HUDSON
INSTITUTE OF MEDICAL RESEARCH

CENTRE FOR CANCER RESEARCH

2022 Student Research Projects

MHTP Monash Health Translation Precinct | MONASH University | HUDSON INSTITUTE OF MEDICAL RESEARCH | Monash Health

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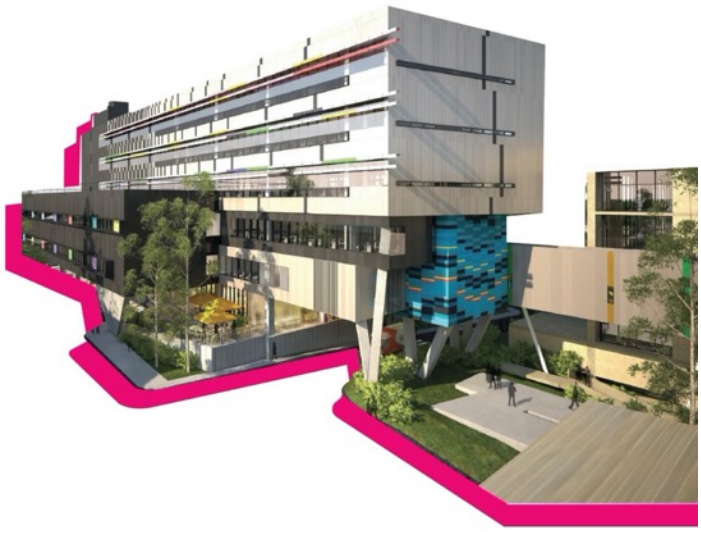

The Translational Research Facility is connected via a link bridge to Monash Health. The facility provides a crucial link between our scientific discoveries and medical treatments, housing nine world-leading technology platforms and an eight-bed, 21-chair Clinical Trials Centre that support the transition of discoveries from initial Phase I testing through to Phase IV primary health trials.

Welcome to Hudson Institute

Hudson Institute specialises in discoveries in five areas of medical need

- **Inflammation**
- **Reproductive health and pregnancy**
- **Infant and child health**
- **Cancer**
- **Hormones and health**

Our 443 scientists and students focus on laboratory discovery science, plus translational research – taking discoveries to patients and industry for real-world impact.

285 STAFF

158 STUDENTS

43 RESEARCH GROUPS

285 RESEARCH PUBLICATIONS

Students at a glance 2020

60 POSTGRADUATE AND HONOURS STUDENTS COMPLETED

158 STUDENTS 113 PHD 6 MASTERS 38 HONOURS

31 STUDENTS WITH MEDICAL TRAINING

We educate and train more than 150 students through our academic affiliation with Monash University. Our postgraduate training is predominantly through the School of Clinical Sciences at Monash Health, part of the Faculty of Medicine, Nursing and Health Sciences at Monash University.

Our students

- Are exposed to university, institute and hospital research
- Attend national and international conferences
- Publish their research (there were 41 student first author publications in 2020)
- Are mentored by leading supervisors and their teams
- Regularly win prestigious prizes and awards
- Take part in regular networking and learning and development programs.

All work and no play …

Our students can join in a range of student networking and social events organised by Hudson Institute Student Society (HISS), including being part of the management committee.

Our precinct

Hudson Institute is a leading Australian medical research institute recognised internationally for discovery science and translational research into inflammation, reproductive health and pregnancy, infant and child health, cancer, hormones and health.

Our Institute is home to 443 world-class scientists, who push the boundaries of scientific knowledge to answer complex questions about human disease, including prevention and treatment.

We are a founding member of the Monash Health Translation Precinct with partners Monash Health and Monash University. Our close ties with clinicians and industry enable us to translate our discoveries into new preventative approaches, therapies and devices for patients.

Our location at Monash Medical Centre means our research is informed by patient need and our discoveries are rapidly transitioned into practical treatments.

Working alongside clinicians in Melbourne hospitals for more than 50 years, our scientists pioneered IVF and stem cell discoveries and are now leading developments in cell therapies, paediatric cancer and the human microbiome. Our worldwide scientific and medical collaborations provide a foundation for transformative healthcare programs across the globe.

Centre for Cancer Research

Location: Hudson Institute of Medical Research
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Centre Head

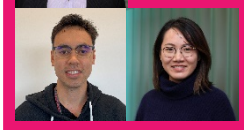
Assoc/Prof Ron Firestein

Scientists working in the Centre for Cancer Research undertake basic research into the molecular mechanisms underlying the development, growth and metastasis of tumours, as well as the relationship between the innate immune system and cancer. The discovery and development of novel therapies for the treatment of cancers is also an important aspect of the team's work.

