

# 2023-24

## STUDENT PROJECTS



**QIMR Berghofer**  
Medical Research Institute



# Director's Welcome

**By all measures, QIMR Berghofer is one of the leading medical research institutes in Australia. Our mission is to deliver ‘better health through impactful medical research’, and we do that by developing new diagnostics, better treatments and more effective strategies to prevent disease. Research at the Institute is channelled through four clinically relevant programs: Cancer Research, Infection and Inflammation, Mental Health and Neuroscience, and Population Health.**



The Institute is home to more than 600 scientists, staff and students who consistently generate formidable, high-quality research. Each year, our work gives rise to more than 700 publications, cited over 2,000 times in 2022, and more than \$32 million in commercial revenue.

As a student at QIMR Berghofer, you will be joining an elite cohort of exceptionally talented young scientists from around the globe. You will work alongside leading investigators in state-of-the-art laboratories. You will attend seminars showcasing the latest research findings, and you will be encouraged to ask questions and help find answers to some of the world's most pressing problems. While here, you will be well supported by a professional team who will help you to navigate your chosen academic path. In addition, you will receive mentoring advice and acquire the skills you need to pursue research to the highest levels of integrity and scholarship. At QIMR Berghofer we have a long tradition of running a very collegial and cohesive PhD student program. PhD students benefit from a yearly conference where they can showcase their work, experience excellent peer group support and activities, and a much enjoyed awards presentation. The student life at QIMR Berghofer is truly unique and fondly remembered by our alumni.

This booklet gives you an insight into the world that awaits at QIMR Berghofer. The projects presented with this booklet can often be adapted to suit your particular skills and strengths, so I encourage you to talk to the Faculty members about any projects that take your interest and find one that works for you. Lastly, I always advise prospective students to ‘shop around’. You are making a big decision, so you want to be sure that you are enthusiastic and inspired by the project you end up pursuing.

I hope you choose QIMR Berghofer as your next home and, if so, I look forward to welcoming you to this Institute for the next step in your academic career.

**Professor Fabienne Mackay, Director and CEO, QIMR Berghofer Medical Research Institute**



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# Quick facts about QIMR Berghofer

**QIMR Berghofer is a world leading translational research institute focused on cancer, infections and inflammation, mental health and neuroscience, and population health.**

**QIMR Berghofer Medical Research Institute was established in 1945.**

The Institute is home to more than 600 scientists (of which approximately 140 are students) in about 65 separate research groups.

**The QIMR Berghofer student body is very multinational and they are strongly supported by a Higher Degrees Committee dedicated to mentoring and guiding students through their candidature.**

The Institute's logo contains three superimposed hexagons representing benzene rings, which are the molecular structure of carbon and the basis of all life.



**QIMR Berghofer**  
Medical Research Institute



# QIMR Berghofer Student Society

## Welcome Future Medical Leaders!

The QIMR Berghofer Student Society is a dynamic organisation that serves as a support system, a social hub, and a source of lifelong memories for students at the QIMR Berghofer Medical Research Institute. It provides a network of support where students can connect with peers and mentors who share their research interests and offering academic resources and social support to help them excel in their research endeavours.

The QIMR Berghofer Student Society organises various social events such as lunch BBQs, trivia nights, bake sales, and the Postgraduate Student Conference in an effort to create opportunities for students to make friends, establish meaningful connections, and foster a sense of community within the Institute. Moreover, through engaging events and activities, the QIMR Berghofer Student Society encourages students to create lasting memories that they will cherish throughout their scientific journeys, adding a unique dimension to their overall research experience. We are so excited for you to join us!



## Why study at QIMR Berghofer?

Studying at QIMR Berghofer provides students with a unique opportunity to have access to diverse clinical and cutting-edge research. Our proximity to the Royal Brisbane and Women's Hospital (RBWH) and the [Herston Health Precinct](#) makes us ideal for clinical research collaborations.

In addition to your research training, QIMR Berghofer is committed to your overall professional development. This includes expanding your skills in critical scientific writing, statistics, leadership, communication and protecting your intellectual property. After studying at QIMR Berghofer, your broader skill base will allow you to compete for your desired future career.

### Advantages of studying at QIMR Berghofer include:

- Expert supervision from world leaders in their field of research.
- Access to and support from high-quality purpose-built facilities and technical experts.
- Access to advanced technologies and equipment.
- Exposure to a wide range of interdisciplinary research encompassing everything from population studies to statistics, public health, tropical medicine, immunology and cancer.
- Opportunities for international collaboration and travel.
- Competitive Honours and PhD top-up scholarships.
- Travel support for attending international conferences to promote collaborations and future postdoctoral positions.
- Student mentoring and professional development.
- Dynamic process of review to monitor student progress and ensure timely completion of your degree.
- A regular student seminar program.
- A weekly seminar series presented by QIMR Berghofer researchers, national and international speakers.
- An active student society, symposium and retreat for networking and training.

The QIMR Berghofer student body is a diverse group of Australian and international students involved in a wide range of research endeavours. We are working to make a real difference to health issues affecting Australians and the rest of the world.



# QIMR Berghofer Scientific Services

## ANIMAL FACILITY

The QIMR Berghofer Animal Facilities are secure Breeding and Experimental holding facilities which are primarily for the use of rodents. Each area incorporates state of the art modern facilities with quality animal caging, high containment and quarantine holding and up to date equipment and technologies. The qualified staff of the animal facilities provide high quality animal care. Our mandate is to provide QIMR Berghofer research groups with the best possible research and animal welfare outcomes.

## CELL LINE QC TESTING

The use of contaminated and misidentified cell lines in biomedical research has proliferated to a point where high impact journals require diagnostic evidence that cell lines are free from Mycoplasma contamination and authenticated as the correct cell line via Short Tandem Repeat DNA sequencing.

Did you know that that 15% to 35% of established cell lines are contaminated with Mycoplasma.

While good cell culture practice reduces the incidence of Mycoplasma contamination, it still occurs, and can spread easily. Mycoplasma contamination can seriously impact the reliability, reproducibility, and consistency of experimental results.

While good cell culture practice reduces the incidence of cross contamination, 29% of cell lines can be same species contaminated with the HeLa cell line.

The Nature Group of publications and an ever growing list of publishers now require evidence that your cell lines are validated as being mycoplasma free.

## CRYOGENICS

The cryogenics facility will manage the Liquid nitrogen resources at QIMR Berghofer with the intention of expanding the service to -80C Freezers in the future. The Cryogenics facility uses large capacity vapour phase Dewars connected to portable storage vessels. The benefits of this system are that less liquid nitrogen is required, Mycoplasma contamination is minimised and storage services can be provided at a cheaper rate than traditional, liquid phase Dewars.

A dedicated "Mycoplasma free" Dewar is provided for clients with Mycoplasma screened samples.

The facility will provide "FreezerPro" sample management software for the samples. All vapour Dewars are connected to the institutes BMS (Building management system) and any alarms from the equipment are reported to the on call engineer.

## DNA SEQUENCING

The QIMR Berghofer DNA Sequencing Facility enables both Next Generation and Sanger sequencing to deliver high-quality and reproducible data. This facility caters to the needs of scientists and postgraduate students from QIMR Berghofer as well as external and international institutions. It provides technical services and also trains and consults on matters relating to Sanger (Big Dye) sequencing and Next Generation Sequencing (NGS).

## FLOW CYTOMETRY AND MICROSCOPY

The Flow Cytometry and microscopy core facility provides world-class support for scientists at QIMR Berghofer. Thanks to the support of the Australian Cancer Research Fund (ACRF), the facility has expanded and is now the ACRF Centre for Comprehensive Biomedical Imaging. We endeavour to stay up-to-date with the ongoing acquisition of equipment, techniques, and analysis software to meet the needs of the facility customers. As the facility is held in high regard, our services are sought not only by QIMR Berghofer scientists but those in the broader south-east Queensland region, Australia, and overseas.

## GLASSWARE AND WASTE MANAGEMENT

Glassware services provides cleaned and/or sterilised glassware and cleaned plastic ware's required for most tissue culture and wet laboratory work carried out within QIMR Berghofer. All used and laboratory decontaminated plastic ware, glassware including GL45 glass bottles are cleaned either manually or by automated dishwashers.

Glassware and GL45 bottles are sterilised by steam sterilisation or by high temperature dry ovens. Quality can be assured by the use of temperature an/or biological indicators for each sterility process. All stock is extensively quality controlled for cleanliness and sterility.

Waste management services decontaminates GMO and infectious waste material by steam sterilisation and eventually incineration. Steam sterilisation is routinely monitored by SCBI's and temperature indicators as required by OGTR and Biosecurity Australia.

