, Prof. Rick Pearson
PROJECTS SUMMARY

PHILLIPS, WAYNE
Understanding the biology of Barrett’s oesophagus
Supervisors: Prof. Wayne Phillips, Dr. Nicholas Clemons, Dr. Cuong Duong
Exploring the biological consequences of PIK3CA mutation in colorectal cancer
Supervisors: Prof. Wayne Phillips, Dr. Nicholas Clemons, Dr. Cuong Duong

RISBRIDGER, GAIL
New human models for rapid preclinical testing of prostate cancer
Supervisor: Prof. Gail Risbridger
Defining epigenome changes in the tumour microenvironment
Supervisor: Prof. Gail Risbridger
Pre-clinical testing of novel combination therapies in mouse models of prostate cancer
Supervisor: Dr. Luc Furic
Reconstructing the evolution of therapy-resistance metastatic prostate cancer
Supervisor: Dr. David Goode

RUSSELL, SARAH
Single cell pedigree analysis to understand the mechanisms of fate determination during T cell development, leukemia, and immune responses
Supervisor: Dr. Sarah Russell

STACKER, STEVEN
Understanding the role of the Ryk receptor in cancer
Supervisors: Prof. Steven Stacker, Dr. Michael Halford, Prof. Stephen Fox
Understanding the signaling networks within lymphatic endothelial cells
Supervisors: Prof. Steven Stacker, Prof. Marc Achen, Prof. Stephen Fox
Are angiogenesis receptors drivers of epithelial malignancies?
Supervisors: Prof. Steven Stacker, Prof. Marc Achen, Prof. Stephen Fox
Role of prostaglandins in tumour metastasis
Supervisors: Prof. Steven Stacker, Prof. Marc Achen

VOSKOBOINIK, ILIA
Killer cell biology regulation and function of cytotoxic lymphocytes
Supervisors: Dr. Ilia Voskoboinik, Prof. Joe Trapani

WICKRAMASINGHE, VI
Mechanisms of regulating gene expression via selective mRNA transport
Supervisor: Dr. Vi Wickramasinghe
Impact of alternative mRNA splicing on the human proteome
Supervisor: Dr. Vi Wickramasinghe
Peter MacCallum Cancer Centre is Australia’s only public hospital solely dedicated to cancer, and home to the largest research group in Australia.

For over 65 years, Peter Mac has been providing high quality treatment and multidisciplinary care for cancer patients and their families.

Our 2,500-strong team is the largest specialised cancer workforce in the country, and includes more than 500 researchers.

Together, we are dedicated to working with local and international partners to minimise the impact of cancer in our communities. In the words of Sir Peter MacCallum, ‘Nothing but the best is good enough for the treatment of cancer’.

Cancer is a complex set of diseases, and modern cancer research institutes such as Peter Mac conduct research covering a diversity of topics that range from laboratory-based studies into the fundamental mechanisms of cell growth, translational studies that seek more accurate cancer diagnosis, clinical trials with novel treatments, and research aimed to improve supportive care.

The proximity and strong collaborative links of clinicians and scientists provides unique opportunities for medical advances to be moved from the ‘bench to the bedside’ and for clinically orientated questions to guide our research agenda. As such, our research programs are having a profound impact on the understanding of cancer biology and are leading to more effective and individualised patient care.

CANCER RESEARCH OVERVIEW

Peter Mac’s commitment to research is based on the belief that treatment informed by research, and research informed by treatment, is the key to progressing better cancer care.
Cancer Research Division

Peter Mac’s comprehensive and internationally renowned cancer laboratories seek fundamental biological and biomedical discoveries, and aim to facilitate the development and application of these discoveries to their full therapeutic potential.

The Cancer Research Division at Peter Mac is home to over 430 laboratory-based scientists and support staff, including approximately 100 higher degree (mainly PhD) and Honours students. Supported by nine core technology platforms, our research laboratories are organized into six programs of laboratory-based and translational research:

• Cancer Genetics & Genomics
• Cancer Immunology
• Cancer Therapeutics: Haematological Cancers
• Cancer Therapeutics: Solid Cancers
• Oncogenic Signalling and Growth Control
• Organogenesis and Cancer
• Prostate Cancer
• Tumour Angiogenesis and Microenvironment

Our core facilities and platform technologies are the backbone of our research and ensure that the researchers are outfitted with the equipment and expertise needed to facilitate their research. An important role of the core platform technologies is to also identify, import, and develop new technologies.

Peter Mac is home to many large, group studies collecting biospecimens, blood samples and survey data from people with cancer to build large open-access resources for innovative research projects. Some studies also collect information from people who have never had cancer.

Cohort studies give not only our researchers, but researchers worldwide, access to a vast array of ethically collected clinical samples and associated clinical data.

Clinical Research

At Peter Mac there are many specialised groups actively engaged in clinical research. Our aim is to improve treatment, and care and experience outcomes of cancer patients and their support networks.

Research in the clinical services is included in the following areas:

• Allied Health
• Cancer Experiences Research
• Cancer Imaging and Diagnostics
• Cancer Medicine
• Cancer Surgery and Anaesthesia
• Familial Cancer Research
• Infections Diseases
• Pain and Palliative Care
• Pharmacy
• Physical Sciences
• Radiation Oncology and Therapy
• Victorian Epigenetics Group
• Cancer Services:
  • Breast
  • Gynae- oncology
  • Genitourinary oncology
  • Haematology
  • Head and Neck
  • Lung
  • Melanoma and Skin
  • Neuro-oncology
  • Paediatrics and Late Effects
  • Sarcoma
  • Lower Gastrointestinal
  • Upper Gastrointestinal
  • Cancer of Unknown Primary

Platform Technologies

Peter Mac has platform technologies that underpin our research and allow our researchers to be internationally competitive in an increasingly technology-driven environment.

Peter Mac’s core technologies and expertise are also made available to external researchers on a collaborative or costrecovery basis, thereby increasing research output in the wider bioscience community. Key technologies at Peter Mac include:

Flow Cytometry and Cell Sorting

This facility provides researchers with access to state-of-the-art equipment and expertise that enables isolation, separation and analysis of cell populations based on their biological and therapeutic properties.

The facility offers multi-parameter flow cytometric analysis for identifying rare populations of cells within complex mixtures such as human bone marrow, and two fully supported fluorescent activated cell sorting (FACS) instruments for isolating cells such as blood progenitor cells under sterile conditions.

Advanced Microscopy and Histology Platforms

The Centre for Advanced Histology and Microscopy (CAHM) underpins a multitude of cancer research projects and houses four core platforms:

• Optical Microscopy, a suite of state-of-the-art high-end optical microscopes including laser scanning confocal microscopes, a multi-modal super resolution microscope and multiphoton microscope, a dual laser multiphoton microscope, and a laser capture microscope.

• Electron Microscopy, inclusive of both transmission and scanning electron microscopy.

• Image Analysis.

• Histology.

The facility also provides an array of ancillary equipment for the processing of cells and tissues for optical and electron microscopy. Importantly, researchers utilising the facility receive the appropriate support, training, and advice from technical specialist staff members.
RESEARCH STRUCTURE

Functional Genomics
The Victorian Centre for Functional Genomics (VCFG) at Peter Mac offers biomedical researchers Australia-wide the ability to perform novel discovery-based functional interrogation all genes in the genome, or selected boutique collections using multiple platforms including short hairpin RNA (shRNA), small interfering RNA (siRNA), micro RNA (miRNA) and long non-coding RNA (lncRNA).

The VCFG also facilitates small scale drug screens using commercially available compounds or your own. We have a dedicated team of experts who help guide the process from assay optimisation, to screening and analysis. Recently the VCFG has established a Reverse Phase Protein Array platform, another high throughput discovery technology that allows for rapid quantitation of the expression of native and phosphor-specific protein isoforms in very small sample populations.

The VCFG primarily operates a ‘researcher driven, staff assisted’ model whereby the researcher is embedded in the facility, trained on appropriate equipment and fully supported by the VCFG team.

Molecular Genomics
The Molecular Genomics Core facility offers researchers access to state-of-the-art genomics technology platforms, providing service and expertise in conducting genomics experiments. The facility operates three major platforms: Illumina Sequencing, Nanostring nCounter and QX200 Droplet Digital PCR.

Next Generation Sequencing key applications at Peter MacCallum include whole genome and targeted DNA sequencing for the discovery of mutations and structural variations, transcriptome sequencing (RNA-seq), and epigenomics (ChIP-seq). The NanoString nCounter Analysis System is mainly used for gene expression signatures. This platform is part of a new wave of genomic technologies for the rapid and reliable analysis of nucleic acids at single-molecule resolution. It tolerates the use of small amounts of input material (down to a single cell), crude cell lysates or DNA/RNA from archival formalin-fixed paraffin embedded (FFPE) samples.

The MGC works in close collaboration with researchers, clinicians, the Molecular Pathology and the Bioinformatics’ teams to enable and develop tools for the translation of genomic information into clinical practice.

Bioinformatics Consulting Core
The Bioinformatics Consulting Core at the Research Division of Peter Mac provides services and know-how for the analyses of high-throughput genomics data. Bioinformaticians and postdoctoral scientists of the Core work alongside laboratory and clinical researchers to ensure their biological assumptions and the translational relevance of studies are fully considered when building and analysing models of biological systems. The Core contributes to experimental design, grant application and the analysis and publication of genomic and transcriptomic data. Data types analysed by the Core include whole-exome sequencing, targeted re-sequencing, RNA-sequencing and different types of microarray data.

Research Computing Facility
The Research Computing Facility is responsible for administering Peter Mac’s Computing Cluster and Linux environment, providing leadership in the area of data governance, managing the Research Data Repository/Archive, administering cloud computing resources, and providing specialised software solutions and/or systems to support research. The facility also provides training for the software systems they administer and general bioinformatics.

Tissue Bank
Peter Mac has been a leader in the development of sophisticated biospecimen and clinically annotated cancer samples collection. We are the host institute for the Australian Biospecimen Bank a federally funded project to enable national cancer sample collection and facilitated access to tissue resources. The Tissue bank provides researchers with ethically collected, high quality human tissue, blood and data samples for their investigative projects; it also supports clinical trials at Peter Mac by processing and storing blood and tissue specimens in accordance with trial-specific protocols.

Transgenic and SPF Facility
We currently breed and maintain approximately 20,000 mice, representing over 130 different strains of transgenic and gene-targeted mice. Peter Mac’s Animal Ethics Committee (AEC) has an important role in overseeing the ethical conduct of any work involving the use of animals for scientific purposes, conforming to the NHMRC Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.

Molecular Pathology
Molecular Pathology is a central platform to successful translational research by providing robust Diagnostic molecular analyses of tumours. Molecular Pathology at Peter Mac provides diagnostic testing for familial breast and colorectal cancer, and is a national reference centre for testing for specific mutations in cancer samples.

Molecular Imaging
The Centre for Cancer Imaging is a world leader in the clinical use of PET scanning in cancer. The facility includes three chemists, contains a cyclotron, two small animal PET scanners for translational research and automated production facilities for a number of novel tracers. These tracers provide the capacity to image diverse biological processes including hypoxia, lipid synthesis, cell proliferation and amino acid transport.

Biostatistics
Peter Mac is the leading biostatistical centre focusing on cancer clinical trials in Australia. The centre provides statistical expertise for national cancer trials groups including the Trans Tasman Radiation Oncology Group (TRROG) and the Australasian Leukaemia and Lymphoma Study Group (ALLG).

Clinical research nurse core.
Peter Mac currently has a team of research nurses to support a sophisticated clinical and translational research program. These nurses provide necessary skills to coordinate phase I first-in-man clinical trials involving complex procedures such as tumor biopsies for evaluation of molecular targets, serial PET scans and complex pharmacokinetic sampling.
CANCER RESEARCH PROGRAMS

Organogenesis and Cancer Program
https://www.petermac.org/research/programs/organogenesis-cancer

Kieran Harvey Lab
Louise Cheng: Lab
Andrew Cox Lab

The primary focus of the Organogenesis & Cancer program is to investigate the process of organ development and how failure of organogenesis contributes to cancer. Despite being a fundamental part of life, we still lack a clear understanding of how individual organs know how to grow to the right size and maintain this size. The roles of stem and progenitor cells in the growth of different organs are also unclear, as is the impact of diet and nutrition on organ growth. To investigate these questions our program leverages the unique strengths that are offered by different experimental systems including Drosophila, zebrafish, mice and organoid cultures. We also collaborate with clinicians from within the VCCC network to examine how deregulation of organogenesis signalling networks drive cancers such as melanoma, mesothelioma, glioblastoma and hepatocellular carcinoma.

Cancer Genetics and Genomics Program
https://www.petermac.org/research/programs/cancer-genetics-genomics

David Bowtell Lab
Ian Campbell Lab
Kylie Gorringe Lab
Kara Britt Lab

Cancer is fundamentally a polygenic disorder, imparted by germline and somatic mutation. With advances in DNA sequencing and other genomic technologies, it is feasible to obtain high-dimensional genomic information about an individual patient’s tumours and relate this to clinical outcome. The CGG program applies genomic technologies to large patient cohorts, with a particular focus on breast, ovarian and prostate cancer. Familial (KConFab, ViP) and population-based (Lifepool) breast and ovarian (Australian Ovarian Cancer Study) cancer cohorts are embedded in the program and are highly enabling of the research program due to the large numbers of patient samples with rich clinical information and associated biospecimens. More recently the program has established CASCADE, a unique rapid autopsy study that provides an enabling platform for a variety of solid and haematological malignancies. Sophisticated genomics, functional genetics and bioinformatics capabilities are also highly enabling of the program.

Cancer Immunology Program
https://www.petermac.org/research/programs/cancer-immunology

Joe Trapani Lab
Ilia Voskoboinik Lab
Michael Kershaw Lab
Phil Darcy Lab
Jane Oliaro Lab
Sarah Russell Lab
Paul Neeson Lab
Rob Ramsay Lab

The Cancer Immunology Program is identifying ways in which the immune system can be harnessed to prevent and control cancer. We are interested in the very early stages of how immune cells can pick up and respond to the presence of cancer cells. We have demonstrated that specific toxins made by “killer T cells” can prevent the onset of certain cancers (immune surveillance), and are developing genetic technologies to modify and expand the activity of these cells to treat established malignancies. In addition, we are defining the molecular means by which new classes of anti-cancer drugs kill cancer cells, so that rational choices can be made on the most appropriate cancer chemotherapy for a patient.
CANCER RESEARCH PROGRAMS

Cancer Therapeutics Program
https://www.petermac.org/research/programs/cancer-therapeutics

Grant MacArthur: Translational Research Lab
Mark Shackleton Lab
Sarah-Jane Dawson Lab
Rod Hicks Lab
Sherene Loi Lab
Charbel Darido Lab
Ben Solomon Lab
Kristen Brown Lab

The Cancer Therapeutics Program aims to discover, develop, characterise and refine novel cancer therapeutics for clinical use.

