



**HUDSON**  
INSTITUTE OF MEDICAL RESEARCH

# CENTRE FOR CANCER RESEARCH

2020 Student Research Projects

# Contents

<b>Centre for Cancer Research .....</b>	<b>4</b>
<b>Cancer .....</b>	<b>5</b>
Cancer Genetics and Functional Genomics .....	5
Developmental and Cancer Biology .....	6
Immunohaematology .....	7
Ovarian Cancer Biomarkers .....	9
STAT Cancer Biology .....	10
RNA Biology in Health and Disease .....	11
<b>Contact our Supervisors .....</b>	<b>12</b>



The Translational Research Facility is connected via a link bridge to Monash Health, and provides a crucial link between our scientific discoveries and medical treatments. The facility houses nine world-leading technology platforms and an eight-bed, 21-chair Clinical Trials Centre supporting 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 four areas of medical need

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

Our impact is on precision medicine, stem cell therapies, women's health, hormone disorders, fertility, infection, chronic disease and child development.

Our 475 scientists and students focus on laboratory discovery science, plus translational research – taking discoveries to patients and industry for real world impact.



## Students at a glance 2018



We educate and train nearly 180 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

- Get exposure to university, institute and hospital research
- Attend national and international conferences
- Publish their research (74 student first author publications in 2018)
- Are mentored by leading supervisors and their teams
- Regularly win prestigious prizes and awards
- Have continuous opportunities for networking, learning and development

## All work and no play ...

Hudson Institute is not all about work. Our students have the opportunity to join in a range of student networking and social events organised by the Hudson Institute Student Society (HISS).

## Our precinct

Hudson Institute is a partner in the Monash Health Translation Precinct (MHTP), a major medical and scientific research hub at Monash Medical Centre in Clayton.

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

With our precinct partners, Monash University and Monash Health, our site brings together world-leading scientists, clinicians and educators to collaborate on innovative discoveries that advance human health.

Our Translational Research Facility (TRF) is connected to Monash Health via a walkway and provides a crucial link between our scientific discoveries and medical treatments.

The facility houses laboratories alongside nine state of the art technology platforms and an eight-bed, 21-chair Clinical Trials Centre supporting the transition of discoveries from initial Phase I testing to Phase IV primary health trials.



# Centre for Cancer Research

**Location:** Centre for Cancer Research, Hudson Institute of Medical Research, Monash Medical Centre, Clayton

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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

## Research Group Heads and Project Supervisors



**Cancer Genetics and Functional Genomics**  
Research Group Head  
Assoc/Prof Ron Firestein



**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 Scientist  
Dr Jim Vadolas



**Ovarian Cancer Biomarkers**  
Research Group Head  
Dr Andrew Stephens



Research Scientist  
Dr Maree Bilandzic



**STAT Cancer Biology**  
Research Group Head  
Dr Daniel Gough



**RNA Biology in Health and Disease**  
Research Group Head  
Dr Minni Änkö



**Genetics and Molecular Pathology**  
Research Group Head  
A/Prof Elizabeth Algar

- Role of the microenvironment in tumour progression, chemoresistance and metastasis
- Cancer precision medicine, including childhood brain cancer and solid tumours

# Cancer

## Cancer Genetics and Functional Genomics

### 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 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

### 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 metastasis. 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

## Precision Medicine for Childhood Brain Cancer

**Suitability:** PhD/Doctorate, Masters by Research, Honours

**Project leader:** Assoc/Prof Ron Firestein

**e:** ron.firestein@hudson.org.au

**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. For more information see the Affiliations and Partners section below.

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

## Functional genomic screens to identify new therapeutic targets for bowel cancer

**Suitability:** PhD/Doctorate, Masters by Research, Honours

**Project leader:** Assoc/Prof Ron Firestein

**e:** ron.firestein@hudson.org.au

**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

## Understanding cancer resistance to chemotherapy

**Suitability:** PhD/Doctorate, Masters by Research, Honours

**Project leader:** Assoc/Prof Ron Firestein

**e:** ron.firestein@hudson.org.au

**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



## Developmental and Cancer Biology

### Defining the roles of epigenetic dysregulation in Diffuse Intrinsic Pontine Glioma (DIPG)

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr Jason Cain

**e:** jason.cain@hudson.org.au

**Project description:** Diffuse Intrinsic Pontine Glioma is a highly aggressive cancer that arises in the brainstem of children and is universally fatal. Using next-generation sequencing strategies, significant advancement has been made in understanding the genetic profile of these tumours. Mutations in either of two genes encoding the Histone H3 protein converge on a critical lysine residue resulting in substitution with a methionine residue (K27M) have been described in the vast majority of DIPG patients, suggesting a pathogenic role in this disease. The purpose of this project is to elucidate potential mechanisms of H3K27M tumorigenesis and identify likely therapeutic interventions that could be rapidly progressed into the clinic.