## HISTOLOGY FACILITY

The Histology Facility caters to the needs of scientists and students within QIMR Berghofer and external institutions.

The unit provides a broad range of technical services including; paraffin wax and frozen tissue sectioning, routine and special stains, immunohistochemical and immunofluorescence labelling, chromagenic and fluorescence in situ hybridisation as well as consultation on matters relating to histology, antibody optimisation and histopathology.

## SAMPLE PROCESSING

The Sample Processing Facility provides support to facilitate high throughput medical and epidemiological research. Specimens are efficiently processed to produce the highest-quality product possible for downstream experiments and/or analysis.

The team can help you with any aspect of your sample collection and preparation:

- Assistance with project planning
- Sample collection
- Transportation of samples
- Reception, Accessioning and Sample Tracking
- Automated Liquid Handling
- Blood fractioning
- PBMCs preparation
- Nucleic Acid isolation from tissues including blood, saliva, cell-free samples (e.g. plasma), fresh-frozen tissues, Formalin-fixed tissue, urine, faeces, swabs.
- Sample QC testing – including Spectrophotometric, Fluorescence, Agarose gel
- Normalisation and plating of samples
- Packaging, Logistics and Transportation for off-site analyses
- qPCR, PCR set-up
- Biobanking and storage solutions for samples

## VETERINARY SERVICES/ANIMAL WELFARE

The Veterinary Officer contributes to ensuring that the welfare of animals used in research at QIMR Berghofer is safeguarded.

The Veterinary Officer's role at QIMR Berghofer is to:

- Provide advice to animal facility staff, researchers and students on animal welfare
- Provide veterinary advice on a wide range of issues which have direct and critical impact on regulatory affairs and ethics management related to institutional animal activities.
- Provide veterinary services and oversee a program of veterinary care.
- Provide training to staff and students regarding: animal laboratory techniques and animal welfare.
- Act as a direct contact for the communication of any animal welfare concerns from staff and students.

# QIMR Berghofer Facilities

## GENOMIQA

GenomiQa specialises in somatic and germline analysis of whole genome, whole exome, and RNA sequencing. GenomiQa's bioinformatics analysis software and processes were developed and refined with quality as a guiding principle. Our founders based the services we provide on robust research published in top-tier, peer-reviewed scientific journals, such as Nature. GenomiQa's analysis pipelines are flexible, custom-made, and customisable. Big data analytical services, from genomic sample preparation to clinical interpretative reports, can be provided to pharmaceutical and biotechnology companies, researchers, clinical research organisations, and pathology service providers.

## METABOLOMICS

The Metabolomics Core Facility supports QIMRB scientist in their research by providing mass spectrometry-based metabolomics and bioinformatics capabilities.

We offer untargeted and targeted metabolomics, including lipidomics, services from experimental design to conducting the metabolomics analyses. Specific training can be provided following discussion.

The facility is equipped with a high resolution 6545 QTOF mass spectrometer for untargeted global profiling experiments and a 6470 triple quadrupole mass spectrometer for targeted metabolomics. Both Agilent mass spectrometer are coupled to Agilent 1290 Infinity II UHPLC systems via electrospray interface. Sample preparation methods have been established for monophasic (butanol/methanol) and biphasic (methanol/methyl tert-butyl ether) extraction of matrices like plasma/serum, faeces, and cell culture. Monophasic extraction can also be performed in plate format on a liquid handler.

## QIMR BERGHOFER STATISTICS UNIT

The QIMR Berghofer Statistics Unit is comprised of 10 statisticians, who provide statistical consultancy and research collaboration services to medical and clinical researchers. Services range from laboratory research to clinical trials, epidemiology, and biomarker development. We can help you with:

- The formulation of research questions
- Study design

- Analysis plans
- Power and sample size calculations
- Writing of research grants and protocols
- Data management plans
- Analysis using statistical methods appropriate for medical and health research
- Presentation and interpretation of data and analysis
- Preparation of and co-authorship on publications; addressing reviewers' comments
- Expertise in design and analysis of clinical trials; public health and epidemiology
- Laboratory methods development and validation
- Animal studies
- PK/PD modelling

## Q-GEN CELL THERAPEUTICS

Q-Gen Cell Therapeutics is a fully integrated facility for translational research within QIMR Berghofer providing GMP standard manufacturing facilities for translating clinical research to the bedside. These facilities are also available for external researchers and organisations requiring clean room facilities for GMP manufacture.

The Q-Gen Cell Therapeutics facility has 2600m<sup>2</sup> of dedicated floor space within the Clive Berghofer Cancer Research Centre. It comprises a QC testing laboratory, office space, inventory storage rooms and up to 13 clean rooms, available to meet ISO Class 7 and PC2 standard, with dedicated air handling units for the majority of rooms. All rooms within the Q-Gen Cell Therapeutics facility are access controlled.

Q-Gen Cell Therapeutics is licensed by the TGA (Licence # MI-11112004-LI-000153-1) and provides a range of services in addition to clean room lease, outlined in the adjoining services tab. Along with cleanroom lease, Q-Gen Cell Therapeutics can also provide a range of cell processing and research equipment, maintained and validated for GMP use. All critical equipment is continuously connected to an independent back-up power generator, which includes 24 hour monitoring and recording of the equipment parameters through our building management system.



All services offered by Q-Gen Cell Therapeutics to QIMR Berghofer research projects attract a 50% subsidy off cost. This enables you to minimise your budgets for processing, while still receiving world class translational facilities and support. Q-Gen Cell Therapeutics is a fully integrated facility for translational research within QIMR Berghofer providing GMP standard manufacturing facilities for translating clinical research to the bedside. These facilities are also available for external researchers and organisations requiring clean room facilities for GMP manufacture.

### PC3 FACILITY

The PC3/BC3/BIC3 Facility is the highest containment facility at QIMR Berghofer. It has viral, bacterial, small animal and insect research capability at physical and biosecurity containment level 3 standards as defined by Office of Gene Technology Regulator and Department of Agriculture and Water Resources.

### PROTEOMICS

Proteomics at QIMR Berghofer can be accessed as core service (mass spectrometry access or standard proteomics sample analysis) or collaboration with one of the academic leads.

The Proteomics Facility supports QIMR Berghofer scientists in their research by providing a comprehensive mass spectrometry based proteomics and bioinformatics capability. Services include:

- In-depth proteome profiling of complex protein mixtures
- Differential protein expression analyses
- Data analysis

The Proteomics Facility can also provide technical advice and can help researchers design their proteomics experiments. Please contact the facility team for direct sample submission.

# Medical Research Opportunities

Join one of the largest medical research institutes in Australia. The options for students to be part of QIMR Berghofer are:



## Research Higher Degree Student at QIMR Berghofer Medical Research Institute (PhD, MPhil, Masters Coursework or Honours)

We have a wide range of student projects, and many can be tailored to a student's research interests. Some projects have the flexibility required for clinical students.



## Vacation Research Program

Through The University of Queensland, QUT, and Griffith University, we offer vacation research experience. These are small projects carried out over a 6-10 week period during the university summer (November-February) vacation breaks giving students research experience and some financial support.



## Volunteer Program

Students who have an interest in medical research and would like to gain some research experience can apply to be a research volunteer. This is not associated with any university course. These unpaid placements run for a limited period of time and acceptance is at the discretion of QIMR Berghofer.



# Quick Admissions Guide for Students

- 1** Check you are eligible for the degree you are interested in undertaking. This is specific to the university you are enrolling through.
- 2** Check the QIMR Berghofer website and identify a student project or Research Group that matches your research interests.
- 3** Contact the QIMR Berghofer scientist via email providing the following information:
  - i) Whether you want to undertake Honours, MPhil, or PhD study.
  - ii) Discuss your research interests and any previous research experience.
  - iii) Provide your academic CV and university transcript.
- 4** Arrange to meet in person or have a Skype/Zoom interview. If a supervisor accepts you as a student, then continue the rest of the steps below.
- 5** Enrol through an Australian university.\*
- 6** Complete the admission process to QIMR Berghofer. An approval notification will be sent to you via email.
- 7** International students must also have an appropriate visa from the Department of Immigration and Citizenship. #
- 8** Provide evidence of full admission/enrolment to an Australian university and scholarship (if you are joining the PhD program).

**Congratulations, you are ready to begin your candidature.**

**PLEASE NOTE:** This is only a **BRIEF GUIDE** and it is your responsibility to familiarise yourself with the details or requirements for each step.

**\*IMPORTANT:** Apply for admission to QIMR Berghofer and your chosen university at the same time. Many university departments will not approve your application until you have at least provisional approval from QIMR Berghofer.

**#** This process may take up to 12 weeks to finalise, and this should be taken into consideration when determining your start date.