This integrated Program allows insight into fundamental aspects of cancer biology through the identification of novel tumour-suppressor and tumour-initiating genes and the functional relationships between altered cancer genetics and aberrations to the cancer epigenome, and a deeper understanding of the molecular events that drive oncogenic signalling networks. These findings serve as a basis for extensive translation-based studies to determine the potential therapeutic benefit of interfering with, or augmenting the activity of key proteins involved in these signalling networks through pharmacological intervention.

Translational Haematology Program
https://www.petermac.org/research/programs/translational-haematology

Mark Dawson Lab
Ricky Johnstone Lab
Sarah-Jane Dawson Lab
Lev Kats Lab

The Cancer Therapeutics Haematology Program contains a diverse set of laboratories that focus on understanding the molecular pathogenesis of a range of haematological malignancies.

The program spans the breadth of basic science and translational medicine with the goal of identifying novel therapies that will improve the outcome of patients with haematological cancers.

Oncogenic Signalling and Growth Control Program
https://www.petermac.org/research/programs/oncogenic-signalling-growth-control

Rick Pearson Lab
Grant McArthur: Molecular Oncology Lab
Wayne Phillips Lab
Vihandha Wickramasinghe Lab
Nicholas Clemons Lab
Ygal Haupt Lab

Targeting these pathways is beginning to profoundly change the management of patients with cancer. A key feature of oncogenic signalling is a requirement for cells to grow and proliferate, processes that are intimately linked to protein synthesis and the provision of metabolic substrates for replication of cellular components. Specifically, increases in ribosomal assembly, mRNA translation and glycolysis are key downstream events in many of the most important pathways involved in malignant transformation. However, it is increasingly recognised that tumour heterogeneity both between lesions and within lesions in individual patients and development of resistance, represent fundamental challenges to attainment of durable responses to targeted therapies. Unravelling the links between oncogenic signalling and their influence on cell biology will be critical to designing new therapeutic approaches and improving patient outcomes.

The global effort to understand the molecular drivers of cancer is now coming to fruition with the identification of specific genomic events that influence signalling through key oncogenic pathways.
CANCER RESEARCH PROGRAMS

Prostate Cancer Program
https://www.petermac.org/research/programs/prostate-cancer

Gail Risbridger Lab
Ygal Haupt Lab

The Prostate Cancer program is new to PMCI and aims to answer significant questions that arise at diagnosis and during treatment of men with Prostate cancer.

Research in this program includes but is not limited to:
• Which tumours are aggressive vs indolent and put men at high risk of progressing to aggressive disease?
• What returns predict tumour progression?
• What treatments can prolong and improve patient survival?

The group uses patient specimens and clinically relevant models of prostate cancer to provide practice changing outcomes to benefit men with prostate cancer.

Tumour Angiogenesis and Microenvironment Program
https://www.petermac.org/research/programs/tumour-angiogenesis-microenvironment

Marc Achen Lab
Steven Stacker Lab
Stephen Fox Lab

The program is interested in understanding the key role played by the non-malignant cells within the tumour microenvironment, which includes stromal cells, blood vascular endothelial cells, lymphatic endothelial cells and immune cells.

The interaction of these cells types with tumour cells can either support or inhibit tumour progression. The spread of cancer to lymph nodes and distant organs is a critical aspect of cancer progression and is facilitated by lymphatic and blood vessels. The cells that line these vessels (the endothelial cells) are the control points for changes to vessel structure and activity.

The program provides broad opportunities for training of postgraduate students, postdoctoral fellows, pathology fellows and clinically trained researchers in areas of basic scientific research, translational research and molecular pathology.

Computational Biology Program
https://www.petermac.org/research/programs/computational-biology

Tony Papenfuss Lab
Research Computing Facility

The Computational Biology program uses mathematics, statistics and computing to generate new discoveries in cancer. We develop new models, algorithms and software tools, and apply these to make sense of cancer data. This includes whole genome, exome, transcriptome and epigenome sequencing data.

Our research interests encompass:
• bioinformatics algorithm and methods development
• computational cancer biology
• cancer evolution and genomics
• software tool development
• personalised medicine.

The Program includes research laboratories, as well as the Bioinformatics Consulting Core and the Research Computing Facility.

Scientists come from a range of disciplines including biology, computer science, mathematics, and statistics, as well as software engineering. Many researchers in the program hold joint appointment with other Programs or institute.
RESEARCH EDUCATION PROGRAM

Research Education
With strong links to local and international universities and research institutes, our research education program provides a training and support framework for the academic and professional development of our staff and students.

Peter Mac is home to over 100 research students undertaking postgraduate and honours research programs.

Most students completing projects at Peter Mac are enrolled through The University of Melbourne. We also host students from all Universities throughout Australia and overseas.

Peter Mac and the Sir Peter MacCallum Department of Oncology also provides research placements for medical research programs, for international postgraduate students, for undergraduate students associated with the Summer Vacation Research Program, undergraduate work experience and undergraduate research projects undertaken in the laboratories.

Postgraduate research students based in clinical settings are supported by the Cancer Research Education program in addition to the support offered by their clinical service teams.

Sir Peter MacCallum Department of Oncology
The Sir Peter MacCallum Department of Oncology is located within the Peter MacCallum Cancer Centre.

The Sir Peter Mac Department brings to the university the strengths of world-class laboratory and clinical research conducted within a public cancer hospital, including:

- the largest cancer research group in Australia, with laboratory-based researchers and clinicians working side-by-side;
- a strong academic program, driven by internationally renowned laboratory and clinical researchers, with a strong focus on educating future generations of cancer researchers;
- highly sophisticated equipment and technology, enabling complex research projects through access to cutting-edge core research technology platforms
- a cancer stream-based and holistic model of care where multidisciplinary experts come together to provide tailored treatment at all stages of a patient’s disease, across all common and rare cancer types.

The co-location of research and research training capability with a hospital dedicated to cancer treatment enables researchers and clinicians to work side-by-side to make significant contributions to basic research, translational research and clinical trials for cancer.

About our program
Our program provides opportunities for students to develop knowledge and expertise in their chosen research area, and also develop professional skills that will help them fulfil their career ambitions.

Our model for research education and training, includes

1) Postgraduate Program Requirements, including support for the research project, progress reviews and supervisor training and management,
2) Research skills development, including mastery of core technologies, critical analysis through exposure to journal clubs, scientific seminars and presentations,
3) Professional and Career development, including generic and transferrable skills, mentoring, networking, leadership, and career opportunities and
4) Science Communication including thesis and journal writing skills and oral or poster presentations at conferences.

Complementing established conventional training for biomedical research students, our program allows our students to develop a higher degree of independence and leadership during their candidature to enhance preparation for a competitive and broader job-market.

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3) Professional and Career development, including generic and transferrable skills, mentoring, networking, leadership, and career opportunities and
4) Science Communication including thesis and journal writing skills and oral or poster presentations at conferences.

Complementing established conventional training for biomedical research students, our program allows our students to develop a higher degree of independence and leadership during their candidature to enhance preparation for a competitive and broader job-market.
We provide a world-class research education program at a leading Australian cancer research institution for students from The University of Melbourne and other national and international universities.

There are two general stages in preparing to become a student in our postgraduate and honours programs.

Students must:
1. Find a project and supervisor for their research program, and
2. Meet the University degree eligibility and entry requirements.

Postgraduate students

Applicants for postgraduate student positions at Peter Mac enrol through a University program that approves your project placement at Peter Mac. You must therefore satisfy the minimum entry requirements at the university through which they plan to enrol.

Entry to the Peter Mac postgraduate program is based on the availability of projects, student suitability and academic background.

To undertake a postgraduate project at Peter Mac, students need to:

- Demonstrate a genuine interest in biomedical research.
- Be happy to conduct your research candidature full time off-campus at Peter Mac.
- Look through the available project summaries and contact the project supervisor directly by phone or email.
- Discuss your interest in the project with the supervisor.
- Meet with potential supervisors at Peter Mac to discuss the project, your interests, visit the lab and meet others in the research group. At this meeting, supervisors will also want to view your academic record.
- International students will ‘meet’ supervisors via Skype or similar.
- Meet university eligibility requirements for postgraduate degree candidature.
- Apply for candidature at The University of Melbourne or at an equivalent university when supervisor and project are confirmed. University of Melbourne students enrol with The Sir Peter MacCallum Department of Oncology, through the Faculty of Medicine, Dentistry and Health Sciences.

Peter Mac staff will work with students to facilitate these processes.

- Apply for a postgraduate scholarship. Note the different deadlines that apply to different scholarships, and for local versus international scholarships.

Honours students

Each year we accept students from biomedical science and science programs to undertake one-year, full time Honours projects in cancer-related biomedical research. Students undertake all of their scientific research work on site at Peter Mac, while undertaking their course work at the university department through which they are enrolled.

Our honours students come to us with a range of majors and backgrounds including biochemistry, chemistry, biomedical science, immunology, cell biology, medicine, pharmacology, molecular biology, pathology, physiology, anatomy and other similar subjects.

Most of our Honours students are enrolled at The University of Melbourne through departments of the Faculty of Medicine, Dentistry and Health Sciences, such as: Biochemistry & Molecular Biology, Pathology, Microbiology & Immunology, Anatomy & Cell Biology and Pharmacology.

Students who have completed their undergraduate degree at another university in Australia or overseas are also encouraged to contact us directly for further information on how to apply.

Students interested in undertaking an Honours project at Peter Mac need to:

- Demonstrate a genuine interest in biomedical research.
- Ensure their university/department approves them conducting their research project full time off-campus at Peter Mac.
- Look through the available project summaries and contact the project supervisor directly by phone or email.
- Discuss your interest in the project with the supervisor.
- Meet with potential supervisors at Peter Mac to discuss the project, your interests, visit the lab and meet others in the research group. At this meeting, supervisors will also want to view your academic record.
- Apply for candidature at the University, meeting the university’s application and eligibility requirements.

Assistance in the application process

Further information about the postgraduate and honours application process is available online at: www.petermac.org/education/research-education

For application assistance, contact:
Dr Caroline Owen
Research Education Manager
Email: caroline.owen@petermac.org
Phone: +61 3 855 95948
“As a doctor involved in the treatment of blood diseases, I’ve always been interested in the science behind the medicine. The seamless integration of clinical and laboratory based research, excellent facilities and friendly, collaborative environment at Peter Mac provide the ideal setting to pursue this. The ‘bench to bedside’ ethos at Peter Mac means that our research findings are directly relevant to improving patient outcomes. This is the ultimate goal of every clinician scientist.”

Dr Jake Shortt
PhD student, Cancer Therapeutics Program, now Haematologist at Monash Medical Centre, and Head, Haematological Research, School of Clinical Sciences, Monash Health.

“Using genetic technologies to study tissue growth in vinegar flies, we discovered three candidate human tumour suppressor genes with the potential to inform the design of novel anti-cancer drugs.”

This work is now informing the next cycle of laboratory studies to further clarify the role of Tao kinases in human cancer, and has the potential to inform the design of novel anti-cancer agents for assessment in pre-clinical studies and, ultimately, in clinical trials.

Dr Carole Poon
PhD Student, Cell Cycle & Development Laboratory, now a Postdoctoral Fellow in the Harvey Laboratory at Peter Mac. Joint winner of the Professor Joseph Sambrook Research Excellence Award in 2012.

“Effective collaboration between laboratory and clinical researchers is vital for improving the outcomes of patients with cancer. One of the most exciting aspects of being a researcher at Peter Mac is the opportunity to take discoveries from the lab to the clinic.”

While undertaking his specialist training in medical oncology, Arun witnessed the emergence of targeted therapies into clinical practice, stimulating his interest in research. Arun’s work involved using novel targeted agents to improve the efficacy of ionizing radiation.

Dr Arun Azad
PhD Student Translational Research Laboratory, followed by a position as Genitourinary Medical Oncology Fellow at the British Columbia Cancer Agency and now leads pre-clinical and clinical translational research in genitourinary cancers in the School of Clinical Sciences at Monash University.
**AVAILABLE PROJECTS BY RESEARCH GROUP**

**ACHEN, MARC**

**TUMOUR ANGIOGENESIS**

**PROGRAM**

The control of vascular remodeling in cancer by microRNAs

Supervisors: Prof. Marc Achen, Prof. Steven Stacker, Prof. Stephen Fox

The remodeling of blood vessels and lymphatic vessels in tumours is critical for metastatic spread which is the most lethal aspect of cancer. We have extensive experience in studying key protein growth factors and cell surface receptors that drive these processes, but there are many signaling pathways involved that are yet to be characterized. MicroRNAs are a group of small regulatory RNA molecules that can coordinately modulate expression of multiple proteins in a signaling pathway; they are central players in gene regulation.

This project will identify microRNAs that regulate vascular remodeling in cancer. This, in turn, will lead to identification of novel signaling pathways required for tumour angiogenesis and lymphangiogenesis (i.e. the growth of blood vessels and lymphatics in tumors). The project will involve molecular and cell biology; vascular biology; systems biology; pathology and bioinformatics. It will provide exciting opportunities for translational studies aimed at restricting the growth and spread of cancer.


