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Pathology

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2018 HONOURS IN PATHOLOGY RESEARCH PROJECTS

contact:

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Honours in Pathology

For application instructions see:

<http://sc.mdhs.unimelb.edu.au/how-apply>

Undertaking the Honours course represents a challenging opportunity for students to investigate their potential for a future career in biomedical research and/or beyond. The objectives of the course include the development of individual student skills in planning and design of experiments, acquisition, interpretation and critical analysis of data, reporting of scientific data consistent with that published in scientific journals and oral communication of research projects.

The coursework is composed of 3 subjects, Critical Analysis of Pathology Research (semester 1 only), Introduction to Biomedical Research (semester 1 only) and the Research Project (semester 1 & 2):

PATH40001 - 40005 Research Project (75 credit points)

15%	Literature Review*
65%	Research Thesis
5%	Introductory Seminar#
15%	Completion Seminar#

PATH40002 Critical Analysis of Pathology Research (12.5 credit points)

20%	Data Assessment Exercise (Oral)
80%	Data Assessment Exercise (Written)

BIOM40001 Introduction to Biomedical Research (12.5 credit points)

See University Handbook

The Honours year starts in mid-February (Semester 1) and ends in November.

Entry requirements

To undertake B.Sc. and B.Biomed (Hons) in the Department of Pathology, you must fulfil the requirements of the Department and Faculty of MDHS and have the agreement of a supervisor in the Department of Pathology or associated institute and the approval of the Head of Pathology. Students must have completed a suitable degree (B.Sc. B.Biomed.Sci. or equivalent) and achieved a Faculty Honours Score of 65 or above (or external university equivalent). Many supervisors specify a minimum Faculty Score of 70, so students must discuss this with potential supervisors to clarify this.

Note that the project listed herein are designed as 1 year Honours projects. However, some projects may be offered as 2 year Masters of Biomedical Science projects. Students should determine this for specific projects, with the project supervisor.

HONOURS IN PATHOLOGY PROJECTS

Investigating the role of novel signalling-transcriptional mechanisms in tumour cells

Supervisor: Dr Theo Mantamadiotis
 Email: theom@unimelb.edu.au
 Telephone: 83445861
 Location: Cancer Signalling Lab, Level 10, Victorian Comprehensive Cancer Centre (VCCC), Parkville
 Co-Supervisor(s): Dr Martin Tymms

THIS PROJECT IS OFFERED AS AN HONOURS OR M.BIOMED.SCI. PROJECT

Project Description:

This project will use molecular and cell-based techniques to investigate the role of key factors involved in regulating brain tumour growth, drug resistance and cancer stem cell biology. We recently reported a novel role of the cAMP pathway in triggering death in some brain cancer cell lines (1). The sensitivity or resistance of these cells to cAMP-induced death correlates with the MAPK pathway and CD44 expression. We have since developed a hypothesis that the transcription factors, Ets1 and Myb form a signalling-transcription network, cooperating with the cAMP, MAPK and PI3K pathways to enhance brain tumour cell malignancy and drug resistance.

Human and animal cell lines, patient-derived brain tumour cells and patient specimens will be used for experiments. PCR, IHC and other molecular techniques will be used to investigate how upstream signalling pathways cooperate with the Ets1 and Myb transcription factors to regulate malignant brain cancer tumour cell function.

1. DANIEL P, FILIZ G, MANTAMADIOTIS T. 2016. Sensitivity of GBM cells to cAMP agonist-mediated apoptosis correlates with CD44 expression and agonist resistance with MAPK signaling. *Cell Death & Disease*, 7(12):e2494.
<http://www.nature.com/cddis/journal/v7/n12/abs/cddis2016393a.html>

Developing a multifactorial classification model for germline variants in the colorectal cancer susceptibility genes *POLE* and *POLD1*

Supervisor: Dr Daniel Buchanan
 Email: daniel.buchanan@unimelb.edu.au
 Telephone: 8559 7004
 Location: Colorectal Oncogenomics Group, Level 10 VCCC, Parkville
 Co-Supervisor(s): Dr Mark Clendenning, Dr Bernard Pope, Dr Khalid Mahmood

THIS PROJECT IS OFFERED AS AN HONOURS OR M.BIOMED.SCI. PROJECT

Project Description:

Colorectal cancer (CRC) is a major health issue in Australia, with 20,000 individuals per year expected to be diagnosed with the disease by 2020. One way to reduce the incidence of CRC is to identify high-risk individuals in the population and target them with preventative strategies (i.e. colonoscopy). These high-risk individuals include those who carry rare, likely pathogenic variants in established CRC susceptibility genes. In the current era of genetic testing for inherited CRC, multiple susceptibility genes are tested simultaneously (referred to as multi-gene panel or gene panel testing) enabling cost-effective, personalized CRC risk determination. The increasing clinical problem resulting from multi-gene panel testing is the difficulty in assigning pathogenicity to rare genetic variants identified in these high risk genes. Recently identified CRC susceptibility genes, *POLE* and *POLD1* (1), have been added to these panels without well developed and validated models for variant classification and as such, the majority of rare variants identified in these two genes are classified as variants of uncertain clinical significance (VUS). The classification of VUS has important implications for patients and their family members. Clinicians in Family Cancer Clinics across Australia cannot assign the most

appropriate clinical management for individuals and their relatives, leaving them potentially at risk of developing CRC or being over-treated.

Commonly used computational tools can aid in predicting the effect each genetic variant has on protein function, and therefore, can aid in rare variant classification. However, these tools alone generally do not accurately classify the pathogenicity of rare genetic variants. In this project, you will develop a multifactorial model to classify rare VUS in *POLE* and *POLD1* identified in individuals affected with CRC. The new classification model will be inclusive of tumour molecular and histological features, protein structure, RNA expression, clinical and family history data and computational predictions. This project will develop expertise in molecular biology, genetic testing and analysis including bioinformatics, and statistics. The outcomes of this project will have significant international impact through improved risk categorization for patients with an unclassified variant in *POLE* and *POLD1*.

1. Palles C, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, et al. Germline mutations affecting the proofreading domains of *POLE* and *POLD1* predispose to colorectal adenomas and carcinomas. *Nat Genet.* 2013;45(2):136-44.

Identification of novel dietary chromatin-modifying using molecular dynamic simulations

Supervisor: Dr Tom Karagiannis

Email: karat@unimelb.edu.au

Telephone: 0400 857 906

MRI & Location: Baker IDI, AMREP (Commercial Road, Prahran)

Co-Supervisor(s): Dr Andrew Hung

Project Description:

Chemical modification of histones represents an important epigenetic mechanism critical for DNA metabolism including, transcription, replication and repair. A well-known example is maintenance of histone acetylation status by the opposing actions of histone acetyltransferase and histone deacetylase enzymes (HDACi) which add and remove acetyl groups on lysine residues on histone tails, respectively.

Although numerous compounds have been developed to specifically alter the function of chromatin modifying enzymes (for example, histone deacetylase inhibitors are relatively well-investigated), we are only at the early stages of understanding the long-term epigenetic effects of dietary biomolecules. In this project the student will utilise *in silico* molecular modelling approaches combined with known experimental affinities for controls, to identify potential dietary chromatin modifying compounds. Acetate and sodium butyrate, which are well known dietary HDACi will be used as starting points for simulations. The student will have access to all of the software (including, Autodock Vina in PyRx, Swissdock and Hex-Server) and expert tuition to complete the relevant simulations.

Molecular mechanisms of action of dietary antioxidants and chromatin modifying compounds

Supervisor: Dr Tom Karagiannis

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Telephone: 0400 857 906

MRI & Location: Baker IDI, AMREP (Commercial Road, Prahran)

Co-Supervisor(s): Dr Andrew Hung

Project Description:

The medicinal properties of the leaves and fruit of *Olea europaea* (olive tree) have been known since antiquity, and consumption of olive oil has been associated with a decreased risk of cardiovascular disease and certain cancers. Increasingly, there is interest in the biological properties of the molecular constituents of olives. For example, hydroxytyrosol has been shown

to be a potent antioxidant and has anti-atherogenic and anti-cancer properties. However, the specific constituents responsible for various beneficial effects of olives, as well as their molecular targets, are not well known. The main aim of this project is to use molecular computational modeling and simulation methods to identify key molecular targets of specific bioactive components of olives, and to produce molecular-level characterisation of their mechanisms of action. The outcomes of this project will aid development of novel therapies derived from dietary compounds, which may have substantial advantages over synthetic drugs, including lower dosage requirements and reduced risk of adverse side effects. This project will focus on identifying the mechanisms of action of dietary olive compounds in inflammation.

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used therapeutic agents around the world, commonly used to reduce pain. However, there are adverse effects with the use of NSAIDs, including gastrointestinal bleeding and cardiovascular effects. Hence, there has been a rise in the development of alternatives to traditional NSAIDs. A previous study found that oleocanthal, a phenolic compound derived from olive, had similar effects to ibuprofen, a commonly used NSAID. But there is a multitude of additional compounds in olive that have yet to be investigated. Hence, this project will study the mechanisms of olive derived compounds in inflammation using molecular computational modeling and simulation approaches. Enzymes involved in inflammation pathways will be explored as potential targets for olive-derived compounds, including cyclooxygenase (COX). Elucidation of the mechanism of action in the inhibition of COX and other related enzymes will be valuable in developing novel drugs for the treatment of inflammatory diseases.