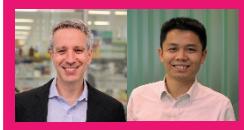
Current key areas of interest include:

- Links between innate immunity, inflammatory processes and cancer – Role of embryonic signalling pathways in cancer, and the targeting of these pathways with novel therapies
- Cell signalling pathways involved in tumour survival and growth, and the development of monoclonal antibodies to treat glioma and other cancers
- Role of integrin-linked kinase in cell migration and oncogenesis
- Molecular pathways involved in the metastasis of tumours, including colorectal, ovarian, prostate and bladder cancers
- Role of steroid hormones and nuclear receptors in breast cancer development and progression
- Role of peptidase activity on inflammatory signalling and tumour microenvironment in ovarian cancer
- Molecular links between obesity, oestrogens and cancer, and therapies aimed at breaking the linkage
- Role of the microenvironment in tumour progression, chemoresistance and metastasis
- Cancer precision medicine, including childhood brain cancer and solid tumours

Research Group Heads & Primary Project Supervisors

Hudson Monash Paediatric Precision Medicine Program (HMPPMP)
Research Group Head
Assoc/Prof Ron Firestein
Postoctoral Scientist
Dr Paul Daniel
Bioinformatician
Dr Claire Sun



Cancer Genetics and Functional Genomics
Research Group Head
Assoc/Prof Ron Firestein
Postdoctoral Scientist
Dr Chunhua Wan

Developmental and Cancer Biology
Research Group Head
Dr Jason Cain

Cancer and Innate Immunity
Research Group Head
Prof Bryan Williams

Immunohaematology
Research Group Head
Dr George Grigoriadis
Research Group Head
Dr Jim Vadolas

Ovarian Cancer Biomarkers
Research Group Head
Dr Andrew Stephens

STAT Cancer Biology
Research Group Head
Dr Daniel Gough

Functional RNAomics
Research Group Head
Dr Minni Änkö

Genetics and Molecular Pathology
Research Group Head
Assoc/Prof Elizabeth Algar

Structural Biology of Inflammation and Cancer
Research Group Head
Dr Wilson Wong

Cancer

Hudson Monash Paediatric Precision Medicine Program (HMPPMP)

Precision Medicine for Childhood Brain Cancer

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Assoc/Prof Ron Firestein

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Project description: The Hudson Monash Paediatric Precision Medicine Program marks a significant investment in future clinical management and novel research discovery in childhood cancer.

The program includes:

The development of a living tumour biobank for paediatric solid tumours

At present, very few reliable patient-derived preclinical models are available to researchers. To bridge this gap, our program will establish and bank organoid, cell lines, and xenograft models directly from childhood tumour tissue. The establishment of a living biobank for paediatric solid tumours will provide a critical renewable resource for local, national and international researchers.

The establishment of a functional genomics pipeline

We capitalise on the living biobank tumour samples to integrate genomic data (next generation sequencing) with functional data obtained from high-throughput genetic (Cas9/CRISPR) and results from global pharmacological drug screens.

Translation of genomic data into targeted therapy

The comprehensive molecular analysis of individual patient tumours will help identify both new and existing therapies that can be rapidly implemented in the clinic. This approach will facilitate clinical implications of data from the functional genomics pipeline for individual paediatric patients.

Unique national and global collaborations

The establishment of a living biobank and functional genomic testing for paediatric solid tumours provides a critical resource for local, national and international researchers. Thus, a key element of the program includes national and international stakeholders' involvement to build expertise, share resources and disseminate results that will advance the field of precision medicine for paediatric cancer patients.

Keywords: cancer, genetics, paediatrics, brain cancer, CRISPR, drug screens, genomics, personalised medicine, precision therapy

Evolution of drug resistance in paediatric and adult high grade glioma

Suitability: Honours

Project leader: Dr Paul Daniel (co-supervisor Assoc/Prof Ron Firestein)

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Project description: High grade malignant glial tumours can arise in paediatric or adult populations where the outcome of patients is similarly lethal. Multi-modal therapy including surgery, chemotherapy and radiotherapy are largely ineffective, whereby rapid relapse is inevitable and ultimately lethal. Despite the initial promise of molecularly informed treatment approaches, the clinical impact of personalised therapy has been limited for CNS tumours. We now know that rapid evolution of resistance occurs in many patients and limits durability of response.

Using preclinical models of glioma, the successful candidate will investigate fundamental differences between adult and paediatric diseases in their capacity to evolve resistance to targeted therapies. Identifying the underlying features contributing to evolution of resistance in these tumours is a priority for extending the duration of response to these next-generation targeted therapies and may be key towards defining combinatory treatments for high grade glioma.