**Keywords:** DIPG, Histone H3, epigenetics, mouse models

### Improving Childhood Sarcoma Risk Stratification and Outcomes for Recurrent Disease

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr Jason Cain

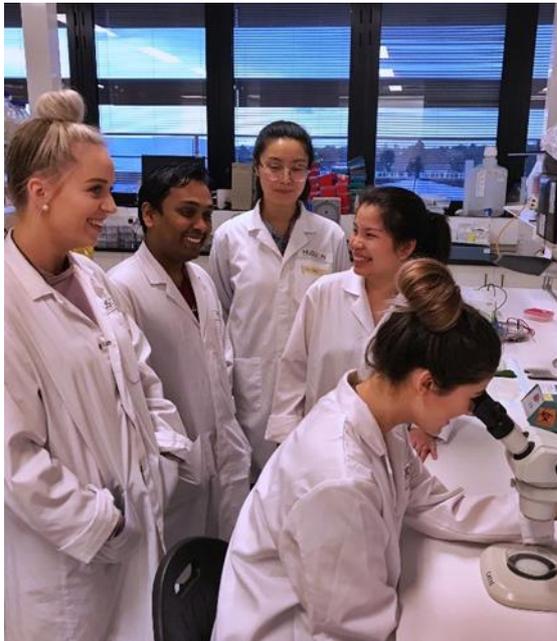
**e:** jason.cain@hudson.org.au

**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- $\kappa$ B 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 NF $\kappa$ B1 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<sup>+/-</sup>) to elucidate the impact of Nfkb1 haploinsufficiency. The Nfkb1<sup>+/-</sup> 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<sup>+</sup> 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 NF $\kappa$ B-Inducing Kinase (NIK) – a key kinase that regulates the function of NF $\kappa$ B2. NF $\kappa$ B2 is a related family member of NF $\kappa$ B1, 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.

#### Project Aims:

1. To examine the role of NF $\kappa$ B1 deregulation in developing B cells and how this relates to disease pathogenesis;
2. To assess the function of NF $\kappa$ B1 in CD4<sup>+</sup> T cells, and understand how the impaired function of NF $\kappa$ B1 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- $\kappa$ B

### Role of NF- $\kappa$ B in haematological malignancies

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr George Grigoriadis

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**Project description:** The alternate NF- $\kappa$ B pathway is increasingly being recognised as an important player in chemo-resistance in haematological malignancies like multiple myeloma, chronic lymphocytic leukaemia (CLL) and mantle cell lymphoma (MCL). The NF- $\kappa$ B inducing kinase (NIK) is the driver of this pathway that promotes cancer cell proliferation and survival. This project will use state of the art techniques including CRISPR and shRNA mediated knockdown, ChIP sequencing and mouse models to understand the mechanism of NIK-dependent growth of malignant cells.

**Keywords:** NF- $\kappa$ B

## Role of bone marrow inflammation in the progression of myelodysplastic syndrome

**Suitability:** PhD/Doctorate, Masters by Research, Honours

**Project leader:** Dr George Grigoriadis

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**Project description:** Myelodysplastic syndrome (MDS) is a group of diseases characterised by ineffective haematopoiesis, bone marrow dysplasia resulting in peripheral cytopenias in one or more myeloid lineages associated with transformation to AML. MDS patients have been purported to have a pro-inflammatory bone marrow environment that is believed to support the growth of the malignant clone and therefore plays a crucial enabling role in disease progression. We have found that inhibiting the NF- $\kappa$ B pathway dampens inflammation resulting in improved haematopoiesis in MDS patients. This project represents the interface of basic and translational research as findings from this study can be directly applied to clinical trials.

**Keywords:** myelodysplasia

## Predicting response to lenalidomide based induction: Real World Experience

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr George Grigoriadis

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**Project description:** This correlative study aims to translate our increasing understanding of the genetic networks underpinning MM into clinical practice. It will utilise both whole genome (WGS) and transcriptome (RNA-seq) sequencing as well as flow cytometry of normal immune subsets, to determine:

1. Can genomic mutations predict treatment response and risk of relapse after initial therapy for myeloma?
2. Which mutations predict response to lenalidomide based induction?
3. How does the presence of specific mutations correlate with subsequent gene expression?
4. Can specific transcriptional signatures predict for treatment response and guide clinical decision-making?
5. How does composition of immune milieu at diagnosis impact upon outcomes following lenalidomide?
6. Can an integrative (unbiased) bioinformatics approach be used combining genomic, transcriptomic, immunological and clinic data for more accurate risk stratification?