**General info:** [www.qimrberghofer.edu.au](http://www.qimrberghofer.edu.au)

**University Students Webpage:** [www.qimrberghofer.edu.au/education/for-university-students/](http://www.qimrberghofer.edu.au/education/for-university-students/)

**Projects Webpage:** <https://www.qimrberghofer.edu.au/education/student-projects/>

**For further enquiries, please contact:** [GraduateEducation@qimrberghofer.edu.au](mailto:GraduateEducation@qimrberghofer.edu.au)

## Cancer Program

**At QIMR Berghofer, our leading cancer researchers are developing new techniques that will help us to understand, prevent, detect and treat cancer, which is a leading cause of death in Australia.**

Our researchers are working on a number of projects which include:

**Prevention:** identifying specific modifiable environmental and genetic factors that reduce a person's risk of developing cancer.

**Detection:** developing better screening tests, so that cancer can be detected earlier.

**Treat:** identifying better treatments for cancer and conduct clinical trials to test for effectiveness.

Cancer cases are expected to grow to 185,000 over the next decade as Australia's population ages. It is the second most common cause of death, exceeded only by cardiovascular disease.

Although overall cancer survival rates have improved in the past 20 years, several types of cancer have poor five-year survival rates. These include ovarian, brain, oesophageal, lung, pancreas and colorectal cancer.

The research at QIMR Berghofer is aimed at developing a better understanding of who is at risk of particular types of cancer and how treatment options can be tailored and more effective.

Our researchers continue to pioneer novel strategies and treatments across a broad range of cancers to help save lives and improve the quality of treatment.



## Laboratory of B-lymphocytes in Autoimmunity and Malignancies



**Group Leader,  
Director and CEO:  
Professor Fabienne Mackay**

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[www.qimrberghofer.edu.au/  
our-research/cancer-research/  
b-lymphocytes-in-autoimmunity-  
and-malignancies/](http://www.qimrberghofer.edu.au/our-research/cancer-research/b-lymphocytes-in-autoimmunity-and-malignancies/)

The **Laboratory of B-lymphocytes in Autoimmunity and Malignancies** studies the immunobiology of B-lymphocytes, particularly the B cell survival factors BAFF and APRIL and their receptors BAFF-R, TACI, and BCMA. Professor Mackay has shown that excess BAFF leads to autoimmunity in mice and is associated with human autoimmunity, in particular systemic lupus erythematosus (SLE). This has encouraged the development of Belimumab, a therapeutic BAFF-blocking antibody that has been approved for use in SLE in the clinic. The laboratory's effort has been extended to understand how dietary interventions lower the risk of developing SLE and how diet/dietary metabolites can be used as therapeutic modalities.

Another research area of the lab is Chronic Lymphocytic Leukaemia (CLL), a blood cancer caused by the clonal expansion of mature B cells. Patients with CLL show severe systemic immunodeficiency that results in death in a quarter of CLL patients despite therapeutic intervention. Our lab has shown that CLL cells rely on BAFF/APRIL to suppress the immune system through IL-10 production. We aim to identify novel therapeutic targets that will be able to restore patient immune function in CLL and halt CLL progression. Hence, the lab is developing a therapeutic antibody against CLL, which would not compromise the host's protective immunity. In an attempt to identify a novel therapeutic target for CLL, we have identified that a fat-rich diet halts CLL progression. We are now investigating the cellular and molecular mechanism underlying this protection against CLL.

### Investigating the therapeutic effect of a ketogenic diet in a xenogeneic (PDX) mouse model of chronic lymphocytic leukaemia



**Co-Supervisor:  
Dr M Arifur Rahman**

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This project is suitable for a PhD student or Honours followed by a PhD.

#### BACKGROUND

Chronic lymphocytic leukaemia (CLL) is a blood and bone marrow cancer that slowly worsens over time. CLL is one of the most common types of leukemia in adults and typically occurs during or after middle age. Most patients have a form of CLL that develops slowly and remain stable for many years without treatment, while others develop aggressive disease hallmarks.

CLL patients have too many abnormal B lymphocytes, along with poor responses to infections and low anti-tumour immunity. Infections are a major cause of death in CLL patients; current treatments used to reduce the number of tumour cells further compromise patient immune systems, and resistance/intolerance to treatment adds to the disease burden. Restoring immune system functions in CLL patients is currently an unmet need and developing new drugs and treatments is critical.

Using a mouse model of CLL, we have recently discovered that mice fed a ketogenic diet are protected against developing disease. However, the clinical relevance of this dietary intervention has not been tested. The protective molecular mechanisms that are triggered by the keto diet are also unknown. However, it is likely that the protection provided by the diet against CLL is associated with a set of metabolites with a potentially anti-leukaemic effect, creating hypotheses for exploration.

This project will create a patient-derived xenogeneic (PDX) model of CLL, using blood cells from CLL patients injected into mice without T, B or NK cells, which allows for the engraftment of human cells. The mice will then be fed a range of diets, and CLL progression will be monitored using flow cytometry and other biochemical assays.

#### AIMS

- Evaluate the therapeutic effect of diet in a patient-derived xenogeneic (PDX) model of CLL.

- Identify the metabolites associated with the ketogenic diet-mediated protection against CLL in the PDX model.
- Test the anti-leukaemic function of the metabolites in-vitro.
- Understand the molecular function of these metabolites (such as receptors, target cells, and signaling)
- Evaluate the anti-leukaemic metabolites in mouse and PDX models of CLL.
- The identification of anti-leukaemic metabolite/s will facilitate development of a new class of drugs, with a novel mechanism of action and minimal side effects. Through these studies, the student will gain significant expertise in mouse models of disease, cell culture, flow cytometry, immunohistochemistry, and metabolomics. This project has a high potential for translation and interaction with industry.

#### PROJECT POTENTIAL

The development of first in class metabolite-based therapies for CLL, a much-needed source of treatments for patients with CLL developing resistance to existing and recently introduced new treatments for CLL.

### Discovering novel immunoregulatory molecules underlying the pathogenesis of systemic lupus erythematosus

This project is suitable for an Honours, Masters or PhD student.

#### BACKGROUND

Many important metabolites that signal via purinergic receptors (molecules in the plasma membrane) are obtained from food or synthesized by the body. BAFF is a B cell survival factor, and the overexpression of BAFF in BAFF-transgenic (BAFF-Tg) mice causes the expansion of autoreactive pathogenic B cells leading to systemic lupus erythematosus (SLE). Research has shown that BAFF-Tg mice are deficient in a range of these metabolites.

We have demonstrated that BAFF-Tg mice fed a high-fibre diet express a high level of a particular metabolite, which is associated with a reduction in autoreactive B cell numbers and protection from SLE. Supplementation also protects the BAFF-Tg mice against SLE. However, the cellular and molecular mechanism by which the metabolite protects against SLE is not known. We have generated mice deficient in the purinergic receptor (PR) associated with the metabolite for use in this project.

#### AIMS

- Investigate the requirement of a purinergic receptor in the high-fibre diet-mediated protection against SLE.
- Investigate if metabolite- purinergic receptor signalling is critical for the protection against SLE.
- Characterise a novel metabolite therapy for SLE.

#### PROJECT POTENTIAL

To develop an entirely new treatment avenue for lupus and explore a novel set of metabolites and signaling pathways with significant clinical potential.

### Investigating the role of purinergic receptor signalling in the onset and progression of systemic lupus erythematosus

This project is suitable for an Honours, Masters or PhD student

#### BACKGROUND

Many important metabolites that signal via purinergic receptors (molecules in the plasma membrane) are obtained from food or synthesized by the body. BAFF is a B cell survival factor, and the overexpression of BAFF in BAFF-transgenic (BAFF-Tg) mice causes the expansion of autoreactive pathogenic B cells leading to systemic lupus erythematosus (SLE). Research has shown that BAFF-Tg mice are deficient in a range of these metabolites.

We have demonstrated that BAFF-Tg mice fed a high-fibre diet express a high level of a particular metabolite, which is associated with a reduction in autoreactive B cell numbers and protection from SLE. Supplementation also protects the BAFF-Tg mice against SLE. However, the cellular and molecular mechanism by which the metabolite protects against SLE is not known. We have generated mice deficient in the purinergic receptor (PR) associated with the metabolite for use in this project.

#### AIMS

- Investigate the requirement of a purinergic receptor in the high-fibre diet-mediated protection against SLE.
- Investigate if metabolite- purinergic receptor signalling is critical for the protection against SLE.
- Characterise a novel metabolite therapy for SLE.

This project will use a range of immunological techniques (mouse models of experimental SLE, flow cytometry, confocal microscopy, ELISA), metagenomic sequencing, microbiome analysis and metabolomics to characterise

the immunological mechanisms of action. We will validate the research findings using clinical samples.