Keywords: cancer, paediatric, glioma, brain, therapy, resistance

Allele-specific transcription of tumorigenic mutations in paediatric cancers

Suitability: Honours

Project leader: Dr Claire Sun (co-supervisor Assoc/Prof Ron Firestein)

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Project description: The Hudson-Monash Paediatric Precision Medicine (HMPPM) Program focuses on utilising genetic profiles of patients' tumour models to identify new therapeutic targets and repurpose existing ones using high-throughput functional CRISPR screens. Advancements in next-generation sequencing and computational biology techniques have facilitated a deeper understanding of the genetic underpinnings of cancers, paving the way for the advent of the next generation of targeted therapy for paediatric tumours. However, less than 15% of paediatric cancer patients harbour actionable mutations, of which fewer respond to targeted therapies. This underscores an urgent need to delve beyond driver mutations to identify biomarker coupled therapies. Transcriptomics not only enable characterisation of genetic alterations at the RNA level but also quantitatively capture how tumorigenic genotypes are transcribed into the malignant phenotype. It has been shown that allele-specific expression result in preferential expression of mutant or wild-type products. Using best-practice computational pipelines running on high-performance computers, the successful candidate

will firstly identify the genetic alterations in a large compendium of patient derived tumour models. Secondly, they will then identify allele-specific expression of these key driver mutations. This project aims to describe whether allele specific expression contributes to tumorigenesis and identify the underlying mechanisms that unbalance transcription between alleles.

Keywords: paediatric cancer, computational biology, bioinformatics, trancriptomics, genomics

Cancer Genetics and Functional Genomics

Understanding cancer resistance to chemotherapy

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Assoc/Prof Ron Firestein

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Project description: The majority of cancers initially respond very well to standard of care chemotherapeutics but invariably become resistant, leading to cancer relapse and patient mortality. This project seeks to identify novel therapeutic targets that will synergise resensitize tumours to chemotherapies in the resistant setting.

Keywords: chemotherapy, cancer treatment, drug targets, screen, genetics

Transcriptional regulators as cancer targets: new models and therapeutic approaches

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Assoc/Prof Ron Firestein

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Project description: Transcriptional regulators play a key role in activating oncogenic pathways that impinge on tumour growth, invasion and mestasasis. We have recently used CRISPR to generate cancer cell lines with fluorescent and luminescent reporters of key transcriptional pathways in colorectal cancer. In this project, the student will utilise cell biology and molecular biology techniques to dissect the components of the transcriptional machinery in cancer and identify new therapeutic targets.

Keywords: genetics, genomics, cancer, oncogenes, transcription

Functional genomic screens to identify new therapeutic targets for bowel cancer

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Assoc/Prof Ron Firestein

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Project description: Bowel/colon cancer is a major cause of cancer related morbidity worldwide. We will use novel genomic technologies (e.g. CRISPR, shRNAs) to screen the cancer genome in an effort to identify novel therapeutic targets to colon cancer patients.

Keywords: genetics, genomics, cancer, screen, personalised medicine

Development of new 3-dimensional models of cancer to model drug resistance and develop new cancer treatment

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Assoc/Prof Ron Firestein

e: ron.firestein@hudson.org.au

Project description: The development of clinically relevant cancer models that recapitulate human cancer is key to both understanding biological mechanisms of cancer growth as well as fine tuning therapeutic cancer treatments. In this project, the student will work with both human tissues and animal models to develop 3-dimensional organotypic culture of genetically defined cancer models. Using CRISPR and other technologies we will genetically manipulate these models, and assess the contribution of new targets in mediating cancer growth.

Keywords: colon cancer, organoids, models

Targeting colorectal cancer stem cells using genome-scale CRISPR screens

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Dr Chunhua Wan

e: chunhua.wan@monash.edu

Project description: Colorectal cancer stem cells (CSCs) play a determinant role in colorectal cancer initiation and progression. We will utilise genome-wide CRISPR screen, organoid culture to interrogate the regulatory mechanisms underlying CSCs. This project aims to develop novel therapies to induce the differentiation of colorectal CSCs as targeted therapies against colon cancer.

Keywords: colorectal cancer, translational medicine, cancer stem cells, CRISPR-Cas9 screen, druggable targets

KMT2A as a druggable therapeutic target against β-catenin-driven colorectal cancer

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Dr Chunhua Wan

e: chunhua.wan@monash.edu

Project description: Our recent systemic investigations revealed KMT2A as a key player in β-catenin-driven colorectal cancer (CRC). This project aims to promote potent KMT2A inhibitors into clinical use for CRC. We will employ *in vitro* (e.g. human CRC organoid culture) and *in vivo* (e.g. patient derived xenografts (PDX) and conditional KMT2A knockout mice) models, to clarify the potential of targeting KMT2A as a CRC therapeutic strategy.