Examination of cross-neutralising immunity following HPV vaccination in Fiji

Supervisor: A/Prof Paul Licciardi

Email: paul.licciardi@mcri.edu.au

Telephone: 9345-5554

MRI & Location: Murdoch Children's Research Institute

Co-Supervisor(s): Ryan Toh

Project Description:

Cervical cancer is the fourth most common cancer in women worldwide, caused by infections with the human papillomavirus (HPV), with highest rates in low- and middle-income countries. Most cases (70%) are due to oncogenic HPV types 16 and 18 which are included in the two widely used prophylactic HPV vaccines, 2vHPV (Cervarix, GSK Biologicals) or 4vHPV (Gardasil, Merck) given as a 3-dose schedule over six months. Three other oncogenic HPV types 31, 33 and 45, represent an additional 15% of cervical cancer cases. For countries using 2vHPV or 4vHPV, cross-neutralising antibodies to non-vaccine types HPV31/33/45 are important as it may provide broader protection against a wider range of oncogenic HPV types. We have recently completed a study examining immunity in Fijian girls who received 1, 2 or 3 doses of 4vHPV six years earlier as well after a booster dose of 2vHPV. This Honours project aims to specifically examine cross-neutralising immunity in blood following 4vHPV using a combination of approaches, including HPV neutralisation assays and cellular immune assays. This is the first such study to examine the persistence of cross-neutralising antibodies following HPV vaccination

Immunomodulatory effects of Vitamin D on the host response to bacterial and viral infections

Supervisor: A/Prof Paul Licciardi

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Telephone: 9345-5554

MRI & Location: Murdoch Children's Research Institute

Co-Supervisor(s): Dr Lien Anh Ha Do

Project Description:

Infections with the *Streptococcus pneumoniae* and Respiratory Syncytial Virus are a major cause of morbidity and mortality in children less than 5 years of age. In particular, bacterial-viral co-infections cause substantial more inflammation and disease. The host response to infection involves activation of both innate and adaptive immunity both in the mucosal tissue as well systemically. Vitamin D has been shown to have a variety of biological effects including beneficial effects on the immune system. These include modulation of cytokine production, T-lymphocyte function and inflammatory responses, suggesting that Vitamin D may have an important function in the control of bacterial and viral infections. This project aims to characterise the effects of Vitamin D on immune cell populations in response to bacterial and/or viral co-infection. This study will use a variety of techniques including human immune cell culture and stimulation, flow cytometry and cytokine assays.

The role of agglutination in protection against pneumococcal colonisation

Supervisor: A/Prof Paul Licciardi

Email: paul.licciardi@mcri.edu.au

Telephone: 9345-5554

MRI & Location: Murdoch Children's Research Institute

Co-Supervisor(s): Ryan Toh

Project Description:

Pneumococcal infections are responsible for a significant burden of morbidity and mortality in children under 5 years of age globally. Colonisation of upper respiratory tract by pneumococcal bacteria is the critical step in disease pathogenesis and an important target of host immune protection. Recently, it has been shown that the agglutination capacity of pneumococcal-specific antibodies are associated with protection against colonisation in animal models and human challenge studies. However, this has not been shown following vaccination with pneumococcal conjugate vaccines. Using a novel simple assay established in the laboratory, this project aims to measure the agglutination capacity of pneumococcal antibodies in the context of a vaccine trial and its association with pneumococcal colonisation. This project involves several techniques including bacterial culture and flow cytometry.

Characterising the milieu of hepatitis B spliced variants associated with advanced liver disease and liver cancer.

A/Prof. Peter Revill

VIDRL, Doherty Institute.

Peter.revill@mh.org.au

Co-Supervisor

Dr. Margaret Littlejohn

VIDRL, Doherty Institute.

Margaret.littlejohn@mh.org.au

Hepatitis B virus (HBV) is one of the most important human pathogens, infecting 257 million people worldwide, including 239,000 Australians. We have previously shown that splice variants of Hepatitis B virus are associated with liver cancer, the 5th most prevalent cancer worldwide (Bayliss *et al*, J. Hepatol, 2013), and that splice variants are more diverse than previously appreciated (Betz-Stablein *et al.*, 2016). Yet the complexity of splice variants associated with advanced liver disease and liver cancer is unknown. The current quantitative PCR only detects a small proportion of the known splice variants, meaning it is not possible to quantify all splice variants without using prohibitively expensive deep sequencing methods. This project will develop qPCR protocols to detect all known splice variants, across different HBV genotypes. This will be tested using transient transfection and infection cell culture models, as well as patient samples. Techniques utilized will include cell culture, real time PCR/digital PCR, next

generation sequencing and quantitative serology and this project will make a major contribution to our understanding of the role of splice variants in liver disease progression.