#### PROJECT POTENTIAL

To develop an entirely new treatment avenue for lupus and explore a novel set of metabolites and signaling pathways with significant clinical potential.

### Investigating the role of the chemokine receptor ACKR3 in immune signalling and disease

This project is suitable for an Honours, Masters or PhD student

#### BACKGROUND

Chemokines are a class of signalling molecules that are important for maintaining homeostasis and the inflammatory responses of cells. Chemokine receptors respond to these molecules by signalling to cells to proliferate or move. In addition to these classical chemokine receptors, there are also atypical chemokine receptors which are poorly understood.

The atypical chemokine receptor ACKR3 (also named CXCR7) has been implicated in cancer survival and metastasis and is also protective against fibrosis. ACKR3 can bind to the chemokines CXCL11 and CXCL12, as well as other non-chemokine signalling molecules. ACKR3 has been proposed as a key receptor to target developing therapeutics for cancer and fibrosis, however there is a significant gap in the current knowledge about the role of this receptor in normal physiology and immune signalling.

Our research group has begun characterising the role of ACKR3 and the cell populations that express it. This project will further explore how ACKR3 regulates immune cell function at steady-state, following immunization, and in diseases like lupus and cancer.

#### AIMS

- Determining the cell types that express ACKR3 and investigate the role that ACKR3 plays.
- Analyse mice that lack ACKR3 on specific cell types of interest.
- Define the role of ACKR3 in immunity, such as the T cell-dependant and T cell-independent immune responses.
- Investigate the role of ACKR3 on self-reactive B cells.

Through these studies, the student will gain significant expertise in mouse models of disease, cell culture, flow cytometry, immunohistochemistry and other laboratory techniques.

#### PROJECT POTENTIAL

To pioneer knowledge in a neglected area of immunology, validate these findings with human immune cells and publish a high impact, world-first discovery. This project has the potential to uncover aspects of autoimmunity never contemplated before.

### Analysis of the role of BAFF-R in T cell responses

This project is suitable for an Honours or Masters student

#### BACKGROUND

The Mackay lab investigates the immunobiology of B-lymphocytes, particularly the B cell survival factors BAFF and APRIL, and their receptors BAFF-R, TACI and BCMA. The role of BAFF-R signalling in the maintenance of B cells is very well studied. However, even though it has been established that BAFF-R is expressed on T cells (regulatory T cells in particular), little is known about what role this receptor plays in T cell immunology.

BAFF co-stimulation promotes T cell activation with cytokine production via BAFF-R both in-vitro and in-vivo. To understand the function of BAFF-R expression on CD4 T cells, we have generated a mouse line in which BAFF-R is specifically deleted in CD4 T cells. This project will investigate whether BAFF-R expression on CD4 T cells is critical for an antibody response in a T-cell dependent immunisation model.

Given that there are therapeutics available that inhibit BAFF-to-BAFF-R signalling, this is an important avenue of investigation. The results obtained in this project will be applied to develop novel therapeutics for the treatment of B cell dependent autoimmune diseases.

#### AIMS

- Explore the different T cell subsets where BAFF-R is expressed.
- Explore the role of BAFF-R in thymic T cell development
- Explore the role of BAFF-R in T cell activation.
- Investigate the role of BAFF-R expression in the immune response.

Through these studies, the student will gain significant expertise in mouse models of disease, cell culture, flow

cytometry, immunohistochemistry and other laboratory techniques.

#### PROJECT POTENTIAL

To pioneer knowledge in a neglected area of immunology, validate these findings with human immune cells and publish a high impact, world-first discovery.

### Can diet influence immune tolerance?

This project is suitable for an Honours or Masters student

#### BACKGROUND

The Mackay lab has a model of B cell immune tolerance, known as SWHEL. The SWHEL model is a cross between mice with B cells that express a B cell receptor (BCR) specific for the experimental antigen Hen Egg Lysozyme (HEL), and mice that express membrane HEL. In the resulting offspring, the HEL becomes the self-antigen and developing SWHEL B cells in the bone marrow are self-reactive B cells. The resulting SWHEL B cells are eliminated in the bone marrow through a process of negative selection in response to their BCR binding HEL.

These SWHEL mice can be crossed with mice expressing a soluble version of HEL, secreted in the blood. In the resulting offspring the self-antigen is circulating and binding of the SWHEL BCR to soluble HEL is not as strong. With a weaker SWHEL BCR interaction to soluble HEL, SWHEL self-reactive B cells can survive in the bone marrow but are negatively selected in the periphery or are anergised (neutralised and unable to be activated by HEL).

This project will explore the following hypothesis: can diet (eg. high fat) prevent negative selection and therefore promote autoimmunity? To explore this, the above two models of B cell tolerance described will be fed with various diets and the impact of diet on the emergence of self-reactive B cells and their activation status will be investigated.

#### AIMS

- Determine whether diet can affect the emergence of self-reactive B cells.
- Explore whether diet can interfere with negative selection and promote autoimmunity.
- Dissect molecular mechanisms of immune tolerance affected by dietary intervention for the purpose of developing novel therapies promoting immune tolerance.

The work involves animal models, flow cytometry, ELISA, histology and a number of omics methods.

#### PROJECT POTENTIAL

No research group to date has explored the role of diet in this model. This approach is very novel, and as a recent review in Science suggests could lead to alternative therapeutic approaches for autoimmune diseases with huge clinical impact

## Functional Cancer Genomics & Functional Genetics Groups



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The **Functional Cancer Genomics Laboratory** focuses on understanding how DNA variation contributes to cancer risk and development. The laboratory is particularly interested in translating the findings from genome-wide association studies (GWAS) for breast, ovarian, endometrial, prostate and skin (melanoma) cancers. This includes identification of the causal risk variants, connecting these variants to their target genes and understanding how the new genes contribute to cellular phenotypes associated with cancer development. We have already identified several molecular pathways that were not known to play a role in cancer that are suitable targets for drug repositioning or drug development. The ultimate aim of our research is to pave the way for future clinical trials for cancer prevention or treatment.





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**The Functional Genetics Laboratory** investigates how genetic variants in noncoding regions of the genome contribute to cancer risk and progression. Until recently, the genetic basis of cancer has only been examined in coding regions, which accounts for less than 2% of the human genome. However, it is now apparent that noncoding regions are littered with functional elements such as transcriptional enhancers and long non-coding RNAs. The laboratory focuses on how inherited variants identified through genome-wide association studies (GWAS) and cancer-specific mutations identified through whole gene sequencing (WGS) can alter these non-coding elements to promote the development of cancer. The ultimate aim is to use genetics to pinpoint the key genes and pathways implicated in the development of cancer to identify new therapeutic opportunities.

**Identifying new long-noncoding RNAs involved in breast cancer development**

Can be adapted in scope for Honours or PhD student

It is now clear that the majority of the human genome is transcribed from both DNA strands but only 2% encodes protein. Much of this transcription is derived from DNA sequences that do not encode functional proteins. The majority of these transcripts are long non-coding RNAs (lncRNAs) defined as being >200 bp in length. While it is generally accepted lncRNA transcription is functionally significant, the scope and function of lncRNAs in cancer are still not well understood. In the last five years, genome-wide association studies (GWAS) have identified 170 common variants (or SNPs) associated with an increased risk of breast cancer. Importantly, the majority of these disease-associated SNPs lie within intergenic regions and within introns of protein-coding genes, suggesting that undiscovered RNA transcripts such as lncRNAs, may be responsible for the risk in a subset of breast cancers. We have recently used a targeted RNA

sequencing approach called RNA CaptureSeq to identify lncRNAs transcribed from breast cancer risk loci. This key experiment has identified hundreds of candidate breast cancer-associated lncRNAs.

In this project, we will use multiple in vitro approaches to identify lncRNAs whose expression is altered by breast cancer risk SNPs. These include eQTL analyses, chromosome conformation capture (3C)-based techniques and reporter assays. We will also generate isogenic cell lines using CRISPR/Cas9 technology, which will be used to measure lncRNA expression and identify allele-specific chromatin interactions. We expect that some of the lncRNAs will have cancer-related biological functions. We will therefore overexpress or silence lncRNAs in breast cells and examine their effects on cell proliferation, response to DNA damage, apoptosis, migration, invasion and tumour formation. We will also assess the function of lncRNAs in breast tumour formation using explant assays in mice. The discovery of novel regulatory RNAs influencing breast cancer development may reveal entirely new avenues for breast cancer therapeutics.

Students will have access to unique expertise and reagents and will acquire skills in tissue culture, CRISPR/Cas9, RNA manipulation, and other basic molecular biology techniques.