**Key Words:** Angiogenesis, Bioinformatics, Endothelial Regulation, Gene Regulation

**Target Students:** PhD/postgraduate, Honours.

**For more information about this project contact:**

**Prof. Marc Achen**

marc.achen@petermac.org

**BOUSSIOUTAS, ALEX**

**CANCER THERAPEUTICS**

**PROGRAM**

Twist as a regulator of EMT in gastric cancer and its role in invasion

Supervisors: A/Prof. Alex Boussioutas, Dr. Rita Busuttil

Gastric cancer (GC) is often diagnosed at advanced stages, giving patients a 5-year survival of less than 20%. Advanced stage GC is directly correlated with increased local invasion of the cancer through the gastric wall and, at more advanced stages into adjacent structures. Epithelial Mesenchymal Transition (EMT) is one mechanism which has been proposed as a modulator of invasion in GC as well as other cancer types. This project seeks to expand on previous work in our laboratory exploring the role of TWIST, a master regulator of EMT, in gastric cancer. We have previously shown that TWIST is more highly expressed at the invasive front of the tumor compared to its core indicating that EMT is occurring in this area. It is conceivable that reducing TWIST expression could be used as a means to decrease the invasive capacity of a cancer. This project will aim to further explore the role of TWIST in the invasion of GC and its potential utility as a therapeutic target. A broad range of techniques including bioinformatics, cell culture, shRNA lentivirus mediated gene knockdown, and molecular biology will be applied.

**Key Words:** Gastric Cancer; Cancer Diagnosis; Cancer Genetics; Genomics; Upper Gastrointestinal Cancers.

**Target Students:** PhD/postgraduate, Honours.

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

Supervisors: A/Prof. Alex Boussioutas, Dr. Rita Busuttil

Gastric cancer (GC) is the fourth most common cancer globally and 7th in incidence in Australia. It has a poor survival rate which can be attributed to the advanced stage at diagnosis in most patients. The molecular and cellular mechanisms underlying the development of GC are not well described. Traditionally cancer research involved studying the cancer cell itself. More recently, there has been growing interest in studying the normal cells and molecules which surround the cancer cell. This tumor microenvironment consists of a variety of stromal cell types including cells such as fibroblasts. It is believed that the dynamic communication between tumor cells and the surrounding cell types may play a major role in cancer initiation, progression and establishment of metastatic disease.

The aim of this project is to investigate tumor-stromal interactions in gastric cancer utilizing established and primary cell lines. Once the molecular pathways by which a tumor cell
For more information about this project contact:
**Prof. David Bowtell**
david.bowtell@petermac.org;
**Dr. Jessica Beach**
jessica.beach@petermac.org.

**BRITT, KARA**

**CANCER GENOMICS PROGRAM**

Finding a therapy for triple negative breast cancer patients

Supervisors: Dr. Kara Britt, Prof. Robin Anderson, Prof. Kelly Phillips

Triple negative breast cancers are a poor prognosis breast cancer with limited therapeutic options as they do not express estrogen receptors, progesterone receptors or Her2. Recent clinical studies have shown that women who have triple negative breast cancers, but also express the alternate estrogen receptor, ERβ, respond well to Tamoxifen.

We will use our mouse model of triple negative breast cancer, engineered to express ERβ, to determine how Tamoxifen exerts benefits to these patients. This project will involve RNA sequencing of tumours.

**Developing breast cancer preventatives by mimicking parity’s protective role**

Supervisor: Dr. Kara Britt

Women who have children (parous) have a reduced risk of breast cancer and this protection is strongest for those bearing children early. Women having children later in life are not protected against breast cancer, but instead at an increased risk. We have developed a mouse model to determine the role of mammary stem cells and stromal fibroblasts in parity-induced protection and will now test therapies aimed at modulating these cells.

**Reversing mammographic density to decrease breast cancer risk**

Supervisors: Dr. Kara Britt, Prof. Rik Thompsonn, Prof. Michael Henderson

Mammographic Density (MD) detects variations in tissue composition. Fat appears dark, stroma/epithelial tissue attenuate x-rays and appear light. Women with the highest MD have 4–6 times the risk of breast cancer, compared to women with the lowest MD, establishing high MD as a major breast cancer risk factor. With 50% of the population having moderate or highly dense breasts, the development of therapies aimed at reducing breast density has the opportunity to broadly decrease breast cancer risk in these women and breast cancer incidence.

**BROWN, KRISTEN**

**CANCER THERAPEUTICS PROGRAM**

Breast cancer is one of the leading causes of cancer-related death in women due in large part to a lack of effective therapies. The Brown laboratory is committed to:

(1) investigating the contributions of oncogenic signalling pathways to breast cancer initiation and progression, and

(2) identifying mechanisms that drive resistance to chemotherapy and targeted therapy agents in breast cancer.

We apply this knowledge to the pre-clinical development of novel and more effective interventions for breast cancer therapy with the ultimate goal to improve patient survival.
Identifying metabolic reprogramming events that fuel chemotherapy resistance in triple-negative breast cancer
Supervisor: Dr. Kristen Brown

Triple-negative breast cancer (TNBC) is a subtype of breast cancer for which treatment options are limited to conventional chemotherapy agents. Chemotherapy resistance is a major barrier to the successful treatment of TNBC and there is a critical need to identify novel and actionable strategies to circumvent resistance and enhance the efficacy of chemotherapy.

In recent years there has been renewed interest in understanding how cancer-associated reprogramming of cellular metabolism promotes tumorigenesis. Using an unbiased metabolomics platform we have identified the spectrum of metabolic reprogramming events induced when TNBC cells are exposed to clinically relevant chemotherapy agents and have identified metabolic pathways that act as critical nodes of regulation by chemotherapy.

Using a variety of in vitro and in vivo techniques we seek to:

(1) thoroughly characterize the contribution of the identified metabolic pathways to chemotherapy resistance and breast cancer progression, and

(2) identify novel therapeutic approaches to exploit these adaptive metabolic reprogramming events and sensitize TNBCs to chemotherapy. This research will lead to the identification of critical mechanisms driving chemotherapy resistance in TNBC and establish combination therapy strategies with potential to have a major impact on patient survival.

Identifying downstream effectors of oncogenic serum and glucocorticoid-regulated kinase 1 (SGK1) signalling in breast cancer
Supervisor: Dr. Kristen Brown

The phosphoinositide 3-kinase (PI3K) pathway is a master regulator of processes that contribute to tumour development and maintenance. Deregulation of the PI3K pathway is implicated in virtually all cancers and as a consequence the pathway has been aggressively targeted for cancer therapy.

Although most work has focused on the Akt kinase family as major downstream effectors of PI3K, the closely related serum and glucocorticoid-regulated kinase (SGK) family (comprised of SGK1, SGK2 and SGK3) has by comparison received little attention. SGK1 plays a critical role in driving the expansion of tumour cells and can promote resistance to both conventional chemotherapy and targeted therapy agents. The molecular mechanisms that permit SGK1 to elicit its oncogenic activities are largely unknown, in part because the substrates and interaction partners of SGK1 are poorly defined.

Using the proximity-dependent biotin identification (BioID) method, we seek to identify SGK1 substrates and interacting proteins in breast cancer cells. The contribution of the identified candidate substrates and interacting proteins to breast cancer progression and therapy resistance will be determined using a variety of in vitro and in vivo techniques. These studies will elucidate critical downstream effectors of oncogenic PI3K/SGK1 signalling and identify novel targets for therapeutic intervention.

Key Words: Breast Cancers, Cancer Therapy, Molecular Biomarkers, Molecular Targets.

Target Students: PhD/postgraduate.

For more information about these projects contact:
Dr. Kristen Brown
kristen.brown@petermac.org

CAMPBELL, IAN
CANCER GENOMICS PROGRAM
Identification of genetic variation predisposing to ovarian cancer
Supervisors: Prof. Ian Campbell, A/Prof. Paul James

Ovarian cancer (OC) has a strong heritable component but BRCA1 or BRCA2 mutations account for only ~40% of the heritable fraction. We hypothesize that analogous to our findings in breast cancer families, much of the ‘missing’ heritability of OC is explained by mutations in many moderate or high penetrance genes, but that any one gene defect is present in only a few families. Given the likely heterogeneity for non-BRCA1/2 OC families, family-based whole exome sequencing (WES) will be a powerful means of identifying new predisposition genes. Following familial WES analysis, candidate genes will be screened in 1000 additional familial ovarian cancer index cases and matching controls. Genes will also be investigated by segregation analysis in positive families and LOH analysis in tumour DNA. In addition to discovery of new genes by WES, all cases and family members will be genotyped for all highly validated low penetrance SNPs to calculate a polygenic risk score that will determine if co-inheritance of low penetrance risk alleles may explain some familial OC aggregation.

Key Words: Bioinformatics, Breast Cancers, Cancer Genetics, Familial Cancer.

Target Students: PhD/postgraduate.

For more information about these projects contact:
Prof. Ian Campbell
ian.campbell@petermac.org
A/Prof Paul James
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CHENG, LOUISE
ORGANOGENESIS AND CANCER PROGRAM
Metabolic regulation of tumour growth

Studies of neural stem cell biology in model organisms have revealed many similarities in the regulation of self-renewal, multipotency and cell-fate determination between vertebrate and invertebrates. We use the fruit fly Drosophila as a model system to study the processes that regulate proliferation in the central nervous system, and when disrupted result in neural tumours due to uncontrolled growth and proliferation.
How does amino acid metabolism affect tumour growth?

Supervisors: Dr. Francesca Froldi, Dr. Louise Cheng

The effect of diet on tumour growth is hotly debated but poorly characterized. Due to the heterogeneous nature of the tumours, dietary studies in patients with varied genetic background often led to inconclusive outcome. Dedifferentiation is a cellular process by which a partially or terminally differentiated cell reverts to a less differentiated, more multipotent state. The bidirectional conversion between differentiated cells and stem cells often underlies carcinogenesis. Cancer such as glioblastoma, the most aggressive subtype of the gliomas are thought to originate from terminally differentiated cortical astrocytes and neurons. Similarly, through expressing the right combination of transcription factors, non-cancer stem cells can also convert to highly proliferative cancer stem cells found in intestinal tumours. Using a combination of genetics, metabolic and genomic techniques, the student will address the knowledge gap of how diet, in particular amino acid metabolism, impacts on cellular dedifferentiation, and tumour growth. These studies will allow us to quickly and systematically identify tumour metabolic dependencies, and shed light on important metabolic targets, which can be assessed in other stem cell and tumour settings. The student participating in this project will use a combination of Drosophila genetics, confocal microscopy, FACS analysis and molecular biology techniques to address this question.

Key Words: Cancer Cell Biology, Cell Metabolism, Differentiation, Molecular Imaging, Stem Cells.

Target Students: Honours.

Identification of factors which regulate neural dedifferentiation

Supervisors: Dr. Francesca Froldi, Dr. Louise Cheng

It has been known that differentiated cells can switch fates, more recently, we and others have uncovered mechanisms by which postmitotic cells use in vivo to reverse their differentiation state. This sort of cellular reprogramming is a fundamental process, which can invoke regenerative cells from mature cells, and can act as a reserve to generate stem cells when required. We are interested in identifying signals which regulates reactivation of stem cells from quiescence. The student will use a range of genetic tools, to uncover the mechanism by which the stem cell niche regulates stem cell reversion.

Key Words: Cancer Cell Biology, Stem Cells.

Target Students: Honours.

How do tumours grow at the expense of other tissues?

Supervisors: Dr. Francesca Froldi, Dr. Louise Cheng

Cancer cells are known to drive altered metabolic circuits to meet the bioenergetic and biosynthetic demands of increased cell growth and proliferation. Under nutrient restriction, when growth of most organs shut down, cancer cells can bypass these brakes imposed on cellular growth, thus gaining a growth advantage under these conditions. Furthermore, during calchexia, which causes more than one third of cancer death, tumour derived factors can also induce the break down of fat and skeletal muscles, in order to generate metabolic intermediates necessary for the preferential tumour growth. The signalling between tumours and other tissues is highly complex, and the adaptations that allow cancer cells to preferentially activate growth are largely unknown. The student will: utilise a brain tumour model to study how tumour cells communicate with other tissues to gain a growth advantage; and utilise Drosophila genetics, transplantation assays, confocal microscopy, FACS analysis and molecular techniques to address this question.

Key Words: Cancer Cell Biology, Cell Metabolism, Differentiation, Molecular Imaging, Stem Cells.

Target Students: Honours.

AVAILABLE PROJECTS BY RESEARCH GROUP

CLEMENS, NICHOLAS

ONCOGENIC SIGNALLING AND GROWTH CONTROL PROGRAM

Novel therapies to reactivate p53 function in mutant p53 cancers

Supervisors: Dr. Nick Clemons, Prof. Wayne Phillips, Dr. Cuong Duong

We have recently commenced a clinical trial of APR-246, a novel drug that restores wild-type function to mutant p53, in chemotherapy resistant oesophageal cancer (STAMPEDE Trial). The next stage of our laboratory studies is to evaluate novel combination therapies with APR-246 that enhance its efficacy, and develop biomarkers that predict therapeutic response.

This project will use patient samples and innovative pre-clinical models that we have developed to establish the most effective drug combinations and companion biomarkers for testing in future clinical trials.

Key Words: Cancer Cell Biology, Cancer Therapy, Molecular Biomarkers, Molecular Targets, Solid Tumours, Tumour Suppression, Upper Gastrointestinal Cancers, Animal Models.

Target Students: PhD/Postgraduate, Honours.

Developing strategies to combat chemoresistance in oesophageal cancer

Supervisor: Dr. Nick Clemons

Oesophageal cancer has a poor prognosis with many patients succumbing to their disease within a year of diagnosis and fewer than 20% surviving beyond 5 years. This dismal outcome is largely due to intrinsic or acquired chemoresistance that almost invariably occurs and remains a major challenge.

This project will explore the mechanisms leading to chemoresistance in cell line models of innate and acquired resistance we have established, and develop strategies to combat chemoresistance, including a novel strategy targeting ALK4/5 to restore sensitivity to platinum based therapies.
AVAILABLE PROJECTS BY RESEARCH GROUP

Key Words: Cancer Cell Biology, Cancer Therapy, Molecular Biomarkers, Molecula Targets, Solid Tumours, Tumour Suppression, Upper Gastrointestinal Cancers, Animal Models.

Target Students: Honours.

Targeting redox balance in mutant p53 cancers
Supervisors: Dr. Nick Clemons, Prof. Wayne Phillips, Dr. Cuong Duong

The tumour suppressor p53 is mutated in over half of all cancers and is associated with tumourigenesis, resistance to chemotherapy and poor prognosis. We have recently shown that mutant p53 suppresses glutathione synthesis, disrupting redox balance and providing a weakness that we can exploit using therapies that target anti-oxidant synthesis.

This project will determine the mechanism by which mutant p53 suppresses this pathway and develop novel therapeutic strategies in vitro and in vivo models to target this Achilles heel.