Determining the role of secreted hepatitis B virus (HBV) RNA in the HBV life cycle and pathogenesis.

Primary Supervisor:
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VIDRL, Doherty Institute.
Peter.revill@mh.org.au

Co Supervisor:
Dr. Margaret Littlejohn
VIDRL, Doherty Institute.
Margaret.littlejohn@mh.org.au

Hepatitis B virus (HBV) is a global health issue, affecting over 2 billion people worldwide with 257 million people chronically infected. There are nine different genotypes of HBV (A to I) which show a distinct geographical distribution, and different disease outcomes. At present, there is no known cure for HBV, due mainly to the presence of a pool of transcriptionally active cccDNA that has to date proved almost impossible to eliminate from infected hepatocytes. This reservoir of cccDNA is one of the major barriers to HBV cure. Although HBV is a DNA virus, it has recently been shown that viral RNA is also encapsidated in virus particles and secreted from the cell. The role of this RNA in the HBV lifecycle is unclear, but is thought to be an indirect marker of cccDNA expression. This is important, as biomarkers of cccDNA expression will be needed as new curative treatments are developed that target cccDNA. The impact of genotype on secreted RNA expression is also unclear. This project will utilize *in vitro* cell culture and *in vivo* (patient) samples to interrogate the role of secreted viral RNA in the HBV life cycle. Techniques utilized will include cell culture, Southern and northern blotting and real time PCR/digital PCR and quantitative serology. This project will make an important contribution to our understanding of the role of secreted HBV RNA in the HBV life cycle and disease pathogenesis across the globe.

Defining the immune cell changes regulating early breast cancer growth

Supervisor: Dr Kara Britt
Email: kara.britt@petermac.org
Telephone: 03 85597110
MRI & Location: Peter MacCallum Cancer Centre. 305 Grattan St

Project Description: Breast cancer is not considered immunogenic, as its incidence is not increased in immune suppressed patients (transplant patients and HIV patients). However, irrefutable data now show that the immune cell infiltrate of a breast cancer affects its growth and metastasis. Only limited data exist on the role of immune cells in the early stages of BCa. This project will determine whether immune changes occur early in the tumorigenic process of triple negative breast cancers and whether this can be treated with immunotherapy to inhibit cancer development.

Metabolic reprogramming and chemotherapy resistance in triple-negative breast cancer

Supervisor: Dr. Kristin Brown
Email: kristin.brown@petermac.org
Telephone: 03 8559 5457
MRI & Location: Peter MacCallum Cancer Centre

Project Description:

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. 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 reprogramming of cell metabolism promotes tumourigenesis. Our studies suggest that metabolic reprogramming is also a component of the highly coordinated response to chemotherapy exposure. The aims of this project will be to 1) identify adaptive metabolic reprogramming events triggered when TNBC cells are exposed to chemotherapy, and 2) identify novel therapeutic approaches to exploit adaptive metabolic reprogramming events and sensitize TNBC cells 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. Students will gain experience in mammalian cell culture, molecular biology techniques, metabolomics and stable-isotope labelling techniques.

Cutting off the fuel supply to starve cancer: identifying metabolic vulnerabilities in cancer.

Supervisor: Dr. Kristin Brown

Email: kristin.brown@petermac.org

Telephone: 03 8559 5457

MRI & Location: Peter MacCallum Cancer Centre

Co-supervisor: Dr. Andrew Cox

Project Description:

A universal characteristic of all cancer cells is the reprogramming of cell metabolism to provide the energy and building blocks necessary to support proliferation and survival. Reprogramming of cell metabolism occurs as a consequence of oncogenic mutations and renders cancer cells dependent on a unique set of nutrients. It is now widely recognized that the altered metabolic activity of cancer cells provides a window of opportunity to develop tumour-specific anticancer therapies.

Using transcriptomic and metabolomic approaches, the aims of this project will be to: (1) compare and contrast metabolic reprogramming induced by well-described oncogenes; (2) compare and contrast the nutrient requirements of cancer cells dependent on well-described oncogenes and (3) identify and validate key metabolic vulnerabilities that can be targeted for the preclinical development of novel anticancer strategies. Students will gain experience in mammalian cell culture, molecular biology techniques, metabolomics and stable-isotope labelling techniques.