Keywords: colorectal cancer, β-catenin, targeted therapy, epigenetics, translational medicine, cancer treatment, KMT2A

Developmental and Cancer Biology

Exploiting Epigenetic Dysregulation in SWI/SNF-Deficient Solid Tumours

Suitability: PhD/Doctorate, Honours

Project leader: Dr Jason Cain

e: jason.cain@hudson.org.au

Project description: Impaired differentiation is a common feature of cancer. We have recently demonstrated the differentiation potential of histone deacetylase inhibitors (HDACi) in paediatric (rhabdoid tumours) and adult (lung adenocarcinoma) solid tumours that are genetically defined by mutations in the SWI/SNF chromatin remodelling complex. Recent genomic studies have shown that mutations in subunits of this complex occur in at least 20% of all cancer. Using preclinical models of SWI/SNF-deficient and intact cancers, the successful candidate will investigate the mechanisms of epigenetic-mediated differentiation and apply these findings to a broader clinical context.

Keywords: epigenetics, cancer, paediatrics, brain, lung

Improving Childhood Sarcoma Risk Stratification and Outcomes for Recurrent Disease

Suitability: PhD/Doctorate, Honours

Project leader: Dr Jason Cain (co-supervisor Dr Peter Downie)

e: jason.cain@hudson.org.au

Project description: Soft tissue and bone sarcomas represent ~13% of all childhood cancer diagnosis and collectively are the second highest cause of childhood cancer related death, accounting for 20% of all mortalities. Despite the use of neoadjuvant chemotherapy and surgery, survival rates for these patients have remained stagnant for the last four decades. Curative treatment, effective in <70% of all sarcoma patients, leads to lifelong morbidity. For the remaining >30% there is no effective treatment. Whilst molecular markers of disease prognosis at diagnosis are revolutionising the clinical treatment and outcomes of other paediatric cancer types, this approach is largely lacking in childhood sarcoma. This highlights the urgent need for new and improved prognostic modalities and targeted therapies for these diseases.

In this project, we will assess the primary tissue of sarcoma patients to determine molecular and functional pathways predictive of therapeutic response, metastasis and survival outcomes. Furthermore, in patients with relapsed disease, we will assess and compare the molecular and functional pathways with the individual's primary tumour tissue to identify potential targets for therapeutic intervention. The identification of predictive biomarkers of therapeutic response and survival would represent a major development in the field and enable the future risk stratification of patients and appropriate adaptation of therapy to minimise side effects and improve overall side effects.

Keywords: childhood cancer, sarcoma, cancer biology

Immunohaematology

Deregulation of Key Signalling Molecules in the NF-kB Pathway and their links to Chronic Disease Development

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Dr George Grigoriadis

e: george.grigoriadis@monash.edu

Project description: Individuals that lack a normal functioning immune system are susceptible to opportunistic infections when challenged by pathogens (e.g viruses and microbes). Treatment with intravenous antibodies can successfully reduce the infectious burden, however a significant number of patients develop non-infectious complications, including autoimmune disease and cancer. We have found the transcription factor called NFkB1 to be a critical regulator of B and T cell function, and deregulation of this factor leads to aberrant lymphoproliferative disease (de Valle et al., 2016). We have examined young and ageing Nfkb1-haploinsufficient mice (Nfkb1+/-) to elucidate the impact of Nfκb1 haploinsufficiency. The Nfkb1+/- mice developed late-onset complications, including splenomegaly, and a multi-organ immune cell infiltrate in target organs. This pathology coincided with multiple aberrant immunological manifestations, including the excessive differentiation of CD4+ T follicular helper cells and the marked expansion of an atypical B cell population characterized by low levels of cell surface CD21 and high expression of the key transcriptional regulator T-bet.

While the above project is ongoing, new and exciting research initiatives have commenced examining the role of NFkB-Inducing Kinase (NIK) – a key kinase that regulates the function of NFkB2. NFkB2 is a related family member of NFkB1, and human mutations in this gene are linked to immunodeficiency, cancer and autoimmune disease. We have generated unique mouse models of NIK by CRISPR/Cas9 technology, and plan to elucidate NIK function in lymphoid and myeloid cell subsets. We anticipate our research findings will lead to important information about these key signaling molecules, how their deregulation is associated with chronic disease development. Future work will consider such molecules as potential diagnostic markers and facilitate the generation novel drug agents.

Projects Aims

1) To examine the role of NFkB1 deregulation in developing B

cells and how this relates to disease pathogenesis;

2) To assess the function of NFkB1 in CD4+ T cells, and understand how the impaired function of NFkB1 impacts on T – B cell collaboration;

3) To determine the roles of NIK in immune cells and chronic disease pathogenesis;

Techniques

Students will gain an understanding of cell signaling, particularly in lymphoid cells; work with unique mouse models; Tissue Culture assays, Flow Cytometry; and gain experience in molecular biology techniques, including CRISPR/Cas9; Real Time PCR; Chromatin Immunoprecipitation (ChIP) and ChIP-sequencing.