**Evaluation of new long-noncoding RNAs contributing to drug resistance in ovarian cancer**

Can be adapted in scope for Honours or PhD students

Epithelial ovarian cancer (EOC) accounts for >90% of ovarian malignancies, but high-grade serous (HGSOC) is the most common (~70%) and lethal subtype. Nearly half of all HGSOCs show defective DNA repair by homologous recombination (HR), which is a pivotal vulnerability that can be therapeutically exploited. Platinum-based chemotherapy and PARP inhibitor (PARPi) therapy are currently the most effective therapeutic options for HR-deficient HGSOCs. However, while initial response rates to both therapies are high, most patients relapse due to the emergence of chemoresistant disease, typically through the restoration of HR repair. Most studies focus on targeting protein-coding genes to increase therapeutic sensitivity, with limited clinical success. However, long noncoding RNAs (lncRNAs) also play important roles in the DNA damage response.

In this project, we will discover, annotate and prioritise new lncRNAs involved in DNA repair in HGSOC. We will then perform high-throughput CRISPR-based screens to identify specific lncRNAs that enhance PARPi sensitivity. We will also perform multiple functional assays on the lncRNAs that showed the strongest effect in the CRISPR-based screens. These include generating isogenic cell lines using CRISPR technology, which will be used to measure lncRNA expression, perform clonogenic survival assays and measure DNA repair efficiency or kinetics. Finally, we will assess the potential of antisense oligonucleotides (ASOs) to inhibit the expression or function of the lncRNAs in HGSOC cell lines and using established PDX models in mice. We predict that ASOs in combination with PARPi, will make initial treatment of patients more effective and reduce HGSOC recurrence.

Students will have access to unique expertise and reagents, and will acquire skills in tissue culture, CRISPR methods, RNA manipulation, and other basic molecular biology techniques.

## Signal Transduction Group



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The **Signal Transduction Laboratory** researches DNA damage signalling and repair pathways and their impact on cancer susceptibility through preventing DNA mutations. These studies have significant relevance to both basic biology (e.g. understanding the process of cell division, repair of DNA damage and mechanisms of ageing) and clinical medicine (e.g. effect on drug efficacy).

Several genes involved in the DNA damage response pathways are known to contribute to breast cancers. This group seeks to identify other known or new genes in these pathways, which might have similar involvement in cancer susceptibility by preventing mutations in our DNA. This area is of critical importance to cancer research as the pathway controlling the DNA damage response is involved in tumour suppression, and is believed to be mutated at the early stage in the evolution of cancer.

**Repurposing an FDA-approved drug to treat mut-p53 cancers**

Suitable for Honours or PhD students

TP53 is the most frequently mutated gene, with over half of all human tumours harbouring mutation of this gene. Unlike the majority of tumour suppressor genes that are inactivated as a result of truncating mutations, the majority of TP53 mutations are missense, resulting in accumulation of mutant protein and gain-of-function activity. The mutational status of p53 predicts poor outcomes, resistance to chemotherapies, and shorter overall survival in multiple types of cancer, including breast cancer (BC)), which is the focus of this project.

Over several decades considerable effort has been applied to develop drugs to target mutant p53 (mut-p53), with none in routine clinical use. In this proposal, we aim to repurpose an FDA approved drug to target mut-p53 tumours. We propose to develop clinically relevant combinatorial approaches that will yield novel therapeutic strategies to treat cancers with p53 mutations. We have compelling data that an FDA-approved drug (designated as molecule-1) used for another disease indication can be repurposed for therapeutic targeting of mut-p53 cancers. Our data convincingly demonstrates that treatment of mut-p53 expressing cells with molecule-1 can reactivate the wild-type transcriptional activity of mut-p53.

In this project, we will optimise the anti-tumour effect of this molecule in our clinically relevant mut-p53 patient derived xenograft (PDX) models in combination with conventional chemotherapies. Additionally, we will identify other FDA-approved compounds that synergise with this molecule to further improve its efficacy in mut-p53 cancers. We will also establish the mechanism of mut-p53 reactivation by this molecule through p53 structural analysis, providing valuable insights into the actions of this drug on mut-p53, thus identifying further potential opportunities for therapeutic targeting of mut-p53 in tumour cells.

**To understand mechanisms that mediate chemo-/radioresistance of breast cancer stem cells**

Suitable for Honours or PhD students

Precursor metastatic cells, referred to as 'cancer stem cells' (CSCs), play a pivotal role in metastasis and relapse in breast cancer (BC) patients. Thus, effective management of breast cancer will require new therapeutic strategies that eliminate CSCs. Nonetheless, drugs that specifically target CSCs are extremely

under-developed. We have made a novel finding that expression of a new kinase is linked to breast cancer stemness as well as radioresistance. To date, this kinase has not been studied in breast cancer. Moreover, the signalling pathways regulated by kinase or its upstream regulators are unknown at present – not to mention in a context of radiobiology and chemotherapy. It clearly warrants further investigation. The study will establish the clinicopathological importance of identified kinase with other breast CSC markers in primary human BCs with clinical outcome data, providing clinical correlations to underlying biology and paving the way for companion diagnostic. We will study the effect of combined kinase depletion followed by IR treatment or chemotherapy on tumour recurrence in in vivo murine xenograft models in order to generate basic and preclinical data to support the development of kinase inhibitors that target cancer stem cells in women with BC. These studies will determine the role of resistant CSCs in tumour regrowth (recurrence) and how the specific eradication of these cells provides means for successful and curative approaches. It is anticipated that our mechanistic study on this kinase in in vitro cell line models and/or in vivo xenograft models will shed light on a new signalling axis that is critical to regulating breast cancer stemness and improving current clinical radiotherapy and chemotherapy for BC patients. The long-term aim of our research is to develop more effective therapies for advanced breast cancer. The identification of therapeutically exploitable kinase that is an important mediator of CSCs function after chemo- and radiotherapy will improve the success of standard and widely used DNA damage-based chemotherapy. If the proposed mechanistic studies demonstrate a causal role for this kinase and its regulated pathways in causing disease recurrence/relapse, a unique opportunity will exist to develop a new therapy in a group of patients with poor outcome. By inhibiting this kinase, it will be possible to substantially reduce CSC levels thereby diminishing cancer recurrence.

### Unravelling the function of a novel therapeutic target in the tumour microenvironment to prevent breast cancer and metastasis



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Suitable for Honours, Masters or PhD students

#### BACKGROUND

Metastasis, the spread of cancer cells from the primary tumour to surrounding tissues and distant organs, is the major cause (90%) of cancer mortality. Current cancer treatments mostly focus on targeting primary tumours, as the treatment or prevention of metastasis continues to have limited success. The complexity of the tumour-microenvironment (TME) and factors contributing to metastasis are not fully understood; therefore, improving our knowledge is critical for developing better treatment strategies. There is also an unmet need to improve the efficacy of current treatments such as immunotherapies and targeted therapies for metastasis to improve the overall survival of patients. We have identified a cancer-specific protein, which is highly expressed in a wide variety of cancers, its expression correlates positively with metastatic potential and worse patient outcomes. The inhibition of this target can hinder tumourigenesis, and increase survival in patients. Metastasis is regulated by a complex interplay with noncancerous cells (stroma) within the TME. These interactions are regulated at various levels, including direct cell-cell communication and tumour infiltration by immune cell components, binding of extracellular matrix components and secreted factors such as cytokines (immune modulators), and exosomes (type of extracellular vesicles) which are mediators of signalling and cellular communications in TME. How these complex processes happen, is the focus of this project.

#### AIMS

- 1) Underpinning the functional role of a specific gene in TME and metastasis to identify molecular mechanisms of immunoregulation and signalling pathways.
- 2) Exploring the biological role of a specific gene in extracellular matrix remodelling, cytoskeletal rearrangements, migration and signalling events.

#### SIGNIFICANCE

Specifically, we are investigating mouse models of cancer to develop new approaches which exploit the dynamic nature of TME. Professor Khanna's laboratory has generated many tools including but not limited to: genetically engineered mouse models (GEMMs), tumour xenograft models, and cell lines with the constitutive or inducible potential of gene knockdown. These tools can be used for the phenotypic, biochemical and cellular analysis of TME, tumour initiation, progression and metastasis.

#### TASKS

This project will apply a wide range of techniques in cell biology and tumour immunology to understand how cancer cells interact with TME and the student will become familiar with these techniques and possibly be involved in the publication depending on the achieved results.