Key Words: Cancer Cell Biology, Cancer Therapy, Molecular Biomarkers, Molecula Targets, Solid Tumours, Tumour Suppression, Upper Gastrointestinal Cancers, Animal Models.

Target Students: PhD/Postgraduate, Honours.

For more information about these projects contact:
Dr. Nick Clemons
nicholas.clemons@petermac.org

COX, ANDREW

ORGANOGENESIS AND CANCER PROGRAM

In the Cox laboratory, we investigate mechanisms by which oncogenic pathways reprogram metabolism to fuel liver growth in the context of development, regeneration and cancer. Our research team uses a combination of metabolomic and transcriptomic approaches in zebrafish (Danio rerio) to study metabolic reprogramming in vivo. Our ultimate vision is to identify therapeutic strategies that exploit the metabolic vulnerabilities of liver tumors.

Fishing for metabolic clues: Role of the Hippo/Yap pathway in reprogramming metabolism to fuel tissue growth and cancer
Supervisor: Dr. Andrew Cox

The Hippo/Yap pathway is an evolutionarily conserved cascade that plays a fundamental role in governing organ size control, stem cell homeostasis and cancer. The Hippo/Yap pathway is regulated by a range of environmental cues including nutrient status. Although many of the inputs into the Hippo pathway have been identified, less is known about the Yap target genes responsible for tissue growth. Using a combination of metabolomic and transcriptomic approaches in zebrafish, we have discovered that Yap reprograms glutamine metabolism in vivo to stimulate nucleotide biosynthesis and fuel premalignant liver growth. Building on this initial investigation, we currently have research projects that aim to

(1) Examine how Yap coordinates nutrient sensing to metabolic output in the liver.
(2) Elucidate the mechanisms by which Yap reprograms metabolism to fuel liver growth in the context of regeneration and cancer.

The students will use a combination of innovative biochemical, genetic and imaging approaches in zebrafish to identify the metabolic dependencies of tissue growth during regeneration and cancer.

Key Words: Cancer Cell Biology, Cancer Therapy, Cell Biology, Cancer Therapy, Cell Growth, Cell Metabolism, Gene Expression, Solid Tumours, Stem Cells.

Target Students: PhD/Postgraduate, Honours.

For more information about these projects contact:
Dr. Andrew Cox
andrew.cox@petermac.org

DARCY, PHIL

CANCER IMMUNOLOGY PROGRAM

Enhancing the efficacy of Adoptive cellular Immunotherapy for cancer
Supervisor: A/Prof. Phil Darcey, Dr. Paul Beavis

It is becoming increasingly apparent that engaging anti-tumour immune responses is fundamental for effective cancer treatment. However, in many cancer types, the immune system remains ‘ignorant’ of the cancer, leading to the absence of tumour-infiltrating lymphocytes. One effective
available projects by research group

therapeutic option is a process called adoptive immunotherapy. This involves genetically engineering a patient’s peripheral blood lymphocytes with a chimeric antigen receptor (CAR) enabling recognition of tumour antigen, expanding these cells ex vivo and then reinfusion back into the patient. These CAR T cells have been shown to be highly effective in haematological malignancies but have had little impact on other cancer types. Generally speaking these expanded CAR T cells predominantly consist of conventional CD8+ and CD4+ T cells. However, the importance and contribution of other cell types within this population such as NK cells, NKT cells and MAIT cells is not understood.

Using a highly novel transgenic mouse in which all immune cells express the Chimeric Antigen Receptor, this project would evaluate the potential of these immune subsets to promote an anti-tumour immune response both in vitro and in vivo. Techniques that will be used include, cell culture, flow cytometry, chromium release assay, ELISA, cytometric bead array and in vivo mouse experiments.

Key Words: Breast Cancers, Cancer Therapy, Cellular Immunology, Genetic Immunology, Immunotherapy, Solid Tumours, Tumour Immunology.

Target Students: PhD/Postgraduate, Honours.

For more information about this project contact:
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Dr. Paul Beavis
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DARIDO, CHARBEL

CANCER THERAPEUTICS PROGRAM

Investigating the requirements of pro-inflammatory signaling in skin and head & neck Squamous Cell Carcinomas

Supervisor: Dr. Charbel Darido

Squamous cell carcinomas (SCC) are amongst the most common cancer types afflicting man. SCCs most frequently arise from stratified squamous epithelia such as the epidermis or the mucosa of the head and neck. We have recently identified two novel microRNA-21 (miR-21)-dependent proto-oncogenic networks that underpin SCC in skin and head & neck in both mice and humans. Here we hypothesise that inflammation in SCC occurs in a tissue-specific manner leading to miR-21 induction. The project is designed to investigate which upstream pro-inflammatory pathways promote dysregulation of miR-21 in skin versus head & neck.

Successful completion of this project will pioneer novel experimental approaches and will determine the merit to explore tissue-specific targeted therapies of human SCC to improve clinical outcomes in this disease. A wide range of skills will be taught including biochemistry, molecular biology, cell culture and knockout mice. This is an ideal project for a student who wishes to pursue higher studies in cancer research.

Identification of the cell of origin of Grhl3-deficient head and neck squamous cell carcinoma

Supervisor: Dr. Charbel Darido

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading cancer by incidence worldwide. The lack of appropriate animal models prevents the establishment of improved treatment options for HNSCC patients. Our laboratory has recently identified a novel factor, Grhl3, critical for tumour suppression in HNSCC in mice and humans. Through the use of unique HNSCC mouse models that are driven by same cancer-causing molecular drivers as the patients, this project will enable delineation of the origin of HNSCC and testing of targeted therapies. Predicted outcomes have the potential to stratify treatment in HNSCC based on underlying molecular signatures.

This project aims to:
(1) Understanding the biology of HNSCC to comprehend the increasing incidence of the disease
(2) Identify and characterise the cell of origin in Grhl3-deficient HNSCCs
(3) Establish a molecular signature, whereby patients can be stratified to receive drugs that are specific to their tumours

Key Words: Cancer Cell Biology, Cancer Therapy, Molecular Biomarkers, Molecular Targets, Solid Tumours, Tumour Suppression Animal Models.

Target Students: PhD/Postgraduate, Honours.

For more information about these projects contact:
Dr. Charbel Darido
charbel.darido@petermac.org

DAWSON, SARAH-JANE

CANCER THERAPEUTICS PROGRAM, AND TRANSLATIONAL HAEMATOLOGY PROGRAM

Circulating tumour DNA to monitor treatment response and resistance in Hepatocellular Carcinoma

Supervisor: Dr. Sarah-Jane Dawson

Hepatocellular carcinoma (HCC) is the sixth most common cancer and is associated with survival rates of only 3-5% despite treatment. Transarterial chemotherapy (TACE) is one of the most commonly used treatments for HCC, but outcomes after treatment remain poor. There is an unmet need for biomarkers to predict outcomes and optimise treatment decisions in patients with HCC. Novel biomarkers that help assess treatment response following TACE have the potential to assist in the early identification of treatment failure and prioritise the need for alternative therapy.

This research project will utilize cell free circulating tumour DNA (ctDNA) analysis as a “liquid biopsy” alternative to tissue biopsies, to allow the noninvasive molecular monitoring of tumour dynamics, treatment responses and therapeutic resistance in patients receiving TACE treatment for HCC. The study will be conducted through a collaboration within the Victorian Comprehensive Cancer Centre, between Peter Mac (S. Dawson...
This project will investigate the intracellular signaling pathways impacted by loss of Par3 to further understand the onset and progression of AML.

Methodologies will include cell culture, western blotting, quantitative RT-PCR, immunohistochemistry, and live cell microscopy.

Key Words: Cancer Cell Biology; Cancer Epigenetics; Cancer Signalling; Cancer Therapy; Cell Cycle; Cell Growth, Proliferation and Death.; Cellular Immunity; Differentiation; Haematology; Haematological Cancers; Innate Immunity; Tumour Immunology; Tumour Suppression.

Target Students: Honours

For more information about these projects contact:

A/Prof. Sarah Ellis
sarah.ellis@petermac.org

FELLOWS, ANDREW

MOLECULAR PATHOLOGY AND RESEARCH COMPUTING

The Molecular Pathology Department at Peter MacCallum Cancer Centre performs accredited clinical testing of cancer patients by detecting molecular biomarkers that are:

(1) diagnostic of cancer,
(2) predictive of cancer response to targeted therapy, or
(3) prognostic of disease progression.

Clinical Trials Database Design and Implementation

Supervisors: Dr. Andrew Fellowes, Mr. Anthony Bell, Mr Ken Doig, Mr Gareth Reid.

Historically, laboratory activity data has been aggregated and archived in Microsoft Excel spreadsheets located in specific network folders. The spreadsheets contain potentially valuable information relating to laboratory performance and clinical demand over time and, importantly, the molecular epidemiology of cancer within our community and clinical catchment. However in its present form, this information is inaccessible.

In order to capitalize on this historical data, the laboratory requires that it is housed in a relational database application. The application should employ modern best-practice
database standards and be capable of housing both historical testing records from the diverse data sources described above, as well as data from contemporary testing activity generated as part of ongoing clinical and clinical trial activity.

This project would suit a masters student studying in the information technology discipline and with an interest in database design and data management. Supervision will be provided by qualified laboratory and information technology professionals within the Peter MacCallum Cancer Centre Pathology Department and Research Computing Department.

Key Words: Bioinformatics; Data Management. Epidemiology; Database Design;

Target Students: Masters.

**Molecular Pathology Workflow Metrics Data Visualisation**

Supervisors: Dr. Andrew Fellowes, Mr. Anthony Bell, Mr Christopher Welsh, Mr. Reid.

Laboratory workflow activity is changing due to the introduction of massively parallel sequencing technology and a drive toward paperless laboratory records. A paperless laboratory workflow management system, Genologics Clarity LIMS (an Illumina company) and the recently released Clarity LIMS Report Manager (based on Tableau Server 9.3) are now installed and supported in the laboratory. Clarity LIMS contains hundreds of data fields relating to sample quality, workflow performance, and laboratory productivity, and Clarity Report Manager allows both detailed and aggregate real-time reporting at all these levels. The laboratory now requires the development of ‘information radiators’ to convey relevant, visually interpretable, up-to-date workflow information throughout the laboratory environment. We envisage passive HDTV screens networked through low cost WiFi devices displaying custom reports created using the above systems.

This project would suit a masters student studying in the information technology discipline and with an interest in data analytics, data visualization, digital mapping and statistics. Supervision will be provided by qualified laboratory and information technology professionals within Peter Mac’s Centre Pathology and Research Computing Departments.

Key Words: Bioinformatics; Data Management.

Target Students: Masters.

For more information about these projects contact:

**Dr. Andrew Fellowes**

andrew.fellowes@petermac.org

**GORRINGE, KYLIE**

**CANCER GENOMICS PROGRAM**

**Personalised risk evaluation in DCIS**

Supervisors: Dr. Kylie Gorringe, Prof. Ian Campbell

Breast screening using mammography has seen an increased detection of not only invasive breast cancer, but also pre-invasive lesions such as ductal carcinoma in situ (DCIS). The clinical management of DCIS is problematical due to a lack of accurate prognostic and predictive tests. If recurrence risk could be accurately estimated, those with low risk disease could be offered surgery only, and those with high risk of recurrence have excision plus radiotherapy or a full mastectomy, thus optimising patient outcomes while minimising treatment toxicity. Thus, our principal research question is: are there molecular biomarkers that can predict which DCIS are at higher risk for recurrence?

The project will involve molecular analysis of DCIS cases both with and without later recurrence to identify potential biomarkers, which may include DNA mutations, copy number changes, and gene expression. Techniques will include DNA/RNA extraction from tumour tissue, analysis by next-generation sequencing and/or a Nanostring expression assay. Analysis methods may include using in situ methods such as immunohistochemistry and FISH. The project is particularly suited to someone with a clinical focus or background.

Key Words: Breast Cancers; Cancer Genetics; Cancer Genomics; Molecular Biomarkers; Pathology; Precision Medicine; Mammography; CLinical Management.

Target Students: PhD/Postgraduate, Honours.

**Analysis of USP9X in low grade ovarian serous carcinoma**

Supervisors: Dr. Kylie Gorringe, Prof. Ian Campbell, Dr. Dane Cheasley

The focus in this project is on ovarian cancer patients with low-grade serous carcinoma (LGSC), a subtype that tends to occur in younger women and does not respond to current standard chemotherapy. Our exome sequencing identified recurrent mutations in KRAS (18, 30%), BRAF (8, 13%) and NRAS (6, 10%), as expected. Additionally, 4 tumours (13%) had inactivating alterations in USP9X, a novel candidate tumour suppressor gene.

We will test the transformation potential of USP9X by gene knockdown in cell lines using lentiviral vectors. We will assay knock-down efficiency using quantitative RT-PCR and Western blot, and assess proliferation/apoptosis using methods developed by the Victorian Centre for Functional Genomics including high-content cellular imaging. We will measure clonogenic survival and anchorage independent growth (soft agar cloning).

Depending on the length of the degree course project, the project may also entail DNA sequencing of additional candidate genes identified by exome and whole genome sequencing, as well as tissue microdissection and DNA/RNA extraction.

Key Words: Cancer Genetics; Cancer Genomics, Gaenacological Cancers; Gene Knock-down, in vitro Functional Studies.

Target Students: PhD/Postgraduate, Honours.

For more information about these projects contact:

**Dr. Kylie Gorringe**

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HARVEY, KIERAN

ORGANOGENESIS AND CANCER PROGRAM

Control of tissue growth and cancer by the Hippo pathway
Supervisors: Dr. Joep Vissers, A/Prof. Kieran Harvey

Our laboratory is focused on determining how the Hippo signalling pathway controls tissue growth during development and in cancer. The Hippo pathway is the most recently identified major signalling pathway and is a key regulator of organ size. We and others also discovered that the Hippo pathway is deregulated in many human cancers.

We currently have several different projects available aimed at studying the mechanism by which the Hippo pathway controls organ size and cancer, using an array of genetic, cell biological and biochemical techniques. The aims of our laboratory are to:

(1) Understand how the Hippo pathway controls organ size during development.
(2) Define the role of Hippo pathway in human cancers.
(3) Develop drugs to target the Hippo pathway for therapeutic benefit.