Elucidating the protein interaction network of serum-and glucocorticoid-regulated kinase 1 (SGK1).

Supervisor: Dr. Kristin Brown

Email: kristin.brown@petermac.org

Telephone: 03 8559 5457

MRI & Location: Peter MacCallum Cancer Centre

Project Description:

The phosphoinositide 3-kinase (PI3K) pathway is a master regulator of numerous cellular phenotypes associated with cancer including cell survival, proliferation, growth, altered metabolism and malignant transformation. Deregulation of the PI3K pathway is implicated in virtually all human cancers and 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 of serine/threonine kinases has by comparison received little attention.

Recently, SGK1 has been shown to play a critical role in driving the expansion of tumour cells and promoting resistance to conventional chemotherapy and targeted therapy agents. However, the molecular mechanisms underlying the oncogenic activities of SGK1 are poorly characterised. In this project, we will identify SGK1 substrates and interacting proteins using the proximity-dependent biotin identification (BioID) method. Students will gain experience in mammalian cell culture and proteomics (mass spectrometry) techniques. Targets identified in the BioID screen will be validated using a variety

of biochemical and molecular biology techniques.

Enhancing anti-tumour immune responses

Supervisor: Dr Jane Oliaro

Email: jane.oliaro@petermac.org

Telephone: 85597094

MRI & Location: Peter MacCallum Cancer Centre, Melbourne

Co-Supervisor(s): Dr Conor Kearney

Project Description:

Immunotherapy is a new approach to treat cancer, and works by promoting the immune system to attack cancer. Immunotherapies, such as checkpoint blockade and adoptive T cell therapy, are proving to be very successful in certain human cancers. However, not all cancers are responsive to immunotherapy and combining immune-based therapies with drugs that cause direct cancer cell death may be more effective. Resistance to immunotherapy is also an issue, and identifying pathways that are modulated by tumour cells to avoid attack by the immune system is critical for optimising immunotherapy approaches.

We have projects available in the laboratory to investigate the potential of combining immunotherapy with a novel anti-cancer drug to enhance anti-tumour immune responses, in order to develop more effective treatments for cancers such as melanoma and breast. We also have projects designed to investigate novel genes and pathways that confer resistance in tumours to T cell mediated attack. The projects involve a strong immunology component, combined with molecular biology, cell biology and tumour immunology mouse models.

Developing therapeutic strategies to target mutant-p53 cancers

Supervisor: Dr. Nick Clemons

Email: nicholas.clemons@petermac.org

Telephone: 85595273

MRI & Location: Peter MacCallum Cancer Centre, Parkville

Co-Supervisor(s): Prof Wayne Phillips

Project Description:

The tumour suppressor p53 is mutated in over half of all cancers and is associated with tumourigenesis, resistance to chemotherapy and poor prognosis. New therapies, such as the drug APR-246, that aim to restore normal p53 function to mutant p53 protein are currently in clinical trials, including in oesophageal cancer. An alternative approach is to target the gain of function activities of mutant p53 protein.

We have recently shown that mutant p53 suppresses expression of the amino acid transporter, xCT, thereby impairing glutathione synthesis, disrupting redox balance and providing a weakness that we can exploit therapeutically. This project will determine the mechanism by which mutant p53 suppresses this pathway and develop novel therapeutic strategies, including combination therapies with APR-246, to target this Achilles heel. This project will use patient samples and innovative *in vitro* and *in vivo* pre-clinical models to understand the fundamental biology underlying this novel gain of function activity of mutant p53 and establish the most effective drug combinations and companion biomarkers for targeting these tumours.

Defining the functional drivers of oesophageal tumourigenesis

Supervisor: Dr. Nick Clemons

Email: nicholas.clemons@petermac.org

Telephone: 85595273

MRI & Location: Peter MacCallum Cancer Centre, Parkville

Co-Supervisor(s): Prof Wayne Phillips

Project Description:

Oesophageal adenocarcinoma develops in a step-like fashion from Barrett's oesophagus, a benign intestinal-like metaplasia that arises as a consequence of chronic gastro-oesophageal

reflux. Recent genomic studies have shown there are few common oncogenic drivers of this progression, whilst loss of tumour suppressor genes (e.g. TP53 and SMAD4) and genomic instability is common. Recently, we have demonstrated that loss of SMAD4 on a background of mutant p53 induces tumourigenesis in Barrett's oesophagus in *in vivo* models.