### Targeting Breast Cancer and Metastasis by Oligonucleotide Therapeutics with Lipid Nanoparticle (LNP) Delivery System

Suitable for Honours, PhD and clinical students

#### BACKGROUND

Cancer is the second leading cause of death worldwide. The major cause of cancer-related mortality (~90%) is due to metastasis. Breast cancer (BC) is the most commonly diagnosed cancer among women. Of the 10,000 Australians that live with metastatic breast cancer only 32% are alive after five-years (relative survival-rate). While current cancer treatments mostly focus on targeting the primary tumours, the treatment or prevention of metastasis continues to have limited success. We have shown genetic inhibition of Cep55 reduces cancer progression and metastatic potential in mouse models. However, Cep55 is considered undruggable due to its coiled-coil structure; therefore, we have proposed an innovative approach using the antisense-oligonucleotides (ASOs), to inhibit Cep55 expression at the mRNA level. This strategy will generate a proof-of-concept, highlighting the ability and effectiveness of targeting undruggable and hard-to-treat cancers (invasive, aggressive, and advanced cancers) and metastasis preclinically through pilot studies *in-vitro* and *in-vivo*.

#### AIMS

- 1) Screen ASOs in a range of human and mouse metastatic and triple-negative breast cancer cell lines.

- 2) Evaluate preclinically whether ASO-Lipid nanoparticles (LNP) impedes breast cancer growth, progression, and spread and examining the efficacy, stability, specificity, and toxicity in-vivo.

- 3) Investigate the mechanism of action and functional role of Cep55 in tumor-microenvironment and metastasis by spatial transcriptomics.

#### SIGNIFICANCE

To overcome the challenge of undruggable cancer targets, we will use ASOs which target mRNAs and this strategy can be expanded to other undruggable targets in cancer. We utilised the next-generation ASOs design which enhances the potency, stability, binding properties, reduced toxicity, pro-inflammatory and off-target effects, improved therapeutic index, and extended duration of effect. In our human cells and mouse models, we will test the efficacy of LNP-based drug delivery which shall protect ASOs from degradation and permit cellular uptake and drug release. We expect this project will generate proof-of-concept data on the effectiveness of the ASO-LNP system and provide an on-target mechanistic validation in preclinical models of breast cancer. We anticipate this strategy pave the way for a resolution to treat patients with aggressive cancers and overcome the metastatic burden.

#### TASKS

This project will apply a wide range of techniques in medical research, cell biology and tumour immunology to target the cancer cells, mouse works and the student will become familiar with these techniques and possibly be involved in the publication depending on the achieved results.

### Expanding the scope of PARPi for treatment of high-grade serous ovarian cancers



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Suitable for Honours or PhD students

#### BACKGROUND

In Australia, approximately 1600 women are diagnosed with ovarian cancer each year and the majority have high-grade serous ovarian type (HGSOC). Five years survival rate for ovarian cancer is currently just 41% and lags well



behind breast (91% survival) and other cancers. Notably, resistance to standard of care chemotherapy is a common occurrence associated with multiple mechanisms and a poor prognosis of less than 12 months. Thus, development of novel strategies to overcome treatment resistance in HGSOC remains an urgent and unmet clinical need.

Not all HGSOCs are the same, based on expression of different genes, four distinct subtypes with unique clinical outcomes have been identified. Notwithstanding, MYC amplification or activation, linked with tumour aggressiveness, are found in over 50% of HGSOCs. The development of direct inhibitors of MYC has been unsuccessful, with none in routine clinical use. Inhibition of genes/ pathways that regulate MYC oncogenic activity is emerging as an efficient strategy to treat MYC-driven cancers. We have identified an upstream regulator of MYC activity in HGSOCs and we have compelling data that a novel inhibitor, suppresses homologous recombination (HR) repair of DNA damage, can be repurposed for therapeutic targeting of HGSOCs in combination with PARPi in BRCA1/2 wildtype and BRCA1/2 mutant patient-derived HGSOC tumours that have acquired resistance to PARPi. The positive outcomes of this work will therefore not only benefit patients with BRCA1/2 mutation who has progressed on PARPi but also provide a new treatment strategy for the majority of patients who do not carry BRCA1/2 mutation.

### Targeting CEP55 in triple-negative breast cancer



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#### BACKGROUND

Breast cancer in females has now passed lung cancer as the most common diagnosed cancer and affects over 10% of women before age 85, placing an enormous burden on our healthcare system. Despite some spectacular recent successes in fighting breast cancer with new treatments (e.g. immune checkpoint inhibitors, antibody-drug conjugates, PARP inhibitors) and surgical procedures, many patients do not respond long term or at all. Consequently, there is an urgent need for new drugs that can target newly discovered pathways that initiate progress or spread cancer. New therapies are especially needed for difficult-to-treat

cancers, such as triple negative breast cancer (TNBC) and certain drug-resistant metastatic breast cancers, with about one third of breast cancers spreading to other tissues such as lungs and brain even after surgery. There is a pressing need to develop a new approach to treating TNBC.

#### AIMS

To devise a new type of therapy to seek out and destroy a key protein called CEP55 that is highly expressed in a wide range of solid human cancers. This protein plays a crucial role in regulating cancer cell division but is silent in normal cells of adult tissues. Studies have shown that both cancer cells and tumours require CEP55 to survive and grow, and that mice overexpressing it spontaneously induce blood and solid tumours. We aim to chemically silence CEP55 by developing a novel therapy that binds to it and signals other proteins to come and destroy it in the body. The project aims to generate preclinical information on the effectiveness of chemically silencing CEP55 in mouse models of metastatic breast cancer.

#### PROJECT POTENTIAL

The study has the potential to rapidly facilitate translation of a new discovery to the clinic.

## Conjoint Gastroenterology Group



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The **Conjoint Gastroenterology Laboratory** studies molecular genetic alterations, which underlie the progression of benign bowel polyps to bowel cancer. It has a particular interest in serrated polyps, which were previously thought to have no malignant potential but are now recognised to be the precursors of approximately 20% of bowel cancers. This work has led to profound changes in the practice of colonoscopy so that it now better protects against bowel cancer. The laboratory has now developed an animal model of the serrated pathway and are testing chemoprevention strategies. The bowel

cancers, which arise through the serrated pathway, often carry an oncogenic BRAF mutation and develop DNA methylation silencing important genes such as mismatch repair genes. These characteristics are important in predicting prognosis and response to chemotherapy and this is also a focus of our research program. Collaboration with gastroenterologists, surgeons, pathologists and oncologists is a key aspect of its research.

### Colorectal cancer – from genetics to chemoprevention

Suitable for PhD and Honours students

This project will use a well-developed in vivo model to investigate the role of various drugs in the prevention of bowel cancer. Using an inducible BRAF mutant mouse, we have observed the sequential development of intestinal hyperplasia, polyps and ultimately advanced cancer, in a model that closely mimics human serrated neoplasia. This project will investigate therapeutic intervention to reduce the incidence of polyps and prevent cancer. Molecular studies using techniques such as mutation detection, DNA methylation, expression microarrays and immunohistochemistry will also be utilised to study the effects of the interventions.

This project would suit a highly motivated student with an interest in colorectal cancer genetics and therapy, who enjoys working individually and as part of a team.

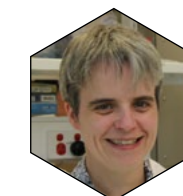
### Genetic changes underlying colorectal cancer initiation and progression

Suitable for PhD and Honours students

In the Conjoint Gastroenterology Laboratory, we are interested in characterising the genetic changes underlying the progression of pre-cancerous colonic polyps to colon cancer. We work closely with clinicians specialising in Gastroenterology, Pathology, Oncology and Genetics to increase our understanding of this disease and improve patient management and outcomes.

Potential projects will examine candidate genes for a role in the development of colorectal cancer, selected from bioinformatic analysis of genome-wide data including expression arrays, DNA methylation array profiling and next generation genomic sequencing. Candidate genes will be examined in a clinically and molecularly well-defined series of colorectal polyps and cancers. Functional studies will be conducted in colorectal cancer cell lines and in xenograft models. Techniques used will include cancer organoid culture, co-culture with immune cells and drug studies to develop new chemotherapy and immunotherapy approaches for improving outcomes for patients with colorectal cancer.

## Medical Genomics Group



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The **Medical Genomics Laboratory** analyses next generation sequence data to address clinical challenges in a variety of diseases.

The approaches taken include:

- Classification of samples into significant subtypes.
- Identification of driver mutations.
- Identification of mutational processes that underlie tumour development.

#### AIM

Ultimately, the aim is to find alternate therapeutic targets. These are important steps towards personalised medicine, where the diagnosis, management and treatment of patients will be based on their individual genomic data.