A broad range of cutting-edge techniques will be used, including confocal microscopy, immunohistochemistry, Drosophila genetics, molecular biology, cell biology. All techniques are routinely used by the laboratory and training will be provided. Our laboratory is looking for intelligent, motivated Honours students to join our team. You should have a willingness to learn a number of different biological techniques, and be able to integrate into a close team environment.

Key Words: Cancer Cell Biology; Cell Signalling; Cell Development; Proliferation and Death; Skin Cancers; Solid Tumours; Developmental Biology.

Target Students: Honours.

For more information about this project contact:
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HAUPT, YGAL

PROSTATE CANCER PROGRAM, AND ORGANOGENESIS AND CANCER PROGRAM

Exploration of novel approaches to anti-cancer treatment: manipulation of mutant p53
Supervisors: Dr. Sue Haupt, Prof. Ygal Haupt

P53 is the most mutated gene in human cancer, affecting about half the cases of human cancer. We have recently identified novel regulators of mutant p53 using sophisticated loss of function whole genome high through put screen (image 1). We have combined computational and bioinformatics analyses together with biochemical assays to select key candidate novel regulators of mutant p53.

This PhD project will study key candidate regulators derived from this screen to explore the regulation of mutant p53, and to define novel target for anti-cancer drugs aiming at mutant p53. The student will explore the efficacy of manipulating these regulators as a novel approach to treating cancer cells bearing mutant p53 (majority of human cancers). The project will involve work with cancer cell lines and transgenic mouse models. In addition the project will expose students to a variety of molecular, cellular and biochemical techniques.

Key Words: Breast Cancers; Cancer Cell Biology; Cancer Therapy; Genomics; Therapeutics; Tumour Suppression; Functional Screen.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:
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Prof. Ygal Haupt
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Restoration of tumour suppression using the ubiquitin proteasomal system as an anti-cancer approach

Supervisor: Prof. Ygal Haupt

A link between proteasomal degradation of proteins and cancer has been firmly established. Specifically, the degradation of tumour suppressors by oncogenic E3 ligases is a key step during cancer development. This suggests an attractive therapeutic opportunity to protect the tumour suppressors from degradation. We have recently discovered that E6AP is the major regulator of the stability of the tumour suppressor PML, by acting as its E3 ubiquitin ligase (Cell Death & Diff, 2009; Blood, 2012). PML is frequently downregulated or lost in many cancers; we hypothesize that this is due to upregulation of E6AP.

The overall aim of this project is to explore the involvement of the E6AP-PML axis in different human cancers and to test whether restoration of PML by interference with E6AP, either alone or in combination with chemotherapy, is an effective anti-cancer treatment. The project will involve a variety of molecular and biochemical assays, as well as cell culture, mouse models and a screen of human cancer samples.

Key Words: Cancer Cell Biology; Tumour Suppression; Proteasomal Degradation; Biochemistry.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:

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Exploring novel regulators of mutant p53 using computational analyses

Supervisor: Prof. Ygal Haupt

Mutations in the gene encoding the major tumour suppressor Tp53 are the most common genetic events in human cancers. Mutations in the resultant protein can eliminate its tumour suppressive capacity and also confer new functions that promote cancer. Identifying the ramifications of p53 mutation for its activities and regulation remains a vital area of research with many questions unanswered. We adopted a discovery approach to identify novel candidates from across the entire genome that can regulate mutant p53. Our screens have generated a wealth of knowledge, which we are analyzing to understand the regulation networks around mutant p53.

For this purpose we are seeking PhD students with relevant experience in computational biology. The appropriate PhD candidate will work with a bioinformatician to develop computational analyses of mutant p53 networks and define its involvement in different cancer types. Information derived from these analyses will be used to design validations studies and to develop novel approaches to target mutant p53 therapeutically.

Key Words: Breast Cancers; Cancer Cell Biology; Cancer Therapy; Computational Biology; Genomics; Therapeutics; Tumour Suppression; Functional Screen.

Target Students: PhD/postgraduate.

For more information about this project contact:

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HICKS, RODNEY
CANCER THERAPEUTICS PROGRAM

Understanding intra-patient disease heterogeneity in human melanoma

Supervisor: Dr. Richard Tothill

Merkel cell carcinoma (MCC) is a rare but aggressive neuroendocrine malignancy of the skin that is linked to viral infection and sun exposure. Conventional treatments (chemotherapy and radiotherapy) do not provide durable responses in MCC patients with advanced disease. Tumours of either viral aetiology or high mutation load are known to induce strong cytolytic T-cell immune responses that may render these cancers sensitive to immunotherapy. As not all patients will respond to such treatments an improved understanding of both the genetics and the tumour immune microenvironment is required in order to identify biomarkers of treatment response and alternative therapeutic strategies.

With access to large cohorts of patient samples, an ongoing prospective biomarker study including patients who are being treated with immune checkpoint inhibitors we have an excellent PhD project available for a motivated student interested in cross-disciplinary translational research using genomic and other cutting edge technologies.

Key Words: Cancer Cell Biology; Cancer Genetics; Cell Signalling; Cancer Therapy; Cell Development; Proliferation and Death; Cell Growth; Molecular Targets; Skin Cancers (incl. Melanoma); Solid Tumours; Therapeutics.

Target Students: PhD/postgraduate.

For more information about this project contact:

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Understanding the mechanisms of biologically targeted radiation on neuroendocrine tumours and the host immune system

Supervisors: Dr. Richard Tothill, Dr. Carleen Cullinane, Prof. Rod Hicks

Peptide receptor radionuclide therapy (PRRT) involves the use of radio-labelled somatostatin analogues targeting the somatostatin receptor that is widely expressed on neuroendocrine cells. Although it is assumed that radiation causes catastrophic DNA damage and cell death, much is still unknown about the direct mechanism of treatment on cancer cells and the potential side effects on the patient’s immune system. Furthering our understanding of these mechanisms will allow improvements in current treatment and the potential to combine PRRT with new immunotherapeutic drugs.

Using a transgenic neuroendocrine model of small cell lung cancer we have the ability to study the localised and systemic effects of PRRT in immunocompetent mice. Furthermore, as the Peter Mac is state-wide referral service for the treatment of NET patients we have access to patient samples.

Key Words: Cancer Cell Biology; Cancer Genetics; Cell Signalling; Cancer Therapy; Cell Development; Proliferation and Death; Cell Growth; Molecular Targets; Skin Cancers (incl. Melanoma); Solid Tumours; Therapeutics.

Target Students: PhD/postgraduate.

For more information about this project contact:

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samples undergoing PRRT through prospective biomarker studies. We therefore have an exciting opportunity for a student project in our lab involving cross-disciplinary research in the cutting edge field of nuclear medicine.

Key Words: Cancer Cell Biology; Cancer Genetics; Cell Signalling; Cancer Therapy; Cell Development, Proliferation and Death; Cell Growth; Molecular Targets; Skin Cancers (incl. Melanoma); Solid Tumours; Therapeutics.

Target Students: PhD/postgraduate, Honours.

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JOHNSTONE, RICKY

TRANSLATIONAL HAEMATOLOGY PROGRAM

Investigating the role of CRLF2/JAK2 Signaling in high-risk B-cell Acute Lymphoblastic Leukemia (B-ALL)

Supervisor: Prof. Ricky Johnstone

Chromosomal translocations leading to overexpression of the cytokine receptor CRLF2 frequently occur in B-cell ALL (B-ALL), and this is closely linked with activating mutations of JAK2 kinase and adverse prognosis. Overexpressed CRLF2 and mutant JAK2 physically associate resulting in activation of important oncogenic pathways.

To investigate the functional role of CRLF2 and JAK2 mutations during leukemia initiation, the laboratory generated transgenic mice expressing murine CRLF2 under the control of the immunoglobulin heavy chain enhancer (EU) to enforce lymphoid-specific expression of our transgene. We retrovirally transduced fetal liver stem cells from day E13.5 embryos of EU-mCRLF2 transgenic mice with GFP-tagged constructs expressing JAK2WT, JAK2R683G, JAK2P933R or an empty vector, followed by transplantation into irradiated recipient mice. Cohorts transplanted with EU-CRLF2 fetal liver cells expressing mutant JAK2 exclusively developed leukemia characterized by hepatosplenomegaly, expansion of c-kit+ GFP+ blasts, and exhibited constitutive JAK-STAT signaling. Hence, our results demonstrate that CRLF2 overexpression and mutant JAK2 cooperate during leukemia initiation.

This project aims to investigate how CRLF2 and JAK2 cooperate in the initiation and progression of B-ALL, and to develop novel therapeutic strategies to treat tumors with aberrant CRLF2/JAK2 signaling.

Key Words: Haematological Cancers; Cancer Cell Biology; Gene Expression; Gene Regulation; Animal Models.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:

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KATS, LEV

TRANSLATIONAL HAEMATOLOGY PROGRAM

Development of targeted therapy for acute myeloid leukaemia with mutations in isocitrate dehydrogenase

Supervisor: Dr. Lev Kats

Acute Myeloid Leukaemia (AML) is an aggressive disease with poor prognosis and development of novel treatment options is urgently needed. Isocitrate Dehydrogenase (IDH)-1 and -2 catalyse the conversion of isocitrate to a-ketoglutarate (a-KG), a crucial metabolite that is an intermediate in the TCA cycle and an essential co-substrate for >60 enzymes with a wide range of functions. IDH1 and -2 mutations occur in ~20% of AML as well as a range of other cancers and pre-malignancy syndromes. Mutations typically confer on the enzymes a novel ability to produce D-2-hydroxyglutarate (2-HG), a molecule that is structurally similar to a-KG and can act as an inhibitor or activator of a-KG-dependent enzymes.

We and others have recently shown that IDH mutations can contribute to leukaemia initiation and maintenance both in vitro and in vivo; and small molecule inhibitors that block production of 2-HG have recently entered clinical trials. However, the precise mechanism and genetic determinants of therapy response to IDH inhibition remain unknown.

The specific aims of this study are to:

(1) Develop a series of clinically relevant, genetically engineered murine AML models wherein expression of mutant IDH is inducible;

(2) Evaluate the requirement for continued expression of mutant IDH for prolonged leukaemia growth and survival by genetically depleting expression (genetic de-induction) and pharmacologically inhibiting the mutant enzymes; and

(3) Understand the mechanism of disease regression following genetic de-induction and pharmacological inhibition of mutant IDH.

Key Words: Haematological Cancers; Cancer Cell Biology; Gene Expression; Gene Regulation; Animal Models.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:

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LOI, SHERENE
CANCER GENOMICS PROGRAM

Breast Cancer remains the biggest killer of women in the Western World. The aim of our lab is to understand response and resistance to breast cancer therapies and to try to develop new drug targets.

Development of new therapeutic approaches for the treatment of Breast Cancer patients: Projects 1 and 2

Supervisors: Dr. Mariam Mansour, A/Prof. Sherene Loi

Project 1: Investigating a novel combination of Neratinib and immunotherapy in HER2 breast cancer subtype.

The aim of this project is to investigate the therapeutic efficacy of combining Neratinib with anti-PD1 antibody. We will examine whether these combinations will be synergistic leading to an increased anti-tumour immune response in HER2 mouse models. Subsequently, we will define mechanisms of action underlying the anti-tumour efficacy of the combination therapy.

Project 2: Developing Trastuzumab Emanstine as a novel therapy for a subset of triple negative breast cancer patients.

The aim of this project is to determine whether T-DM1 may be a viable treatment option for TNBC which express low levels of HER2. First, we will investigate T-DM1 therapeutic efficacy in the low HER2 phenotypes. Second, we will examine if T-DM1 is effective at eliciting an anti-tumour immunity that will render these models more susceptible to the checkpoint blockade. Subsequently, we will evaluate the synergistic effect of the combination in this setting as well as the immunological mechanism of action.

Key Words: Breast Cancer; Cancer Genetics; Cell Biology; Genomics; Personalised Medicine.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:
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Understanding host anti-tumour immunity in preclinical models of breast cancer: mechanisms evading the immune system

Supervisors: A/Prof. Sherene Loi, A/Prof Phil Darcy

Breast cancer has not been traditionally considered an immunogenic cancer type. Data generated from our lab suggests differently and has moved the role of immunity to the forefront of breast cancer research and treatment.

This project will try to understand the mechanisms by which breast cancers evade the immune system and if immunotherapies harnessed with traditional therapies can improve breast cancer outcomes. In particular, we will be looking at certain signaling pathways and effects on immune components of breast cancers. In particular we will focus on triple negative and HER2-positive breast cancer with the aim of translation to the clinic.

We will be using both in vitro and in vivo models, including patient derived xenografts as well as evaluating efficacy of immunotherapeutic agents, many currently in clinical testing as well as combinations with traditional cytotoxic therapies. Students will learn about breast cancer biology, immunology, cell culture, mouse handling, therapeutics, flow cytometry, western blotting, RT-PCR and genominc techniques.

Key Words: Breast Cancer; Cancer Genetics; Cell Biology; Bioinformatics; Genomics; Personalised Medicine.

Target Students: PhD/postgraduate, Honours.

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Understanding host anti-tumour immunity in preclinical models of breast cancer: biological interactions and mechanisms of PIK3CA mutations

Supervisors: A/Prof. Sherene Loi, Prof Wayne Phillips, Dr. Joyce Teo

We have characterised the alterations in 286 cancer-related genes in 538 luminal (estrogen receptor positive) breast cancer tumours from post-menopausal patients. Overall, 28 genes were somatically altered at a frequency of >10%, with the most commonly mutated being PIK3CA. Interestingly, greater than 90% of PIK3CA mutations co-existed with another alteration. Additionally, we have found that the co-existence of alterations in PIK3CA together with certain genes significantly affected overall clinical outcome and response to treatment.

The biological interaction of these altered genes and the biological mechanism underlying their effect on tumour progression, metastasis and response to treatment is unknown. We propose to delineate these mechanisms/interactions, with the use of genetic manipulation, in luminal breast cancer cell lines and xenografts in vitro and in vivo. Project results will guide future clinical trials of targeted-therapies in luminal breast cancer.

Students will learn about breast cancer biology, cell signaling, immunology, cell culture, mouse handling, therapeutics, flow cytometry, western blotting, RT-PCR and genominc techniques.

Key Words: Breast Cancer; Cancer Genetics; Cell Biology; Bioinformatics; Genomics; Personalised Medicine.

Target Students: PhD/postgraduate, Honours.