Keywords: NF-kB

Harnessing RNA interference in gene therapy vectors for β-thalassaemia

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Dr Jim Vadolas (co-supervisor Dr George Grigoriadis)

e: jim.vadolas@hudson.org.au

Project description: The β-haemoglobin disorders such as β thalassaemia, haemoglobin E (HbE), and sickle cell disease (SCD) are among the most prevalent inherited disorders worldwide. The conditions are the result of mutations in the adult β-globin gene, leading to production of either aberrant or insufficient β-globin protein. Symptoms appear in the first year of life, the period when fetal haemoglobin (HbF) is replaced by the adult form (HbA), leaving the patient dependent upon the mutated adult β-globin gene. Much of the pathology of this disease is due to excess α-globin chains forming toxic insoluble precipitates in erythroid cells resulting in cell death, ineffective erythropoiesis and severe anaemia. Interestingly, restoration of balanced globin protein synthesis through the reduction of α-globin expression can ameliorate the disease phenotype, exemplified by individuals who co-inherit α- and β-thalassaemia. This definitive observation forms the basis of a novel therapeutic strategy for β-thalassaemia, involving not an elimination but a targeted reduction of complementary α-globin chains, to mimic co-inheritance of α- and β thalassaemia. While the benefits of increased β-globin expression in the context of β-thalassaemia are very clear, decreasing α-globin expression has not yet been extensively investigated. This project aims to develop novel gene therapy strategies harnessing RNAi in gene therapy vectors for β-thalassaemia. Initial studies will be conducted in vitro using both cell lines and primary haematopoietic stem cells. Further studies will also be conducted in vivo using our unique humanised β-thalassaemia mouse models and patient-derived cells.

Keywords: gene therapy, RNA interferance, anaemia

Epigenetic modifications of the human β-globin locus: new therapeutic targets for haemoglobin disorders

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Dr Jim Vadolas (co-supervisor Dr George Grigoriadis)

e: jim.vadolas@hudson.org.au

Project description: Haemoglobin disorders, such as sickle cell disease and β-thalassaemia are the result of mutations in the adult β-globin gene. When these disorders are co-inherited with hereditary persistence of fetal haemoglobin, (high levels of γ-globin gene expression in adult life) the disease phenotype is much reduced. Understanding the mechanism of γ-globin globin gene regulation through development has been the subject of intense investigation for many years. These studies led to an appreciation of the role of epigenetic modifications such as DNA methylation and histone acetylation in globin gene expression and regulation. Networks of regulatory proteins interact with epigenetic complexes to regulate DNA accessibility and histone modifications, thereby determining appropriate patterns of globin gene expression, giving rise to several developmental stage-specific hemoglobin variants. This study will investigate the potential impact of epigenetic regulators on globin gene expression. Functional genomic screening strategies will be performed using RNA interference (RNAi) or CRISPR/Cas9 genome editing to either suppress or knockout the expression of specific epigenetic regulators in erythroid cells modified to express fluorescent reporter genes under the control of the γ-globin promoter. Further studies will also be conducted in vivo using unique humanised β-thalassaemia mouse models. Positive outcomes of such studies could pave the way for better treatment strategies for sickle cell anaemia and β thalassaemia patients by targeting epigenetic regulators to increase fetal globin expression.

Keywords: epigentics, RNA interference, CRISPR/Cas9 genome editing

Impact of impaired immune function in haemoglobin disorders

Suitability: PhD/Doctorate, Masters by Research, Honours

Project leader: Dr Jim Vadolas

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Project description: Haemoglobin disorders, such as sickle cell disease and β-thalassaemia are the result of mutations in the adult β-globin gene. Patients suffering with the most severe form of the disease require chronic blood transfusion for survival. Ongoing transfusion therapy to counteract anaemia exacerbates iron overload, and necessitates iron chelation therapy. One important clinical feature of these conditions is the increased frequency of infectious complications such as pneumonia and sepsis, which are significantly associated with an increased rate of morbidity and mortality. The increased susceptibility to pathogenic organisms has been attributed to multiple deficiencies affecting both innate and adaptive immune systems. What has become apparent, is that iron overload in chronically anaemic patients contributes to aberrant neutrophil effector functions resulting in increased susceptibility to infection and inflammation-related organ damage. This knowledge, combined with the emergence of novel immunomodulatory function and phenotypes for neutrophils has helped to re-invigorate interest in the field. To further understand the clinical significance of aberrant immune function in β-thalassaemia, we will undertake a comprehensive evaluation of the molecular and cellular mechanisms responsible for aberrant innate immune effector functions in β-thalassaemic mice and β-thalassaemia patients. The work proposed in this project will generate a better understanding of the mechanism underlying aberrant immune functions and provide novel insights into disease progression. Positive outcomes of such studies could pave the way for better treatment strategies for β-thalassaemia and related patients.