### Complex neoantigen prediction in cancers

Suitable for PhD, Masters or Honours students. The project requires knowledge of python or R, preferably both

Next generation sequencing has allowed researchers to characterise the somatic landscape of cancer genomes, which has led to the discovery of biomarkers that may be predictive and prognostic to targeted therapies. However, the efficacy of current targeted therapies has failed to raise the overall survival curve in many tumour types. Immunotherapy has shown a promising benefit in treating many tumours and demonstrated remarkable responses in some patients even at recurrent, relapse and metastasis stage. The challenge now is to determine who and why some patients respond to treatment. Somatic mutations within the genomes of cancer cells may result in neoantigens that are presented on the tumour cell surface. These can then be seen by the immune system and killed by the patient's immune system. This project will test and develop bioinformatic approaches that can be applied to understand complex tumour-immune interactions. Specifically, the project will use genome

and RNAseq data to predict neoantigens and determine which of these are important in immunotherapy. The findings from this work are likely to shed new insight into tumour immunology and may predict which patients will respond to immunotherapy.

## Molecular Oncology Group



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Our team is focused on identifying the most suitable cancer treatment strategies and treatment biomarkers to enable precision oncology. We use bioinformatic and machine learning approaches to analyse cancer molecular profiling data, including genomic, transcriptomic and DNA methylation data, to link it with treatment responses and patient outcomes. Our research spans multiple solid cancer types, including ovarian, endometrial and lung cancers.

### Genomic heterogeneity in KRAS-mutant lung adenocarcinomas



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The project is available on an ongoing basis for PhD students, full time

#### BACKGROUND

Endometrial cancer is the most common gynaecological cancer. Surgery is the standard treatment, however it can be unsafe for elderly or obese women, and it results in fertility loss in young women. Hormone therapy using progestin is an alternative treatment to surgery, but less than 70% of endometrial cancers respond to progestin. Therefore, there is a need for predictive biomarkers. The exact biomarkers for predicting responses to progestin are yet to be defined.

The focus of this project is on identifying genomic biomarkers of progestin response using endometrial cancer samples from the feMMe clinical trial. Around 100 cancer samples will be analyzed using a comprehensive targeted DNA sequencing assay, which covers all key endometrial cancer genes and assesses tumour mutation burden and microsatellite instability. The work in this project will involve assessing the quality of DNA samples, coordinating library preparation, as well as bioinformatic analysis and interpretation of the results. The project is a wet and dry lab hybrid, thus requires a basic understanding of R or Python.

## Translational Cancer Immunotherapy Group



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The **Translational Cancer Immunotherapy Laboratory** studies the interaction between the immune response and tumour control, with a particular emphasis on translating our ever-expanding basic science knowledge into clinically applicable therapeutic platforms.

Our lab has a long-standing interest in bone marrow transplantation (BMT). It is the most established form of cancer immunotherapy but is also associated with life-threatening complications, primarily graft-versus-host disease (GVHD) and infections. A new and increasing focus of our lab is the related field of cellular immunotherapy, especially Chimeric Antigen Receptor (CAR) T cell therapy, which are gene-modified immune cells that have shown to be very effective in eradicating certain cancers. Our lab is one of only a few groups in Australia capable of conducting investigator-driven clinical trials using gene-modified immune cells generated in-house.

### CAR T cells – redirecting T cells for cancer immunotherapy

#### Suitable for Honours, Masters and PhD students

Chimeric Antigen Receptors (CARs) are genetically engineered molecules that can redirect T cells to recognise particular antigens, such as those expressed by cancer cells. T cells that are transduced by CAR targeting CD19 have been effective in treating B cell cancers, e.g. B-cell leukaemia and lymphoma, where conventional treatments have failed. This exciting technology is one of the major breakthroughs in cancer therapy this decade. However, not all patients respond, not all responses are durable and there is limited success to date in CAR T cells targeting solid cancers. This project involves developing and testing new concepts in CAR T cell engineering to make them more effective, safer and more able to target solid cancers. There is also an opportunity for students to be involved in clinical correlative research to better understand the immunobiological determinants of clinical response and toxicity.

### Understanding the Immunobiology of Bone Marrow Transplantation



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#### Suitable for Honours or Master students

#### BACKGROUND

Bone Marrow Transplant (BMT) offers cure to patients with aggressive blood cancers. Its efficacy lies in the ability of the newly transplanted immune system to recognize and destroy recipient malignant cells as foreign, a phenomena known as Graft-versus-Malignancy (GVM). However, if healthy cells and tissues are targeted the complication of Graft-versus-Host disease (GVHD) occurs. Post-transplant all patients are managed with immunosuppression to control the balance between GVM and GVHD, however immunosuppression brings risk of infection and poor response to vaccines. Each of these complications are mediated by immune control, and new therapies to manipulate immunity post-transplant are required. This project will examine a number of factors influencing T cell function in the context of transplantation and the effects on GVM and GVHD, with a focus on

translational research and the development of potential new therapies.

#### FOCUS

To examine the impact of the gastrointestinal microbiome on T cell function and GVHD.

#### APPROACH

Immunophenotyping including flow cytometry and spectral cytometry.

Measurement of soluble immune mediators.

Correlation with clinical outcome data.

## Epigenetics and Disease Group



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Epigenetic modifications change the pattern of expression in genes. In some cases, this can give rise to cancers. The group research uses small molecule inhibitors to reverse some of these changes and block tumour progression. Having successfully identified combinations of epigenetic modifying enzyme inhibitors that stop the growth of tumour cell lines – making them more sensitive to clinical treatments or reversing the resistance of some cancers to some therapies – the group is now testing these combinations in animal models. The epigenetic studies target breast, ovarian, head and neck and lung cancers as well as melanoma.

### Combining epigenetic drugs with immunotherapy in cancer

#### Suitable for Honours and PhD students

Whereas advances in immune and targeted therapies have made tremendous progress recently, they are effective only in distinct subsets of patients or result in the emergence of drug resistance, and patients suffer considerable side effects. Thus investigation of alternative approaches is essential. Recent studies have shed light on the importance of epigenetic regulation in cancer biology, including overexpression of epigenetic enzymes histone methyltransferases in



cancers. Combining inhibitors of epigenetic modifiers with immune checkpoint inhibitors may either enhance the efficacy of immunotherapy or treat those patients that have become resistant to therapy. Side effects from immunotherapy may be alleviated by lower drug doses required when used in combination with other drugs such as small molecule inhibitors. Also, prohibitive cost of immunotherapy can be overcome by therapy that uses relatively inexpensive small molecules.

### HYPOTHESIS

Combining epigenetic inhibitors with immunotherapy will be more effective in treating solid tumours compared to using single drug.

### AIM

The aim of this study is to develop a combined therapy using epigenetic small molecule inhibitors and immunotherapeutic agents in vivo for the treatment of patients at high risk of recurrence and metastasis.

### APPROACH

1. Cellular models and drug treatments.
2. Gene expression analysis – RNA-seq.
3. In vivo mouse model of cancer.
4. Protein complex purification and proteomics.
5. Characterisation of putative target genes by ChIP-seq.

### Novel approaches in overcoming therapy resistance in pancreatic cancer

Suitable for Honours and PhD students

### BACKGROUND

Pancreatic tumours are aggressive and highly resistant to current therapies due to the dense fibrotic stroma, hypoxic tumour microenvironment and immune evasion. Pancreatic tumour cells switch their metabolism to survive better in this hostile environment and recent studies have shown that epigenetic changes play an important role in this adaptation. Studies examining the tumour microenvironment from our lab indicate that aberrant expression of epigenetic enzymes affects therapy-resistance through promoting fibrogenic activation and metabolic switching. Modulating the activity of these epigenetic enzymes in the tumour microenvironment can potentially induce tumour cell death and also enhance the efficacy of other therapies.

### HYPOTHESIS

Inhibiting the activity of epigenetic enzymes will reverse the aggressive phenotype of pancreatic cancer cells and enhance chemotherapy and immunotherapy response.

### AIM

To determine the role epigenetic enzymes play in therapy resistance in pancreatic cancer.

### APPROACH

1. Cellular models and drug treatments.
2. Gene expression analysis by RNA-seq.
3. In vivo mouse model of pancreatic cancer.
4. Spatial transcriptomics and multiplex IHC.
5. DNA and RNA editing using CRISPR-mediated approaches.

### Targeting non-coding RNAs to boost immunotherapy response in cancer

Suitable for Honours and PhD students

### BACKGROUND

Immunotherapy has emerged as a transformative mode of cancer therapy. However, a number of cancer-types do not respond to immunotherapy, and a significant proportion of cancer patients who initially show response develop resistance later in their treatment. Therefore, development of novel approaches to boost immunotherapy response are needed in order to extend the proportion of patients benefiting from immunotherapy. Non-coding RNAs provide the potential to encode novel neoantigens that could be recognised by T cells. Immunopeptidomic studies indicate that many non-coding RNA-derived proteins make up a major source of tumour neoantigens. Increasing the level of these proteins by modulating the expression of non-coding RNAs has the potential to enhance immunotherapy response in cancer.