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MCARTHUR, GRANT

ONCOGENIC SIGNALLING AND GROWTH CONTROL PROGRAM, AND CANCER THERAPEUTICS PROGRAM

Functional genomics of BRAF driven glycolysis in BRAFV600 melanoma

Supervisors: Dr. Lorey Smith, Prof. Grant McArthur

It has long been appreciated that cancer cells must rewire their metabolism in order to satisfy the demands of growth and proliferation. In aerobic conditions normal cells metabolize glucose through the tricarboxylic acid (TCA) cycle, whereas cancer cells metabolize glucose to lactate using a process known as aerobic glycolysis. More recently it has emerged that altered tumour metabolism lies downstream from various oncogenes or tumour suppressors such as RAS, PI3K, MYC and LKB1.

Our laboratory and others have now demonstrated that BRAFV600 regulates glycolysis in melanoma, and importantly, that BRAF inhibition via vemurafenib can suppress this glycolytic response. In order to further explore BRAF-mediated glycolysis in melanoma and how this relates to its anti-proliferative effects, we have now performed a whole genome siRNA screen to identify enhancers of BRAF inhibition within the context of viability and glycolysis in BRAFV600 melanoma cells. For this enhancement screen, WM266.4 cells were transfected with the human genome siRNA library and subsequently treated with either DMSO or vemurafenib in parallel for 48hrs. Both melanoma cell viability and glycolytic responses, as indicated by lactate production per cell, were assessed using a multi-parameter imaging and colorimetric screening approach.

This Honours project will involve the functional validation and characterization of novel genes and pathways that were identified by the screen using a range of experimental techniques including cell culture, glucose uptake assays, lactate assays, extracellular flux analysis, q-RT-PCR, western blot analysis and high content immunofluorescence analysis (HCIF).

Key Words: Melanoma, Targeted Therapies, Acquired Resistance, Metabolism, Molecular Oncology

Target Students: Honours.

For more information about these projects contact:
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Impact of targeted therapy on the melanoma immune microenvironment

Supervisors: Dr. Karen Sheppard, Prof. Grant McArthur

The treatment of melanoma is undergoing a fundamental change due to the success of both targeted therapies directed at the MAPK/ERK pathway and immunotherapies. Targeted therapies block essential cell signalling pathways that are required for tumour cell proliferation and survival, while immunotherapies promote the patient’s own immune system to eliminate the cancer cells. Both approaches have limitations.

Targeted therapies initially elicit excellent tumour regression, but this response is generally short-lived due to the development of resistance. In contrast, immunotherapies lead to sustained tumour regression but are only effective in a small number of patients. The difference in patient responses to these therapies suggests that the two approaches might have complementary roles in cancer treatment, and there are currently several clinical trials combining targeted and immune therapies.

Targeted therapies can also enhance or diminish immune responses, thus understanding the effect of targeted therapies on immune cells is essential in advancing the combination of these agents into the clinic. Using melanoma cell lines, mouse models and patient samples, we are currently investigating the direct effect of these targeted therapies on immune cell function and how these targeted therapies impact on current immunotherapies.

This Honours project will initially assess the impact of several targeted therapies as single agents or in combination on tumour immunogenicity and on immune cell proliferation and function.

Key Words: Melanoma, Targeted Therapies, Acquired Resistance, Metabolism, Molecular Oncology

Target Students: Honours.

For more information about this project contact:
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Targeting CDK4 in melanoma

Supervisors: Dr. Karen Sheppard, Prof. Grant McArthur

Melanoma treatment is undergoing a fundamental change due to the success of both BRAF targeted and immune therapies; however, both have their limitations. Typically, targeted therapies are associated with short-term responses due to acquisition of therapy resistance in patients, while in contrast immunotherapies have a lower patient response rate but long-term responses. In preclinical studies using melanoma cell lines and mouse models we have demonstrated remarkably prolonged responses to a combination of targeted inhibitors to mutant BRAF and CDK4.

This Hons/PhD project will investigate how the combination of BRAF/MEK/ERK and CDK4 inhibitors induce durable responses and investigate the potential mechanisms for development of resistance to each of these therapies. Understanding mechanisms of resistance is now an essential part of targeted therapy development as it can provide both a biomarker for early detection of treatment failure and options for alternative subsequent treatments.

Key Words: Melanoma, Targeted Therapies, Acquired Resistance, Metabolism, Molecular Oncology

Target Students: PhD/postgraduate, Honours.

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### NEESON, PAUL

**CANCER IMMUNOLOGY PROGRAM**

**Exploring multiple myeloma immunotherapy**

Supervisors: A/Prof. Paul Neeson, A/Prof. Phil Darcy

Multiple Myeloma is an incurable disease; however, immunotherapy is providing new dramatically response rates in patients with refractory disease. Elotuzumab (Elo) is a SLAM-F7 targeting humanised IgG1 antibody. (Elo)+Lenalidomide (Len) combination therapy of patients with refractory multiple myeloma induced 84% objective response, with 16% long term remission (Richardson PG et al Lancet Haematol 2015). Whilst SLAM-F7 is expressed on malignant plasma cells, it is also expressed on NK, T and B cells, dendritic cells and monocytes. It is not known whether all SLAM-F7+ immune subsets are targets for the Elo+Len effect or just the malignant plasma cells. This project aims to understand the Elo+Len mechanism of action in order to better design I-O drug combination therapy for patients with multiple myeloma and improve long-term outcome.

Key Words: Cellular Immunology; Haematological Cancers; Immunogenetics; Immunotherapy; Tumour Immunology.

Target Students: PhD/postgraduate.

**Exploring the immune context of human cancer**

Supervisor: A/Prof. Paul Neeson, A/Prof. Paul Neeson,

Immunotherapy clinical trials over the last 5 years have yielded spectacular results in patients with a wide range of solid tumours. Blocking antibodies to the immune checkpoints CTLA-4 and PD-1/PDL1 have produced the first wave of patient responses; there are many more types of immunotherapy drugs in clinical trials and in pre-clinical development. However, predicting which patients will respond to immunotherapy, and what type of immunotherapy is appropriate has proven difficult. To address these issues, we have developed a range of technologies to explore the immune context of human cancer including multiplex immuno-histochemistry, and immune gene expression profile and network analysis on primary or metastatic tumour FFPE sections. We also have ongoing development of a T cell TCR repertoire platform. We have a TIL (tumour-infiltrating lymphocyte) program to explore the immune context in fresh tumour samples from patients with solid tumours including melanoma, breast or prostate cancer and will be using mass cytometry to describe the tumour ‘immunome’.

This project will use these technologies to explore exactly what is the immune context of the primary tumour? How does the immune context change in the primary site in response to immunotherapy? What goes wrong with immune control when the tumour escapes at local or distant sites? Is this a tumour or immune intrinsic problem or both? This information will then be used to inform the design of ongoing immunotherapy clinical trials at the Peter MacCallum Cancer Centre.

Key Words: Cellular Immunology; Haematological Cancers; Immunogenetics; Immunotherapy; Tumour Immunology.

Target Students: PhD/postgraduate.

For more information about these projects contact:

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### OLIARO, JANE

**CANCER IMMUNOLOGY PROGRAM**

**The role of DOCK8 in immune cell biology**

Supervisor: Dr. Jane Oliaro

T cells form a critical arm of the immune system and are essential for protection against cancer and infection. T cells are highly dynamic, and must change shape rapidly in response to extracellular cues. However, the molecular and cellular regulation of T cell polarity is not well understood.

We recently discovered that a protein, DOCK8, is essential for the regulation of T cell polarity, synapse formation and function (Randall, Nature Immunol 2009, Randall & Oliaro, J Exp Med 2011, Randall, Blood, 2013). Significantly, humans suffering from a debilitating, and often lethal, severe combined immunodeficiency disease harbour biallelic DOCK8 mutations;
highlighting the critical requirement of this protein in human immunity. This project will advance our knowledge of the cellular and molecular control of T cell polarity in adaptive immunity, which has implications for our understanding of immunodeficiency disease and the immunosurveillance of cancer.

The aims of this project will be to:
(1) Investigate the role of DOCK8 in T cell migration and immunological synapse formation in vitro
(2) Examine the anti-tumour response in DOCK8 deficient mice

Techniques commonly used in this laboratory include: Tissue culture, flow cytometry, cell sorting, fixed and time-lapse confocal microscopy, cytokine assays, killing assays, real-time PCR, western blotting, mouse experimentation and general immunological techniques.

Key Words: Cancer Cell Biology; Cell Signalling; Cellular Immunology; Haematological Cancers; Immunotherapy; Innate Immunity; Tumour Immunology; Immune Surveillance; Microscopy; Imaging.

Target Students: PhD/postgraduate, Honours.

The role of co-signalling receptors in cytotoxic lymphocyte activity during infection and cancer

Supervisor: Dr. Jane Oliaro

Cytotoxic lymphocytes (CD8+ T and natural killer (NK) cells) are integral for immune protection against infection and in the immunosurveillance of cancer. The activation of T cells, and the cytotoxic activity of T and NK cells, relies on the formation of an immunological synapse with antigen-presenting cells, or target cells, respectively. During synapse formation, T and NK cell activation and function is fine-tuned by a range of co-signalling molecules that positively or negatively modulate lymphocyte activity. Two important receptors in the regulation of T and NK cell function are the co-signalling molecules, DNAM-1 and CD96. We have evidence that tumour cells, such as acute myeloid leukemic (AML) cells, down-regulate the expression of ligands recognised by DNAM-1 and CD96 as an immune evasion mechanism.

Preliminary data show that DNAM-1 is necessary for cytotoxic lymphocyte adhesion and synapse formation during target cell killing. This project will investigate the role of both DNAM-1 and CD96 in T cell responses to antigen, and in T and NK cell cytotoxic activity. We will also investigate the consequences of ligand expression on DNAM-1 and CD96 on NK recognition and killing of AML cells.

The aims of this project will be to:
(1) Investigate the role of DNAM-1 and CD96 in immunological synapse formation and tumour cell killing in vitro
(2) Examine the anti-tumour response in CD96 deficient mice

Techniques commonly used in this laboratory include: Tissue culture, flow cytometry, cell sorting, fixed and time-lapse confocal microscopy, cytokine assays, killing assays, real-time PCR, western blotting, mouse experimentation and general immunological techniques.

Key Words: Cancer Cell Biology; Cell Signalling; Cellular Immunology; Haematological Cancers; Immunotherapy; Innate Immunity; Tumour Immunology; Immune Surveillance; Microscopy; Imaging.

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PAPENFUSS, TONY

CANCER GENOMICS PROGRAM

Making sense of tumour evolution and heterogeneity

Supervisor: Prof. Tony Papenfuss

Cancer is a disease of evolution gone wrong. Accumulation of mutations in the genome and selection of leads to uncontrolled growth of cancer cells. The emergence of resistance in some subclones is the major obstacle in cancer therapy, and so identifying subclones in tumours, understanding how they occur and evolve, and estimating the relationship between them are now important concepts in cancer therapy and to predict patient prognosis.

This project will involve the development of new methods and models to improve the estimation of tumour heterogeneity and understand the relationship between subclones, especially in melanoma. The project will involve access to Peter Mac’s CASCADE Rapid Autopsy Program.

Key Words: Bioinformatics, Computational biology.

For more information about these projects contact:
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MYC-driven lymphoma cells in vitro for control of Pol I transcription in PI3K/AKT/mTORC1 and MYC required

This project aims to:

(1) Define the mechanisms by which PI3K/AKT/mTORC1 and MYC cooperate during malignancy to ensure ribosome biogenesis remains hard wired in tumour cells. Our Science Signalling paper (Chan et al 2011) illustrated MYC and PI3K/AKT/mTORC1 co-operation in the regulation of ribosomal DNA transcription by RNA polymerase I (Pol I) and ribosome biogenesis. More recently, we have demonstrated in Devlin et al., Cancer Discovery (2016) that combination therapy targeting Pol I transcription and the PI3K/AKT/mTORC1 pathway leads to significant improved efficacy in treating MYC-driven lymphoma. Thus, the next step is to elucidate the mechanism(s) underlying the cooperation between the MYC transcription network and the PI3K/AKT/mTORC1 pathway in regulation of Pol I transcription which forms the basis for this project.

(2) Define the interactions between PI3K/AKT/mTORC1 and MYC required for control of Pol I transcription in MYC-driven lymphoma cells in vitro and in vivo.

(3) Investigate interactions between PI3K/AKT/mTORC1 and MYC required for regulating ribosome function by ribosome profiling and translatomics.

Key Words: Cancer Cell Biology; Cell Signalling; Cancer Therapy; Cell Cycle; Cell Growth; Cell Metabolism; Haematological Cancers; Molecular Oncology; Pharmacogenomics; Skin Cancers (incl. Melanoma); PI3K; AKT; mTOR; MYC.

Target Students: PhD/postgraduate, Honours.

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Metabolic control of ribosome biogenesis by PI3K/AKT/mTOR and MYC in cancer

Supervisors: Dr. Jian Kang, Prof. Rick Pearson

Ribosome biogenesis is the major energy consuming process in proliferating cells and is rate limiting for the protein synthesis required for cell growth and division. Given the high-energy demand to make new ribosomes, not surprisingly, ribosome biogenesis is tightly linked to cellular metabolism. We hypothesize that the PI3K/AKT/mTORC1 pathway and c-MYC are critical for nutrient regulation of ribosome biogenesis. We recently demonstrated that amino acid dependent signaling via mTORC1 activation of S6K1 and MYC is essential for regulation of ribosome biogenesis. The following aims will investigate this hypothesis:

(1) Define the mechanism(s) of control of ribosome biogenesis in response to changes in nutrient (& energy) levels.

(2) Define the requirement for nutrient signalling and/or glutaminolysis in the regulation of ribosome biogenesis, cell growth and survival in MYC driven B-cell lymphoma.

(3) Identify effective metabolism modifying therapies that improve the efficacy / overcome the resistance to ribosome biogenesis targeting therapies.

Key Words: Cancer Cell Biology; Cell Signalling; Cancer Therapy; Cell Growth; Cell Metabolism; Haematological Cancers; mTOR; MYC; Ribosome Biogenesis.

Target Students: PhD/postgraduate, Honours.