Keywords: thalassaemia, chronic anemia, immune response, iron overload

Ovarian Cancer Biomarkers

Identifying New Drug Targets in Ovarian Cancer Stem-Like Cells

Suitability: PhD/Doctorate, Honours

Project leader: Dr Andrew Stephens (co-supervisor Dr Maree Bilandzic)

e: andrew.n.stephens@hudson.org.au

Project description: Ovarian cancers are the most lethal of all gynaecological malignancies, with <30% 5-year survival. Cancer progression requires cells to orchestrate a highly co-ordinated program of attachment, migration and invasion into healthy tissues. We have identified that a specialized subset of stem-like cancer cells, termed “Leader Cells”, control these processes in ovarian tumours. Leader cells are also enriched by chemotherapy and exert immune suppressive effects in vivo. Existing therapies do not kill or inhibit the leader cell population, resulting in their enrichment over time and ultimately leading to a poor prognosis for patients.

We hypothesize that therapies targeting leader cells will synergize effectively with standard chemotherapy to achieve stable, long-term disease regression.

This project will use a combination of molecular, biochemical and precision medicine approaches to investigate molecular pathways and identify “druggable” targets in ovarian cancer leader cells, and develop therapeutic strategies for translation into clinical practice.

Keywords: cancer, stem cell, therapeutic, metastasis, ovarian, translation

Photodynamic Therapy for Cancer Treatment

Suitability: PhD/Doctorate, Honours

Project leader: Dr Andrew Stephens (co-supervisor Dr Maree Bilandzic)

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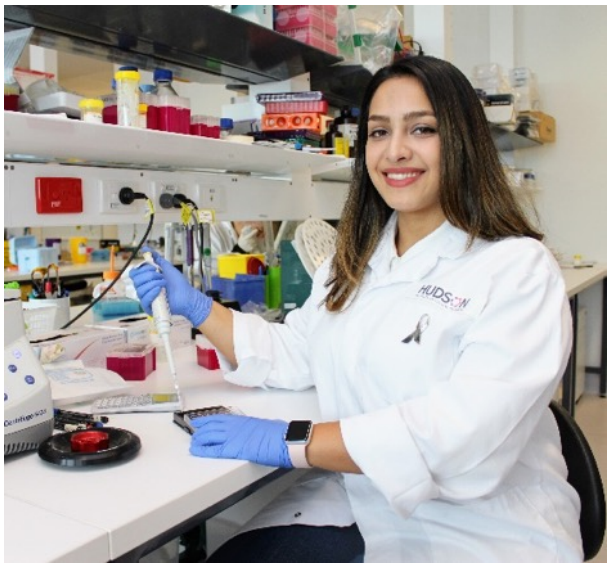
Project description: Photodynamic therapy (PDT) uses light-sensitising agents to directly destroy tumour tissue and initiate anti-tumour immune responses. We have developed a series of novel photosensitising molecules and are currently progressing these through pharmaceutical approvals and phase I clinical trials.

This project will examine the use of two new compounds (INV043 and INV082) to treat ovarian and breast cancers, as a mechanism to improve response to checkpoint inhibition. The data will inform additional phase I human trials, and potentially also translation into veterinary medicine.

Keywords: photodynamic therapy, cancer, PDT, veterinary, chemoresistance, tumour



STAT Cancer Biology

Functional genomic screening to identify novel approaches to overcome drug resistance in Small Cell Lung Cancer

Suitability: PhD/Doctorate, Honours

Project leader: Dr Daniel Gough (co-supervisor Assoc/Prof Ron Firestein)

e: daniel.gough@hudson.org.au

Project description: Small cell lung cancer is an aggressive and highly metastatic disease that represents around 15% of all lung cancer patients. The majority of patients (70%) present in the clinic with advanced disease that has spread beyond the lung. The treatment options available to these patients are limited to platinum-based chemotherapy. This is effective in the majority of patients, however almost all will rapidly relapse with platinum resistant disease. There is no effective second line therapies which has meant these patients have an appalling overall survival rate of 2-5% which has not improved over the past three decades. Therefore, there is an urgent and unmet need to understand the mechanisms of platinum resistance and how to overcome it to provide meaningful improvements in patient outcomes. My laboratory has developed panels of platinum resistant small cell lung cancer cell lines and genetically engineered mouse models. In this project we will use CRISPR/Cas9 technology to perform unbiased pooled screening (whole genome or druggable targets) to identify mechanisms of resistance which will be interrogated *in vitro* and *in vivo*.