**Keywords:** myeloma

## Harnessing RNA interference in gene therapy vectors for $\beta$ -thalassaemia

**Suitability:** PhD/Doctorate, Masters by Research, Honours

**Project leader:** Dr Jim Vadolas

**e:** jim.vadolas@hudson.org.au

**Project description:** The  $\beta$ -haemoglobin disorders such as  $\beta$  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  $\beta$ -globin gene, leading to production of either aberrant or insufficient  $\beta$ -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  $\beta$ -globin gene. Much of the pathology of this disease is due to excess  $\alpha$ -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  $\alpha$ -globin expression can ameliorate the disease phenotype, exemplified by individuals who co-inherit  $\alpha$ - and  $\beta$ -thalassaemia. This definitive observation forms the basis of a novel therapeutic strategy for  $\beta$ -thalassaemia, involving not an elimination but a targeted reduction of complementary  $\alpha$ -globin chains, to mimic co-inheritance of  $\alpha$ - and  $\beta$  thalassaemia. While the benefits of increased  $\beta$ -globin expression in the context of  $\beta$ -thalassaemia are very clear, decreasing  $\alpha$ -globin expression has not yet been extensively investigated. This project aims to develop novel gene therapy strategies harnessing RNAi in gene therapy vectors for  $\beta$ -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  $\beta$ -thalassaemia mouse models and patient-derived cells.

**Keywords:** gene therapy, RNA interference, anaemia

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

**Suitability:** PhD/Doctorate, Masters by Research, Honours

**Project leader:** Dr Jim Vadolas

**e:** jim.vadolas@hudson.org.au

**Project description:** Haemoglobin disorders, such as sickle cell disease and  $\beta$ -thalassaemia are the result of mutations in the adult  $\beta$ -globin gene. When these disorders are co-inherited with hereditary persistence of fetal haemoglobin, (high levels of  $\gamma$ -globin gene expression in adult life) the disease phenotype is much reduced. Understanding the mechanism of  $\gamma$ -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  $\gamma$ -globin promoter. Further studies will also be conducted in vivo using unique humanised  $\beta$ -thalassaemia mouse models. Positive outcomes of such studies could pave the way for better treatment strategies for sickle cell anaemia and  $\beta$  thalassaemia patients by targeting epigenetic regulators to increase fetal globin expression.

**Keywords:** epigenetics, RNA interference, CRISPR/Cas9 genome editing

## Impact of impaired immune function in haemoglobin disorders

**Suitability:** PhD/Doctorate, Masters by Research, Honours

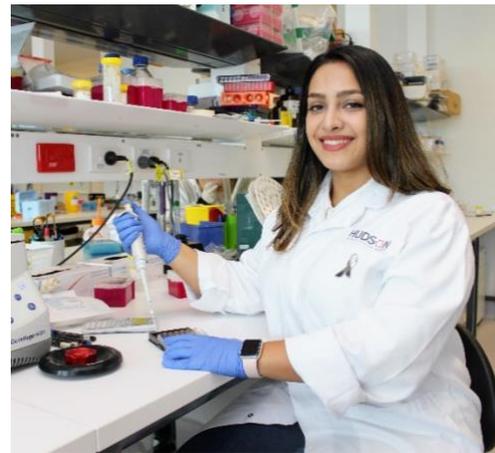
**Project leader:** Dr Jim Vadolas

**e:** jim.vadolas@hudson.org.au

**Project description:** Haemoglobin disorders, such as sickle cell disease and  $\beta$ -thalassaemia are the result of mutations in the adult  $\beta$ -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  $\beta$ -thalassaemia, we will undertake a comprehensive evaluation of the molecular and cellular mechanisms responsible for aberrant innate

immune effector functions in  $\beta$ -thalassaemic mice and  $\beta$ -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  $\beta$ -thalassaemia and related patients.