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AKT driven senescence and cancer

Supervisors: Dr. Keefe Chan, Prof. Rick Pearson

Hyperactivation of the PI3K/AKT/mTORC1 signalling pathway is a hallmark of many sporadic human cancers. However, we and others have demonstrated that chronic activation of this pathway in normal cells induces senescence, which effectively acts as a “brake” on the progression to malignancy.

We hypothesise that specific genetic changes overcome this brake and permit the increased cell proliferation and transformation required for cancer development. Our previous work showed that AKT-induced senescence in normal human cells occurs via a p53 and mTORC1-dependent mechanism (Astle et al, 2011, Oncogene). Understanding the basis of oncogene-induced senescence in normal cells and how this is subverted in cancer cells will provide insight into the mechanism of cancer development and how it can be targeted. To investigate this, we have performed a multi-parametric genome-wide RNAi screen for bypass of AKT-induced senescence and identified several candidates. This project aims to follow up on the screen results to:
is a matter of conjecture. There is epithelium. The origin of this condition metaplastic intestinal-type columnar the oesophagus is replaced by a stratified squamous epithelium of abnormality in which the normal Barrett’s oesophagus is a metaplastic oesophagus. 

This project will utilise cell culture, and techniques such as ribosome profiling, immunoprecipitation, RT-PCR, siRNA screening, proteomics, transcription assays, IHC and western analysis.

Key Words: Bioinformatics; Cancer Cell Biology; Cell Signalling; Cancer Therapy; Cell Cycle; Cell Growth; Cell Metabolism; Haematological Cancers; Molecular Oncology; Pharmacogenomics; Skin Cancers (incl. Melanoma); Solid Tumours; Senescence; PI3K; AKT; PTEN.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:

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PHILLIPS, WAYNE

ONCOGENIC SIGNALLING AND GROWTH CONTROL PROGRAM

Understanding the biology of Barrett’s oesophagus

Supervisors: Prof. Wayne Phillips, Dr. Nicholas Clemons, Dr. Cuong Duong

Over the past thirty years there has been a dramatic increase in the incidence and prevalence of oesophageal adenocarcinoma in Western populations. The reason underlying the increase in this cancer is not clear but is thought to reflect an increase in the occurrence of its recognised precursor lesion, Barrett’s oesophagus.

Barrett’s oesophagus is a metaplastic abnormality in which the normal stratified squamous epithelium of the oesophagus is replaced by a metaplastic intestinal-type columnar epithelium. The origin of this condition is a matter of conjecture. There is compelling etiological evidence that acid reflux is a major contributing factor but the actual molecular and cellular mechanism underlying the phenotypic change is not understood.

Our group has developed novel in vitro and in vivo cell culture models that allow the 3-dimensional, layered structure of the normal oesophageal lining to be reproduced in the laboratory. The student will use these models to investigate the cellular origin and molecular changes involved in the development of Barrett’s oesophagus and progression to adenocarcinoma. Understanding the biology underlying this condition will ultimately help us to design effective strategies for the management and treatment of Barrett’s oesophagus and to predict, and/or prevent, the progression of Barrett’s oesophagus to oesophageal adenocarcinoma.

Key Words: Cancer Cell Biology; Cell Signalling; Cell Growth; Molecular Biomarkers; Pathology; Solid Tumours; Surgical Oncology; Upper Gastrointestinal Cancers; Oesophageal Cancer; Barrett’s Oesophagus; Intestinal Metaplasia.

Target Students: PhD/postgraduate.

Exploring the biological consequences of PIK3CA mutation in colorectal cancer

Supervisors: Prof. Wayne Phillips, Dr. Nicholas Clemons, Dr. Cuong Duong

Oncogenic activation of the phosphoinositide 3-kinase (PI3K) pathway is a common event in colorectal cancer (CRC). Indeed PIK3CA, the gene encoding the p110α catalytic subunit of PI3K, is mutated in approximately 20% of sporadic CRCs. Loss of function of the tumour suppressor APC (adenomatous polyposis coli) occurs in >80% of human CRCs and predisposes to benign intestinal adenomas mice.

We have recently established that Pik3ca mutation alone is insufficient to initiate intestinal tumourigenesis in mice but, in the context of Apc loss, Pik3ca mutation promotes the development of highly aggressive and invasive intestinal adenocarcinomas in vivo.

The student will use our novel mouse model of gastrointestinal cancer

[1] to investigate the molecular mechanisms by which oncogenic mutation of Pik3ca and loss of Apc cooperate to cause accelerated progression of intestinal tumours

This project could lead to the identification of novel biomarkers and/or new therapeutic approaches for CRC patients.

Key Words: Cancer Cell Biology; Cell Signalling; Cell Growth; Colorectal Cancers; Molecular Biomarkers; Molecular Targets; Pathology; Solid Tumours; Oesophageal Cancer; Barrett’s Oesophagus; Preclinical Models.

Target Students: PhD/postgraduate, Honours.

For more information about these projects contact:

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RISBRIDER, GAIL

PROSTATE CANCER PROGRAM

New human models for rapid preclinical testing of prostate cancer

Supervisor: Prof. Gail Risbridger

Prostate cancer is the most commonly diagnosed cancer in Victoria. Unfortunately, our ability to pre-clinically test new therapies is constrained by the paucity of experimental human models because prostatic tumours are more difficult to grow in the laboratory than many other types of cancer. However, our laboratory has successfully developed in vivo and in vitro systems to maintain viability of rare and valuable patient samples as “patient-derived xenografts and explants/organoids”. These samples represent an invaluable resource for testing novel therapeutics for prostate cancer.

The goal of this project is to use
patient-derived xenografts as ex vivo explant cultures or organoids to test drugs of interest that are in development and identify the most promising compounds for further in vivo studies.

The project will involve a variety of techniques including tissue pathology, tissue culture and handling, immunohistochemistry, automated image analysis and qPCR.

Key Words: Cancer Cell Biology; Cell Signalling; Cancer Therapy; Cell Growth; Molecular Targets; Solid Tumours; Therapeutics; Prostate Cancer.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:
Prof. Gail Risbridger
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Defining epigenome changes in the tumour microenvironment
Supervisor: Prof. Gail Risbridger

The tumour microenvironment has a key role in the progression of prostate cancer. Our laboratory recently showed that cells within the tumour microenvironment, known as cancer-associated fibroblasts (CAFs), acquire consistent changes in DNA methylation. These epigenome marks are highly consistent between patients and represent possible new biomarkers for improving the accuracy of cancer diagnosis.

The goal of this project is to use 3D tissue culture models to study how reciprocal signalling between cancer cells and fibroblasts shapes the pattern of DNA methylation in each cell type. The results will identify the most important epigenome marks to validate as new biomarkers for prostate cancer.

The project will involve co-cultures of different cell types in custom-designed 3D scaffolds. The interactions between the cells will be examined using confocal microscopy and image analysis software. DNA methylation and gene expression changes will be examined using targeted bisulphite sequencing and quantitative PCR.

Key Words: Cancer Cell Biology; Cancer Diagnosis; Cell Signalling; Cancer Therapy; Cell Growth; Gene Expression; Molecular Biomarkers; Solid Tumours; Therapeutics; Prostate Cancer; Tumour Microenvironment; DNA methylation.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:
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Pre-clinical testing of novel combination therapies in mouse models of prostate cancer
Supervisor: Dr. Luc Furic

The prostate requires androgens for normal growth and functioning and the vast majority of prostate cancer (PC) are dependent on the androgen receptor (AR) for growth and proliferation. Androgen-deprivation therapy (ADT) remains the mainstay of therapy for advanced PC, but the disease invariably progress to a stage known as castration-resistant PC (CRPC). The last decade has seen the development of many new therapeutic agents targeting AR activity directly by inhibiting its transcriptional activity or indirectly by inhibiting the enzymes responsible for androgens synthesis. These agents have successfully increased survival in CRPC, but resistance emerges in a matter of months. It is therefore urgent to develop and validate new therapeutic targets in PC which are independent of AR activity.

This project will use genetically modified mouse models (GEMM) of PC to test novel small molecule inhibitors targeting key vulnerabilities of PC cells. In addition, we are also developing and testing therapeutic antibodies and a new vaccine technology.

This project will involve animal work, histology, immunohistochemistry, qPCR and analysis of signalling pathways by Western blotting.

Key Words: Cancer Cell Biology; Cell Signalling; Cancer Therapy; Cell Growth; Molecular Targets; Solid Tumours; Therapeutics; Prostate Cancer.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:
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Reconstructing the evolution of therapy-resistance metastatic prostate cancer
Supervisor: Dr. David Goode

Once prostate cancer becomes metastatic (spreads to other organs) it becomes difficult to treat, and disease recurrence is common. We plan to investigate how prostate cancer spreads and becomes resistant to therapy by using next-generation sequencing to detect genetic mutations, epigenetic alterations and changes in gene expression in tumour samples taken from patients at autopsy.

We will use these data to reconstruct how each patient’s cancer evolved before and after treatment, to identify key mutations and regulatory changes driving therapy resistance and metastasis in prostate cancer.

This project will involve in-depth bioinformatics analysis of whole-genome, whole-genome and RNA-sequencing data, as well as the design and implementation of statistical algorithms for studying tumour evolution.

Key Words: Bioinformatics; Gene Expression; Solid Tumours; Prostate Cancer; Therapy Resistance.

Target Students: PhD/postgraduate, Honours.

For more information about this project contact:
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SARAH RUSSELL

CANCER IMMUNOLOGY PROGRAM

Single cell pedigree analysis to understand the mechanisms of fate determination during T cell development, leukemia, and immune responses

Supervisor: Dr. Sarah Russell

Understanding how cell fate programming works will lead to improved diagnostic and therapeutic opportunities for leukemia, and to improved immunotherapies for cancer and infectious disease.

We have developed new methods for imaging single cells and their progeny through many generations of T cell development and activation. These methods mean that we can now assemble pedigrees that describe both the relationships between different differentiation stages, and molecular and behavioral attributes of their ancestors and progeny.

We are now developing new computational approaches to analyse these pedigrees, and to determine the relative contributions of genetic, epigenetic, extrinsic and stochastic influences on fate determination.

This PhD project will involve development of new computational approaches to determine how behaviours in the T cell progeny (differentiation, growth, death, division) are influenced by ancestry, intrinsic and extrinsic cues.

Key Words: Cell Signalling; Cellular Immunology; Differentiation; Haematology; Haematological Cancers; Immunotherapy; Tumour Immunology.

Target Students: PhD/postgraduate.

For more information about this project contact:

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MARK SHACKLETON

CANCER THERAPEUTICS PROGRAM

Understanding intra-patient disease heterogeneity in human melanoma

Supervisors: Dr. Mark Shackleton, Dr. Clare Fedele

One of the most important discoveries in cancer over the past decade has been revelation of the extent of disease heterogeneity within individual patients. Indeed, this heterogeneity is seen on multiple levels – cellular, genetic, epigenetic – and even within single tumors. Elucidating the basis and consequences of cancer heterogeneity is one of the highest priorities in research, as cancer heterogeneity likely impacts disease outcomes in patients, such as the propensities to relapse and metastasize, the development of therapy resistance and responsiveness to immunotherapy.

This project will examine the origins and consequences of intra-patient heterogeneity in melanoma, linking these to features of disease biology and therapy response, using exceptional resources and world-leading technologies for clinically relevant laboratory modeling of human melanoma (Nature 456:593, Cancer Cell 18:510, Sci Transl Med 4:159ra149). It is anticipated that the work will provide fundamental insights into the nature and implications of heterogeneity in melanoma and other cancers.

Techniques used will include working with human tumor specimens and linked clinical data, mouse handling, in vivo/in vitro drug treatment, immunostaining, flow cytometry, NextGen sequencing and molecular biology assays.

Key Words: Cancer Cell Biology; Cancer Genetics; Cell Signalling; Cancer Therapy; Cell Development, Proliferation and Death; Cell Growth; Epigenetics; Gene Expression; Genomics; Skin Cancers (incl. Melanoma); Solid Tumours; Therapeutics.

Target Students: PhD/postgraduate.

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The significance of melanin pigment in melanoma progression

Supervisors: Dr. Mark Shackleton, Dr. Clare Fedele

Intratumoral heterogeneity (ITH), defined by the presence of phenotypically-, genetically- and/or epigenetically-distinct sub-populations within a single tumour, is a feature of most human cancers, including melanoma. We have found that most human melanomas show extensive ITH for production of the pigment, melanin; while some cells produce melanin, others within the same tumour do not. We have developed a novel method to prospectively separate differentially pigmented melanoma cells using fluorescence-activated cell sorting (FACS). Using this approach we have discovered that less pigmented cells are significantly more tumorigenic than more pigmented cells within the same tumour, revealing that effective anti-melanoma therapies must target the pigment-low cell population.

This project aims to discover the basis for the biological disparity between differentially pigmented melanoma cells, with a clear translational focus. In particular, we hypothesize that differences in melanin production will be linked to metabolic variations that may inform anti-melanoma therapy.

Techniques involved will include working with human tumor specimens and linked clinical data, flow cytometry, metabolomics/proteomics/genomics techniques, tissue culture, mouse handling, in vivo/in vitro drug treatment, immunostaining and molecular biology assays.

Key Words: Cancer Cell Biology; Cancer Genetics; Cell Signalling; Cancer Therapy; Cell Development, Proliferation and Death; Cell Growth; Molecular Targets; Skin Cancers (incl. Melanoma); Solid Tumours; Therapeutics.

Target Students: PhD/postgraduate, Honours.
AVAILABLE PROJECTS BY RESEARCH GROUP

Hippo – a new signaling pathway for cancer targeting

Supervisors: Dr. Mark Shackleton, A/Prof. Kieran Harvey

The Hippo molecular signaling pathway, recently discovered by A/Prof Kieran Harvey and collaborators (Cell 114:457, Nat Cell Biol 15:1176), is a key regulatory mechanism in multiple cancers. For example, data is rapidly emerging that central mediators of Hippo signaling, such as the oncoprotein YAP, drive the growth, survival and metastasis of lung cancers, liver cancers, breast cancers and melanomas. These studies are spurring development of novel treatments that inhibit YAP function and that are expected to be effective in a range of cancers.

This project will focus on studies of Hippo pathway regulation in cancer, with a strong translational focus. Techniques involved will include working with human tumor specimens and linked clinical data, patient-derived xenografting, mouse handling, in vivo drug treatment, immunostaining, flow cytometry, genomics techniques and molecular biology assays.