Keywords: Small Cell Lung Cancer, therapy, platinum resistance, functional genomics, screening, mouse models of cancer

How does STAT3 enter the mitochondria?

Suitability: PhD/Doctorate, Honours

Project leader: Dr Daniel Gough

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Project description: The JAK-STAT3 signaling pathway is engaged by many cytokines and growth factor stimuli to control diverse biological processes including proliferation, angiogenesis, survival, immune modulation, and metabolism. For over two decades it has been accepted that STAT3-dependent biology is due to its potency as a transcription factor capable of regulating the expression of many hundreds of genes. However, recent evidence of non-canonical and non-genomic activities of STAT3 has emerged. The most exciting of these activities is its capacity to translocate into the mitochondria where it regulates the activity of the electron transport chain and the opening of the mitochondrial permeability transition pore. These have broad consequences including cell survival and the production of reactive oxygen species and ATP in both normal tissue and under pathological conditions. Despite these fascinating observations there are many key unanswered questions about the mechanism of STAT mitochondrial activity - foremost of these is how does STAT3 get into the mitochondria.

Keywords: STAT3, mitochondria, biochemistry

Teaching an old dog new tricks: STAT3 in health and disease

Suitability: PhD/Doctorate, Honours

Project leader: Dr Daniel Gough

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Project description: Signal Transducer and Activator of Transcription 3 (STAT3) is required for diverse biological processes in mammals including cell proliferation, cell death, migration, differentiation, immunity and metabolism. The importance of the fundamental role of STAT3 in mammalian biology is illustrated by the fact that complete genetic loss of STAT3 is lethal in utero. Indeed, subtle gain or loss of function mutations in STAT3 lead to cancer and debilitating immune disorders respectively. These observations make STAT3 an ideal drug target, but to date this has not been possible. It is therefore critical to define the mechanism of STAT3 activity to enable specific targeting of this protein in disease contexts. The current text-book definition of JAK-STAT3 signalling is a vast over-simplification and cannot account for its diverse biological effects. In this project you will combine cutting edge biochemistry, functional genomics and animal models of disease to define critical and draggable targets.

Keywords: JAK-STAT signalling, biochemistry, cancer, mouse models of disease, functional genomics

Targeting purine and pyrimidine synthesis to treat Small Cell Lung Cancer

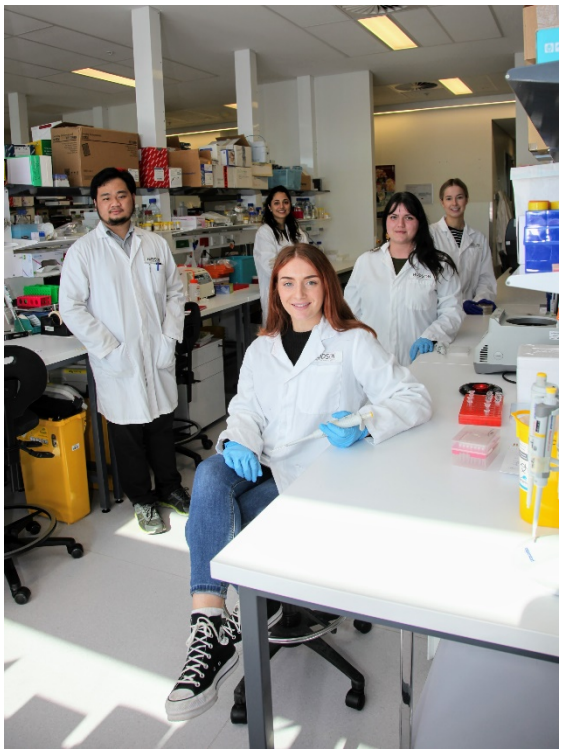
Suitability: PhD/Doctorate, Honours

Project leader: Dr Daniel Gough (co-supervisor Dr Jason Cain)

e: daniel.gough@hudson.org.au

Project description: Small cell lung cancer is an aggressive and highly metastatic disease that represents around 15% of all lung cancer patients. The majority of patients (70%) present in the clinic with advanced disease that has spread beyond the lung. The treatment options available to these patients are limited to platinum-based chemotherapy. This is effective in the majority of patients, however almost all will rapidly relapse with platinum resistant disease. There is no effective second line therapies which has meant these patients have an appalling overall survival rate of 2-5% which has not improved over the past three decades. We have developed mouse models of platinum-resistant small cell lung cancer and performed extensive RNA-sequencing and metabolomics analysis on the primary tumour tissue from these animals which has revealed a dramatic increase in purine and pyrimidine synthesis. Importantly we have shown that inhibitors of these pathways kill small cell lung cancer cell lines. This project will take advantage of our mouse models of small cell lung to investigate the efficacy of these agents in vitro and in vivo as well as their capacity to kill primary or metastatic tumours or both.