The aim of this project is to determine the functional drivers of oesophageal carcinogenesis. The project will utilise gene editing technologies (e.g. CRISPR/Cas9) and lentiviral expression systems to target candidate drivers (e.g. knockout putative tumour suppressors or overexpress candidate oncogenic drivers). The functional effects of these events will be studied in models of Barrett's oesophagus, including human cell lines and primary organoid cultures derived from Barrett's oesophagus grown *in vitro* and as xenografts, to determine whether they contribute to disease progression.

This project will make a significant contribution to our understanding of how this disease develops at the fundamental level and thereby enhance our ability to develop new management strategies for patients with this disease.

Activation of nucleolar-specific DNA damage response as a therapeutic strategy for ovarian cancer

Supervisor: Dr. Elaine Sanij

Email: Elaine.sanij@petermac.org

Telephone: 03 8559 5279

MRI & Location: Cancer Signalling Laboratory, Peter MacCallum Cancer Centre

Co-Supervisor(s): Prof Rick Pearson

Project Description:

Ovarian cancer is the major cause of death from gynecological cancers. The most common and aggressive subtype, high-grade serous ovarian cancer (HGSOC), accounts for 70-80% of all ovarian cancer deaths [1]. HGSOC patients are treated by surgery and/or chemotherapy, yet within 5 years most of these women relapse making new treatment options essential.

We developed a "first in class" drug, CX-5461 that inhibits RNA polymerase I transcription, selectively kills cancer cells [2-4] and is in clinical trials in haematologic (Peter Mac) and breast cancers (Canada). Importantly, our studies demonstrate substantial efficacy of CX-5461 in HGSOC, which is the basis of a new trial in HGSOC we are planning in 2018.

50% of HGSOC is characterized by frequent alterations of genes involved in the homologous recombination (HR) DNA repair pathway [1]. Aberrations in DNA repair provide a weakness that can be exploited therapeutically with genotoxic chemotherapy and inhibitors of DNA repair such as PARP inhibitors (PARPi), now approved in the clinic.

Our data demonstrates that CX-5461 in combination with PARPi has significant therapeutic benefit *in vivo* against HGSOC xenograft models. Thus, we aim to provide direct evidence for the effectiveness of these strategies to facilitate clinical trials that will eventually lead to improved outcomes for HGSOC patients.

This project aims to investigate the molecular mechanisms underlying the improved efficacy of CX-5461 in combination with DNA repair and DNA damage response inhibitors against ovarian cancer. Specifically, we aim to characterise the molecular and cellular response to CX-5461 in combination with PARPi and cisplatin (chemotherapy) in primary and cancer ovarian cell lines.

References:

1. Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. *Nature*. 2011; 474(7353):609-615.
2. Bywater MJ, et al. Inhibition of RNA polymerase I as a therapeutic strategy to promote cancer-specific activation of p53. *Cancer cell*. 2012; 22(1):51-65.
3. Devlin JR, et al. Combination therapy targeting ribosome biogenesis and mRNA translation synergistically extends survival in MYC-driven lymphoma. *Cancer Discov*. 2016.
4. Hein et al., Inhibition of Pol I transcription treats murine and human AML by targeting the leukemia-initiating cell population. *Blood* (2017) [Epub ahead of print]
5. Quin J, et al. Inhibition of RNA polymerase I transcription initiation by CX-5461 activates non-canonical ATM/ATR signaling. *Oncotarget*. 2016.

How loss of the polarity protein, Par3, alters intracellular signalling pathways to drive Acute Myeloid Leukemia.

Supervisor: A/Prof Sarah Ellis

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Telephone: 8559 8722

MRI & Location: Peter MacCallum Cancer Centre

Co-Supervisor(s): A/Prof Phil Darcy

Project Description:

The polarity protein, Par3, is a member of the partitioning defective (Par) polarity complex and consists of three protein binding domains and a self-homologous binding region. The latter allows Par3 to form large complexes; hence Par3 is often referred to as the master polarity regulator. As a scaffolding protein, Par3 interacts with different intracellular signaling pathways, which are frequently deregulated in cancer. Par3 acts in a context dependent manner as either a tumour promoter or suppressor in multiple human epithelial cancers. However, the role of Par3 in haematopoietic malignancies is unknown.

Utilising inducible knockout mouse models, we have shown that loss of Par3 exacerbates the onset and severity of Acute Myeloid Leukemia (AML) by inducing a significant increase in the proportion and number of granulocyte/macrophage progenitors (GMPs) compared to control littermate mice.

Importantly, the GMP stage of development is critical for the progression of AML, suggesting loss of Par3 predisposes mice to the development of AML.

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 western blotting, quantitative RT-PCR, immunohistochemistry, flow cytometry, and live cell microscopy.

SCRIB acts as an oncogene in T-ALL by activating signaling pathways controlling cellular proliferation.