Supervision will be shared by Dr. Mark Shackleton, a clinician-scientist (Nature 539:84, Nature 456:593, Cell 138:822), and A/Prof Harvey. Embedded in the Cancer Therapeutics Division at Peter Mac, the project will integrate dynamic links between pharma and early phase drug development programs. As a result, it is anticipated that the student’s work will define a path to clinical testing of Hippo pathway targeting in a manner that augments current therapies.

Key Words: Cancer Cell Biology; Cancer Genetics; Cell Signalling; Cancer Therapy; Cell Development, Proliferation and Death; Cell Growth; Molecular Targets; Skin Cancers (incl. Melnaoma); Solid Tumours; Therapeutics.

Target Students: PhD/postgraduate, Honours.

For more information about these projects contact:

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STACKER, STEVEN

TUMOUR ANGIOGENESIS PROGRAM

Understanding the role of the Ryk receptor in cancer

Supervisors: Prof. Steven Stacker, Dr. Michael Halford, Prof. Stephen Fox

Ryk is a member of the growth factor receptor family, members of which are key regulators of mammalian cell proliferation, differentiation and migration and are therapeutic targets in the treatment of human cancers. Ryk is a receptor for members of the Wnt family of morphogens and therefore provides a pivotal link between the Wnts and cellular regulation. We have recently demonstrated the key role that Ryk plays in non-canonical Wnt signaling via the planar cell polarity (PCP) pathway (Macheda et al., Journal of Biological Chemistry, 2012).

This project will investigate the role of Ryk in human cancer by identifying and characterizing human tumours in which signaling via a Wnt5a/Ryk axis is important for cancer. Recent studies have shown that Ryk is important for the resistance of a subset of melanomas that upregulate Wnt5a to BRAFV600E inhibitors. Further, a fully human monoclonal antibody developed in our laboratory, which blocks Wnt binding by Ryk will be evaluated for activity and efficacy in appropriate tumor models.

During the project the student will develop skills in the analysis of in vivo cancer models, advanced cell and molecular biology techniques and the further development of a fully human antibody suitable for pre-clinical testing. The student will also work with the Pathology Department and Prof Stephen Fox to identify human tumors expressing Ryk and Wnt5a.

Key Words: Angiogenesis; Cancer Cell Biology; Cell Signalling; Cancer Therapy; Molecular Targets; Receptor Biology; Therapeutics

Target Students: PhD/postgraduate, Honours.

Understanding the signaling networks within lymphatic endothelial cells

Supervisors: Prof. Steven Stacker, Prof. Marc Achen, Prof. Stephen Fox

Lymphatic endothelial cells (LECs) line lymphatic vessels and are essential control points for interaction with immune cells and proteins contained within the lymphatic fluid that fills these vessels. LECs also participate in the generation of new lymphatic vessels and remodelling of pre-existing vessels that occur during embryogenesis and in various pathologies. To gain a detailed understanding of how LECs receive and integrate signals from their environment, we have performed a genomewide siRNA screen to map their signalling networks.

This project will provide key biological and biochemical validation of candidate genes identified during a genomewide siRNA screen for modifiers of LEC migration. Further, the project will allow the detailed analysis of high content morphological data acquired during the screen and provide a key comparison between functional data and morphological changes seen with individual LEC or LEC monolayers. The project will provide the unique opportunity to assess both novel regulators of LEC activity and structure-function analysis within the LEC. The student will develop skills in advanced cell and molecular biology, including developing assay systems to study primary LEC. The project will also integrate bioinformatics and cell morphometric analysis to allow the correlation of functional data and cell morphology changes. Further, collaborations within the Pathology Department of Peter Mac (Prof Stephen Fox) will allow validation of these findings in human tissue.

Key Words: Angiogenesis; Cancer Cell Biology; Cell Signalling; Cancer Therapy; Endothelial Regulation; Molecular Targets; Receptor Biology; Therapeutics

Target Students: PhD/postgraduate, Honours.
Are angiogenesis receptors drivers of epithelial malignancies?

Supervisors: Prof. Steven Stacker, Prof. Marc Achen, Prof. Stephen Fox

Genome sequencing of human cancers has revealed that many known angiogenic receptors also function in the signaling of epithelial cancer cells. For example KDR (human VEGFR-2) has been found to be mutated in human ovarian cancer and angiosarcoma and has been determined to be a likely pathogenic driver in some patients. We intend to study a range of somatic mutations found in receptors from the Receptor-type Tyrosine Kinase family which are potentially clinically actionable.

The project will involve the generation and testing of a range of somatic mutations found in the genomes of human cancer patients through genomic or exomic sequencing. Mutations will be generated in receptor cDNA through standard oligonucleotide-directed mutagenesis technology and advanced molecular biology techniques. These mutants and wildtype genes will be expressed in recipient cells and their capacity for altered signaling determined through biochemical analysis including Western blotting with antibodies to activated signal transduction components. Students will develop skills in advanced cell and molecular biology as well as genome/exome sequencing and the associated bioinformatics analysis. Collaboration with Prof Stephen Fox (Pathology Department, PMCC) will allow for a complete integration with pathological information.

Key Words: Angiogenesis; Cancer Cell Biology; Cell Signalling; Receptor Biology

Target Students: PhD/postgraduate, Honours.

Role of prostaglandins in tumour metastasis

Supervisors: Prof. Steven Stacker, Prof. Marc Achen,

Lymphatic metastasis is a critical initial step in the spread of cancer. Powerful lymphangiogenic growth factors such as vascular endothelial growth factor (VEGF)-D and VEGF-C are secreted by some primary tumors and are capable of altering existing lymphatic vessels, generating new vessels in a process known as lymphangiogenesis, facilitating tumor metastasis. We have recently shown the critical role that VEGF-D plays in metastasis via the collecting lymphatic vessels (Karnezis et al., Cancer Cell 2012), and that this process is dependent on the proangiogenic signaling pathway which is sensitive to inhibition by the group of drugs known as the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

The project will investigate the role of VEGF-D and VEGF-C in the promotion of tumor metastasis and explore the biochemical and biological mechanisms involved in this process. The student will use a combination of in vitro and in vivo tumor models and further define the regulation of metastasis. Furthermore, they will examine the effects of a range of NSAIDs on tumor metastasis, and determine those most effective at preventing tumor spread. During the project, the student will develop a broad range of molecular and cell biology techniques, including in vitro endothelial assays and in vivo tumor experiments and evaluation of anti-cancer drugs by animal imaging.

Key Words: Angiogenesis; Cancer Cell Biology; Cell Signalling; Receptor Biology

Target Students: PhD/postgraduate, Honours.

For more information about these projects contact:
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VOSKOBOINIK, ILIA

CANCER IMMUNOLOGY PROGRAM

Regulation and function of cytotoxic lymphocytes

Supervisors: A/Prof Ilia Voskoboinik, Prof. Joe Trapani

Cytotoxic lymphocytes recognize and kill cancerous and virus-infected cells through cytotoxic granule exocytosis pathway. Cytotoxic granules store a pore-forming protein, perforin, and serine proteases, granzymes. Once released, perforin transiently disrupts a target cell membrane thus permitting the delivery of granzymes into the cytosol, where they initiate various apoptotic death pathways.

This is a fundamental homeostatic process and, when disrupted, has catastrophic consequences: it either leads to fatal hyperinflammation or, in milder cases, results in haematological malignancies in childhood or adolescence. We investigate:

(1) the regulation of cytotoxic granule exocytosis,
(2) the structural bases of perforin pore formation,
(3) the biology of granzymes,
(4) the molecular bases of congenital immune deficiency Familial Haemophagocytic Lymphohistiocytosis,
(5) the genetic predisposition to haematological malignancies.

We offer project(s) in each of these areas, and a specific topic will be selected to cater for the interests and skills of a candidate.

A prospective student will be a part of a successful multidisciplinary research team of immunologists, biochemists, cell biologists, geneticists and clinical scientists, and will gain experience in immunology, cell biology (including various microscopy techniques), molecular biology and biochemistry.

AVAILABLE PROJECTS BY RESEARCH GROUP

WICKRAMASINGHE, VIHANDHA
ONCOGENIC SIGNALLING AND GROWTH CONTROL PROGRAM
This lab investigates the molecular basis of how messenger RNA (mRNA) is selectively processed and exported from the nucleus into the cytoplasm and how deregulation of these processes contributes to human cancer. Specifically, we aim to:

• Understand how selective mRNA export pathways are regulated and activated
• Investigate the impact of alternative mRNA splicing on the human proteome.

Impact of alternative mRNA splicing on the human proteome
Supervisor: Dr. Vi Wickramasinghe
Alternative splicing of RNA transcripts has emerged as a key mechanism for enabling biological complexity within the human genome. Alternative splicing has long been assumed to underlie the expansion of proteomic diversity. However, the extent to which this increased genomic complexity contributes to the generation of proteomic diversity is largely unknown. This fundamental biological question is of critical importance to human health, given the recent identification of perturbed RNA splicing as a causative factor in cancer. We have developed an integrative approach to ask whether dynamic perturbations in mRNA splicing patterns alter the composition of the proteome. This project will reveal the impact of alternative splicing on the proteome.
WHY STUDY AT PETER MAC?
WORDS FROM CURRENT RESEARCH STUDENTS

An important aspect of the Peter Mac Research Education program is the development of a greater awareness of the recent advances and the rapidly changing technologies used in medical research. Our program provides all students with the opportunity to expand their research knowledge and develop this awareness, while also developing important transferable skills that will make an important contribution to their future career directions.

We provide a structured yet flexible program to meet the varied needs of our students. This research environment supports all students during the development of the important research and professional skills that will allow our graduates to demonstrate their development as efficient researchers, and makes a significant contribution to improving the quality of research coming out of our Centre.

“Peter Mac is a very stimulating environment with such a wide array of cancer research being completed here, to an international standard. I’m so excited to be at one of the top-class research institutes in Australia and I’m looking forward to the adventures ahead.”

Rosie completed her honours at Peter Mac in 2012. The cohort of honours students that year was a very tight-knit group who all helped each other throughout the course. The community of researchers, from Lab Heads to Research Assistants, also guided them through and this is one of the main reasons Rosie returned to Peter Mac for her PhD.

Rosemary Millen
PhD Student, Ramsay Laboratory. Awarded Peter Mac’s Nicole Lundie Undergraduate Research Prize in 2012. President of the Postgraduate Student Society, 2016.

“During my surgical training at Peter Mac, I was exposed to the unique structure and environment of this institution, which attracted me to return to undertake a PhD. Since commencing my research, I have been warmly welcomed and supported throughout my research, mirroring my experience as a clinician.”

Glen is one of our growing number of young clinicians undertaking research degrees at Peter Mac. He was attracted by the dynamic work environment fostered by the close collaboration between the research and clinical divisions, facilitated by their co-location. This environment produces high level basic science and clinical research, allows the greatest potential for the evolution of translational research, and is supporting Glen in his aim to be actively involved in working towards improved patient outcomes.

Dr Glen Guerra
Surgeon and PhD student, Phillips Laboratory. Recipient of Royal Australian College of Surgeons PhD Scholarship.

“As an international student from Venezuela, I was concerned about covering my tuition fees and living expenses in Australia. The scholarships awarded by the University of Melbourne have been the key to pursuing my PhD in Petermac.”

Anna completed her Master of Bioinformatics at The University of Melbourne, conducting her research placement at Peter Mac. She commenced her PhD in 2015, attracted to Peter Mac by the multidisciplinary projects and supervisory teams offered in their programs. Her PhD uses bioinformatics techniques to address cancer biology questions, obtaining high-level and systems perspectives of the alterations in cancer.

Anna Tirgos Gomes
PhD Student, Papenfuss Laboratory. Recipient of a Melbourne International Engagement PhD Award.
“My very first impression of Peter Mac even before I thought about the project was how there is a well-structured education and recruitment program for students, described on the website. It’s very important and also encouraging to have project outlines, so students from the other side of the world know what people are currently doing and, more importantly, which researchers are recruiting students here.”

Jirawas came to Australia after completing her Master of Biomedical Science in The Netherlands, and quickly took charge of her project targeting ribosome biogenesis in acute myeloid leukaemia. Jirawas has made an important contribution to the education program at Peter Mac with a leadership role in the 2014 Postgraduate Student Society, helping coordinate the annual Student retreat and other education and social activities to support our students.

**Jirawas Sornkom**
PhD student, Oncogenic Signalling and Growth Control Program
Recipient of an International Postgraduate Research Scholarship & Cancer Therapeutics Top-up Scholarship.

“I have always dreamed of inventing some drugs to cure the cancer since I was a kid. The Functional Genomics facility at Peter Mac is bringing my childhood dream into reality.”

Shunfei Yan came to Peter Mac after completing his Masters in China. Peter Mac’s reputation as an origin of cancer therapies was a key factor in attracting Shunfei to undertake his PhD in the Oncogenic Signalling and Growth Control program. Access to Peter Mac’s sophisticated equipment is allowing allowed Shunfei to define the alterations in the mRNA translation profile induced by novel therapies targeting ribosome biogenesis and function.

**Shunfei Yan**
PhD Student, Pearson Laboratory.
Recipient of a Melbourne INternational Research Scholarship.

“The Peter MacCallum Cancer Centre was an ideal choice for my graduate studies because it provides a platform to answer critical questions in science and translate them into therapeutic outcomes for patients in the future.” An international student who came to Peter Mac in 2014, he finds Peter Mac provides an amiable as well as challenging environment to work alongside clinicians and scientists to integrate research from bench to bedside.

**Dinesh Raghu**
PhD Student, Haupt Laboratory, followed by a position as Genitourinary Medical Oncology Fellow at the British Columbia Cancer Agency

“I chose to study at the Peter Mac because not only does it have world class researchers working in conjunction with some of Australia’s best clinical partners, but it also has the benefit of world leading core facilities run by experienced, knowledgeable and friendly staff.”

Alex commenced his PhD in 2014 after several years as a Research Assistant at Peter Mac. An important aspect of his research is made possible by the Advanced Microscopy Core facility, where Alex uses live-cell microscopy to investigate the biology of chimeric antigen receptor (CAR) T cells interacting with tumor target cells.

**Alex Davenport**
PhD Student, Neeson & Darcy Labs.
Awarded a Fight Cancer PhD Scholarship through Melbourne Health.