Keywords: Small Cell Lung Cancer, therapy, mouse models of cancer



Functional RNAomics

Discovering the role of miRNA processing in cancer

Suitability: PhD/Doctorate, Masters by Research, Honours, Short Projects

Project leader: Dr Minni Änkö (co-supervisor Dr Madara Ratnadiwakara)

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Project description: Previous studies suggest that overexpression of an RNA binding protein called SRSF3 is required for cancer cell growth and survival, however the underlying molecular mechanisms remain unclear. We have discovered a novel gene expression signature that in associated with SRSF3 expression both in normal highly proliferating cells such as embryonic stem cells and cancer cells. We have mechanistically shown that SRSR3 directly regulates the production of defined set of small noncoding RNAs, microRNAs, that are central for this so-called 'Oncomir-1 gene expression signature'. This project investigates how SRSF3 and potentially together other RNA binding proteins regulate the production of oncogenic miRNAs, wiht the focus on colorectal cancer.

Keywords: RNA binding protein, cancer, oncogene, gene expression, Australian Regenerative Medicine Institute

Structural Biology of Inflammation and Cancer

Structural Biology of Infection, Inflammation and Cancer

Suitability: PhD/Doctorate, Honours

Project leader: Dr Wilson Wong

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Project description: My laboratory utilises cryo-electron microscopy (cryo-EM) to investigate the structure and function of protein and protein-nucleic acid complexes important in Infection, inflammation and cancer. Cryo-EM enables visualisation of macro-molecular complexes to atomic resolution without the need for crystallisation and is revolutionising the field of structural biology. Students undertaking a PhD project will obtain expertise in protein chemistry, biochemistry and structural biology using single particle cryo-EM.

Genome maintenance in normal and cancer cells

The human genome is subjected to numerous genetic alterations throughout the lifespan of an individual as a consequence of exposure to environmental mutagens, such as UV-sun irradiation, cigarette smoke, as well as DNA damages induced by endogenous sources, eg, reactive oxygen species. These DNA damages are constantly monitored by genome surveillance mechanisms to ensure genome integrity is maintained. Malfunction of these surveillance and maintenance mechanisms predispose the genome to oncogenic changes, which ultimately led to the development of cancers. Furthermore, cancer cells have adapted specific genome maintenance mechanisms to ensure the appropriate genetic information are passed to the daughter cells during cell division, as well as the need to utilise DNA repair mechanisms in response to cancer chemotherapies. It is important to understand the molecular details on genome maintenance mechanisms to understand how normal cells maintain the heathy state, and how cancer cells develop.

Our research is focusing on protein-nucleic acid complexes that monitor and maintain the genome integrity of normal and cancer cells. Cells have sophisticated molecular machines that detect and repair these DNA alterations. We use cryo-electron microscopy (cryo-EM) and biochemical methods to characterise the mechanisms of these molecular machines to understand how genome integrity is maintained. The ultimate goal is to apply these knowledges to develop therapeutics that can offer new ways to treat disorders or cancers associated with genome instability.

Malaria parasite invasion

Our research also focuses on understanding the mechanisms by which malaria parasite invade human red blood cells. Malaria is an infectious disease of global significance causing close to 0.5 million deaths annually. We study the biology of blood stage infection because infection of red blood cells by malaria parasites is responsible for the clinical symptoms of malaria. Blood stage malaria antigens are important target for drug and vaccine development.

To invade red blood cells, the parasite utilises secretion machinery to display molecular "keys", called invasion ligands that recognise specific receptors on the surface of red blood cells. These parasite ligand-host receptor interactions mediate signalling events in an orderly sequential manner to enable the parasite to move into red blood cells in a short space of 60 seconds. We aim to characterise these molecular ligand-receptor interactions by cryo-EM, as well as how these parasite ligands could be blocked by invasion inhibitory antibodies. This information will be fundamental for designing a potential malaria vaccine to mount effective immune responses to protect against malaria infection.

Keywords: Cryo-EM, structural biology, biochemistry, genome maintenance, CryoEM, Cryo-electron microscopy

Contact our supervisors

Students are encouraged to contact supervisors to discuss projects, arrange a time to visit the lab and view our facilities. Simply email the supervisor to arrange a time.

STEP 1: Find a project that you are interested in.

STEP 2: Email the supervisor: *"I am interested in your student project. Could I please arrange a time to visit you in your lab?"*

All the information you need to enrol is on Hudson Institute's website, or the project supervisor can help you enrol.

w: hudson.org.au/students/courses-available/

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