Supervisor: A/Prof Sarah Ellis

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Telephone: 8559 8722

MRI & Location: Peter MacCallum Cancer Centre

Co-Supervisor(s): A/Prof Phil Darcy

Project Description:

Cellular polarity is maintained by three complexes, the Scribble, Par, and Crumbs complexes and its deregulation is a hallmark of cancer. The focus of this project is SCRIB, a component of the Scribble complex. SCRIB acts as a scaffolding protein, binding to intracellular proteins that are key to signaling pathways controlling cell proliferation, migration, and apoptosis. Thus it is not surprising that SCRIB has been implicated in multiple epithelial cancers including prostate, breast, colon, cervical and skin cancer. SCRIB's role in haematopoiesis and haematopoietic malignancies is an exciting area of burgeoning interest. Previous studies in our laboratory using different inducible knockout mouse models and a reverse transplant assay, have shown SCRIB is involved in B and T cell development and for myelopoiesis in steady-state haematopoiesis. In a mouse model of T-cell Acute Lymphocytic Leukaemia (T-ALL), we discovered SCRIB acts as an oncogene with loss of SCRIB delaying the onset and severity of the disease.

We have analysed the proteins that are up- or down-regulated upon loss of SCRIB in T-ALL through a reverse phase protein array (RPPA). Based on the RPPA data, this project will investigate one or two key intracellular signaling pathways that are inhibited in the absence of SCRIB to discern how loss of SCRIB delays the onset of T-ALL. One of these pathways, the Hippo pathway, is deregulated in epithelial cancers but its involvement in haematopoietic malignancies is entirely novel.

We will confirm RPPA data with western blot and quantitative RT-PCR and will investigate signaling pathway members altered upon loss of SCRIB with RNA seq. The distribution of key signaling proteins in different haematopoietic fractions as well as the levels of proliferation/apoptosis will be examined

with flow cytometry and immunohistochemistry (IHC) including multiplex IHC.

Personalised risk evaluation in DCIS

Supervisor: Kylie Gorringe

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Telephone: +613 8559 6521

MRI & Location: Peter MacCallum Cancer Centre, 305 Grattan St

Co-Supervisor(s): Ian Campbell

Project Description:

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 using in situ methods such as immunohistochemistry and FISH may also be undertaken.

Exploration of novel approaches to anti-cancer treatment: manipulation of mutant p53.

Supervisor: Prof. Ygal Haupt

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Telephone: 61-3-96565871

Facsimile:

Location: Peter MacCallum Cancer Centre

Co-Supervisor(s): Dr. Sue Haupt

Project Description:

P53 is the most mutated gene in human cancer, affecting about half the cases of cancer, and involved in every cancer type. We have recently identified novel regulators of mutant p53 using sophisticated loss of function whole genome high through put screen. In this project the PhD student 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.

Hippo tumour suppressor pathway in organ growth

Name: Kieran Harvey

Phone: 8559 7104

Email: Kieran.harvey@petermac.org

MRI & Location: Peter MacCallum Cancer Centre

Co-Supervisor(s): Dr Lucas Dent

Project Description:

Background

A new frontier in biomedical research will involve watching individual proteins work in real time, in living organs. Traditionally, researchers have drawn conclusions about gene function using indirect techniques that only allow us to infer what a gene normally does, without actually watching it work. For

example, we create organisms that lack a particular gene and determine whether something goes wrong. If the loss of gene X causes organs to overgrow then we assume that gene X normally limits organ size. This has been an extraordinarily powerful approach for interrogating gene function but it cannot substitute the ability to watch gene products executing their function in real time, which allows determination of exactly when, where and how they work.

Aims

You will investigate the role Hippo tumour suppressor pathway in organ growth by watching, for the first time, its, in growing organs, in real time. This will provide novel insights into normal organ growth and pathogenic organ growth in diseases such as cancer.

You will observe Hippo pathway activity in real time in the following situations:

- a) When organs are actively growing
- b) When organs stop growing
- c) In regions of organs that are subject to mechanical compression
- d) Throughout the cell cycle

Techniques

You will be taught an array of techniques including ex vivo organ culture, live multi-photon microscopy, image analysis and *Drosophila* genetics.

Novel drug combinations targeting chromatin and RNA polymerase I transcription in multiple myeloma

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 Co-Supervisor(s): A/Prof. Simon Harrison; Prof. Grant McArthur

Project Description:

Multiple myeloma (MM) is a cancer of plasma cells that is incurable with currently available therapies. Patients who relapse after initial treatment have a very poor prognosis, with few effective drugs available and a lifespan measured in months rather than years. It is well known that single agent therapies rapidly lead to the development of drug resistance and clinical relapse, therefore combination drug therapy is necessary to provide a more durable response.