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



## Ovarian Cancer Biomarkers

### Preventing disease recurrence and increasing disease free survival rates for ovarian cancer patients

**Suitability:** Honours

**Project leader:** Dr Maree Bilandzic

**e:** maree.bilandzic@hudson.org.au

**Project description:** Majority of ovarian cancer patients are diagnosed with widespread disease on first clinical presentation. The initial response to chemotherapy and surgery is promising, however close to 90% develop recurrent, resistant disease at which point therapeutic options are limited. This project is focused on finding ways to prevent the spread of tumour cells following initial diagnosis and treatment, with the ultimate aim of increasing disease free lifespan and preventing disease recurrence in ovarian cancer patients. The project utilizes novel models of ovarian cancer metastasis to examine the early interactions between cancer cells and healthy tissue. You will investigate key changes that occur at the earliest point of ovarian cancer spread and devise ways to target molecules that drive the spread of ovarian cancer cells to stabilise disease, prevent tumour spread and recurrence.

**Keywords:** ovarian cancer, cancer, therapies, treatment, real time modelling, 3D culture

## Photosensitizer Development for Ovarian Cancer Therapy (collaboration with Invion Ltd)

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr Andrew Stephens

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

**Project description:** Photodynamic therapy (PDT) is a treatment involving administration of a photosensitizer compound that localizes in tumours, followed by its activation using specific light wavelengths. We have partnered with Invion Ltd, an ASX listed company, to develop their novel technology Photosoft™ for application in ovarian cancer. Photosoft is a new light-sensitive drug, structurally analogous to plant chlorins, which is non-toxic until activated by exposure to a specific light wavelength. Activated Photosoft causes immediate cancer cell rupture and death, and is equally efficacious in both chemosensitive and chemoresistant cells. Photosoft thus represents an important new weapon for selective cancer therapy, with immediate applications in the clinic. This project will contribute to the further development of Photosoft including tumour specific targeting, combination with immune therapies and its potential application to other tumour types; and will support the progression of Photosoft to clinical trials.

**Keywords:** photodynamic therapy, ovarian cancer, PDT, chlorin, chemoresistance

## Identifying New Drug Targets in Ovarian Cancer Stem-Like Cells

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr Andrew Stephens

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

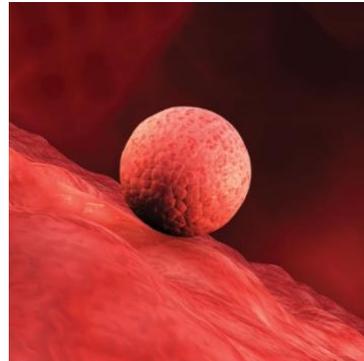
**Project description:** Ovarian cancers are the most lethal of all gynaecological malignancies, with <30% 5-year survival. Cancer progression requires cells to orchestrate a highly co-ordinated program of attachment, migration and invasion into healthy tissues. We have identified that a specialized 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



## STAT Cancer Biology

### Are purine or pyrimidine synthesis inhibitors effective therapies to treat Small Cell Lung Cancer?

**Suitability:** Honours

**Project leader:** Dr Daniel Gough

**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 vivo*.

**Keywords:** Small Cell Lung Cancer, therapy, Mouse models of cancer

## How does STAT3 enter the mitochondria?

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr Daniel Gough

**e:** daniel.gough@hudson.org.au

**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, Metabolism, Biochemistry

## Does fatty liver enhance lung cancer metastasis?

**Suitability:** PhD/Doctorate, Honours

**Project leader:** Dr Daniel Gough

**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. These patients have limited treatment options and an appalling overall survival rate of 2-5%. Through the use of sophisticated genetically engineered mouse models we have identified that increased liver fat content correlates with increased metastasis to this organ. This is despite equivalent numbers of circulating tumour cells suggesting that a fatty liver makes a more permissive environment for metastatic tumour cells to seed and expand. This project will take advantage of our suite of mouse models of small cell lung cancer to define the functional contribution of fatty liver to the metastatic spread of small cell lung cancer.

**Keywords:** Small Cell Lung Cancer, Metastasis, Mouse models of cancer

## RNA Biology in Health and Disease

### Discovering the role of miRNA processing in cancer

**Suitability:** PhD/Doctorate, Honours, Short Projects

**Project leader:** Dr Minni Änkö

**e:** minni.anko@hudson.org.au

**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 is associated with SRSF3 expression both in normal highly proliferating cells such as embryonic stem cells and cancer cells. We have mechanistically shown that SRSF3 directly regulates the production of defined set of small noncoding RNAs, microRNAs, that are central for this so-called 'Oncomir-1 gene expression signature'.

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

# 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 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 our website, or your supervisor can help you.

**w:** [hudson.org.au/students/courses-available/](https://hudson.org.au/students/courses-available/)



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