There is growing evidence that that epigenetic aberrations, i.e. those abnormalities that impact chromatin/DNA function, are important players in MM development. Moreover, there are promising novel agents that target these epigenetic factors (known as “epidrugs”) now entering the clinic for the treatment of MM, presenting an opportunity for renewed investigation of innovative combination therapies.

Our group has undertaken preclinical studies examining another novel drug that inhibits a key requirement for cancer cells – cell growth. Based on our seminal work, this drug CX-5461 is currently in phase 1 clinical trial in haematologic cancers (Peter Mac). We have intriguing data demonstrating that the combination of CX-5461, a highly selective inhibitor of RNA polymerase I (Pol I) transcription of the ribosomal genes, with several candidate epidrugs elicits a surprisingly high level of synergy in models of acute myeloid leukaemia (AML) and MM. Based on this impressive synergy thus far, we propose to screen a large number of epidrugs and validate them in preclinical MM mouse models to rapidly progress these findings to the clinic.

This honors project aims to investigate the fundamental mechanism(s) underlying the synergistic efficacy of Pol I transcription inhibition (CX-5461) and therapeutic disruption of fundamental epigenetic factors. A pilot screen has already identified three epidrug classes that demonstrate synergy with CX-5461: HDAC, BET-protein and CDK9 inhibitors. Thus, this project will use a range of experimental techniques including cell culture, qRT-PCR, chromatin immunoprecipitation (ChIP), Western blot analysis, high throughput cell viability assays, etc. to interrogate the impact on ribosomal gene transcription and chromatin and the downstream signaling pathways leading to synergistic MM cell death.

Obesity and liver disease

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Project Description:

Excess body weight is a major and leading factor in overall disease burden. In 2010 overweight and obesity were estimated to cause some 3.4 million deaths worldwide. Obesity is a key contributor to a myriad of human diseases including non-alcoholic fatty liver disease (NAFLD) and cancer.

NAFLD encompasses a broad spectrum of liver conditions ranging from simple steatosis, to the more severe and progressive non-alcoholic steatohepatitis (NASH), a condition that results in fibrosis and if left unresolved, cirrhosis (late-stage liver disease) and/or liver cancer. Obesity-associated NASH is currently the third leading cause for liver transplantation and is expected to soon surpass hepatitis C as the principal cause for liver transplantation and HCC in the developed world. *Projects are available to determine the mechanisms by which obesity drives the development of NASH, fibrosis and liver cancer*

Functional characterisation of candidate genes involved in the progression of gastric cancer

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 Co-Supervisor(s): Dr Rita Busuttill

Project Description:

Gastric cancer (GC) is the fourth most common cancer globally. It has defined premalignant stages and progresses through Intestinal Metaplasia (IM) in the majority of cases. GC is diagnosed at advanced stage resulting in poor prognosis. Part of this is due to no means to identify and screen persons at risk of GC. Relatively little is known about the key genetic events leading to IM. Our laboratory is currently in the process of completing the first comprehensive analysis of IM in the world and we have identified a number of candidate genes which are likely to be involved in the progression of IM to GC. These could potentially be used to reliably predict the progression to GC in humans enabling clinical stratification of individuals into high-risk groups. This project would involve functional validation of these candidates using cell culture and organoid model systems.

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

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Project Description:

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.

Fishing for metabolic clues: Role of the Hippo/Yap pathway in reprogramming metabolism in liver cancer.

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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.

Metabolic rewiring in liver cancer: Role of oxidative stress and the Nrf2 pathway.

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Many of the major risks factors for developing liver cancer such as alcohol, obesity, smoking and toxin exposure share in common a role for oxidative stress. Nrf2 is a transcription factor activated by oxidative stress that orchestrates an adaptive response remodeling metabolism and promoting cytoprotection. Recent studies have identified that the Nrf2 pathway is frequently mutated in liver cancer (~12% tumors), causing activation of the pathway in the absence of oxidative stress. We have used transcriptomic and metabolic profiling in Nrf2^{-/-} zebrafish to examine the role Nrf2 plays in remodeling metabolism during liver development and regeneration. Building on these preliminary studies, we currently have research projects that aim to 1) Generate a gain of function Nrf2 mutant (Nrf2^{D29H}), frequently recovered in cancer, and characterize the effect the mutation has on metabolic reprogramming. 2) Examine how deregulation of Nrf2 remodels metabolism to stimulate liver tumorigenesis. The students will use a combination of innovative biochemical, genetic and imaging approaches in zebrafish to identify the metabolic dependencies of tissue growth in liver regeneration and cancer.