### HYPOTHESIS

Increasing peptides encoded by non-coding RNAs by targeting epigenetic mechanisms enhances immunotherapy response in cancer.

### AIM

To develop novel approaches in enhancing the expression of neoantigens and identification of non-coding RNAs that encode tumour neoantigens that trigger T cell response in cancer.

### APPROACH

1. Immunopeptidomic analysis.
2. Proteogenomics analysis on non-coding regions of the genome.
3. DNA and RNA editing using CRISPR-mediated approaches.

## Immune Targeting in Blood Cancers Group



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The **Immune Targeting in Blood Cancers Laboratory** focuses on understanding the interplay between immunity and cancer cells in haematological malignancies such as multiple myeloma, B-cell lymphoma, and leukaemia. Although immunotherapy has emerged as an important treatment option, these aggressive cancers are still difficult to cure. Using preclinical models and clinical samples, the group aims to understand how cancer cells escape the immune system, and to develop new therapeutic approaches to prevent relapse.

### Targeting immuno-oncology molecules in blood cancers

Can be adapted in scope for Honours or Masters

### BACKGROUND

Although immunotherapy has emerged as an important treatment option, it is still challenging to achieve durable clinical responses by immunotherapy. Using preclinical models and clinical samples, the project aims to understand 1) how cancer cells escape the immune system and 2) how we can improve efficacies of immunotherapeutic drugs.

### APPROACH

- Targeting stress-adaptive pathways to improve immune-mediated control of blood cancers.
- Understanding effector mechanisms of bispecific T-cell engaging antibodies.
- Harnessing innate immunity to improve efficacies of antibody drugs.

### METHOD

The student will learn the following research techniques: 1) in vivo leukaemia models (animal handling, various drug treatments, bioluminescence imaging), 2) in vitro cell culture (gene transduction, T cell stimulation assays, macrophage activation assays) 3) flow cytometry analysis, and 4) immunoblot analysis.

### REFERENCES

1. Salik et al. Targeting immune checkpoints in hematological malignancies. *Journal of Hematology & Oncology* 2020. 13 (1), 1-19
2. Nakamura et al. Cancer immunoediting and immune dysregulation in multiple myeloma. *Blood* 2020. 36 (24), 2731-2740
3. Nakamura et al. Targeting an adenosine-mediated "don't eat me signal" augments anti-lymphoma immunity by anti-CD20 monoclonal antibody. *Leukemia* 2020. 34 (10), 2708-2721
4. Nakamura et al. Dysregulated IL-18 is a key driver of immunosuppression and a possible therapeutic target in the multiple myeloma microenvironment. *Cancer Cell* 2018. 33 (4), 634-648.

## Cancer Genetic Susceptibility Group



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The **Cancer Genetic Susceptibility Laboratory** primarily studies the role of genetics in endometrial cancer risk and development. Our team leads large-scale genetic studies for endometrial cancer and uses these data to answer a variety of research questions falling under three main themes: prevention, prediction and treatment.

## Identifying the regulatory targets of common endometrial cancer risk variants



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Can be adapted in scope for Honours or PhD student

### BACKGROUND

We and our international Endometrial Cancer Association Consortium collaborators have identified common genetic variation at 16 genomic regions that associates with endometrial cancer risk. Although we have identified potentially causal risk variants, at most regions we do not know which genes these variants target. However, we have conducted global (HiChIP) analyses of DNA looping to identify physical interactions between genes and regulatory elements at endometrial cancer risk regions in endometrial cancer cell lines. These experiments constitute an essential step for the translation of genetic findings into advances in our knowledge of endometrial cancer biology and the identification of potential targets for therapy.

### AIM

To identify high confidence gene regulatory targets of endometrial cancer risk variants using DNA looping analyses and other functional genomic datasets.

### APPROACH

Depending on the applicant's expertise, this project could have either a wet-lab and/or a bioinformatics focus. We already have a wealth of endometrial cell DNA looping data that can be coupled with complementary datasets (gene expression, histone modification and transcription factor ChIP-seq) for bioinformatic analyses to prioritise regulatory target genes. To extend our findings from DNA looping analysis of endometrial cell lines, we are also interested in performing analysis of human endometrial organoids from normal, hyperplastic and tumoural endometrium. These organoids should provide experimental systems that will better recapitulate the morphological and genomic features of human tissue.

### OUTCOME

Through the identification of high confidence gene targets at endometrial cancer risk regions, we will gain a deeper understanding of endometrial cancer aetiology and identify potential targets for endometrial cancer therapy.

## Genetic epidemiology of endometrial cancer

Suitable for PhD students only

### BACKGROUND

Endometrial cancer is the most commonly diagnosed invasive gynaecological cancer in developed countries. In contrast with many cancers, the incidence and mortality of endometrial cancer is steadily increasing. This is largely due to increasing rates of obesity, the strongest risk factor for this disease. Through leadership of the Endometrial Cancer Association Consortium (ECAC), our lab runs the largest genetic study of endometrial cancer. To date, we have identified 16 genetic regions associated with endometrial cancer predisposition by genome-wide association study (GWAS), which account for ~25% of the genetic heritability attributable to common genetic variants (O'Mara et al, Nat Commun 2018). Incorporation of existing GWAS data with newly acquired GWAS datasets from international collaborators will identify further genetic regions associated with endometrial cancer risk. Additionally, we have approved access to large, well-phenotyped international datasets (e.g., UK Biobank, N = 500,000). This allows us unparalleled ability to examine the genetics of endometrial cancer, as well as explore its relationship with risk factors, such as obesity.

### AIM

To identify new genetic risk regions for endometrial cancer, by performing the largest GWAS meta-analysis for this disease. To use computational approaches to identify and explore risk factors of endometrial cancer. To use genetic data to construct and test risk prediction models for endometrial cancer.

### APPROACH

This project will use standard GWAS pipelines to identify genetic variants associated with endometrial cancer risk, including imputation, QC and association testing. Post-GWAS analyses to explore novel regions could also be performed (e.g., eQTL analyses, integration with functional genomic datasets). The relationship between endometrial cancer and potential/known risk factors will be performed using approaches such as genetic correlation (LD Score Regression) and Mendelian randomisation. Endometrial cancer risk prediction models will be constructed using polygenic risk scores in combination with endometrial cancer environmental risk factors and tested for efficacy in independent datasets.

## Transplant Immunology Group



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Research conducted by the **Transplant Immunology Laboratory** focuses on improving our understanding of the pathophysiology of complications following stem cell transplantation. Using unique preclinical models combined with innovative technologies, the group aims to define the immunological mechanisms that underpin these complex disease processes, with the view of translating the basic research findings into clinical practice.

Stem cell transplantation is considered the “gold standard” procedure for the treatment of blood cancers (including leukaemia, lymphoma and myeloma) in both adults and children. Globally, over 9,000 patients per year undergo this high-risk, life-saving therapy. However, graft-versus-host disease (GVHD) occurs in 50-70% of patients, of which 20% will develop severe GVHD that is untreatable. Unfortunately, additional complications such as infection and cancer relapse are common.

## Targeting the gut and the microbiome therein to improve blood cancer treatments

Multiple projects available to suit Honours or PhD students

Stem cell transplantation (SCT) remains the preferred treatment option for the majority of blood cancers providing alloimmunity to eradicate the disease and prevent relapse. However, graft-versus-host disease (GVHD) is a major complication that limits its effectiveness and utility, thus represents a clinical unmet need. Chemotherapy/radiation prior to transplant damages the intestinal epithelium resulting in systemic exposure to microbiota and their by-products, which are normally sequestered in the lumen. The aim of this research is to improve our fundamental understanding of the microbial-host interactions, which regulate protective/pathogenic mechanisms after transplant. This will lead to the identification of new strategies to prevent and/or treat acute gastrointestinal GVHD. This project will

involve animal work, high-parameter flow cytometry, bacterial genomic sequencing, metabolomics, spatial transcriptomics, confocal microscopy, molecular and microbiological techniques, with the validation of findings in clinical samples.

### REFERENCES

Varelias A, *et al.* Acute graft-versus-host disease is regulated by an IL-17-sensitive microbiome. *Blood*. 2017. 129(15):2172-85.

Varelias A\*, Bunting MD\*, *et al.* Recipient Mucosal-Associated Invariant T Cells control GVHD within the colon. *J Clin Invest*. 2018. 128(5):1919-36. \*Joint first authors.

## Understanding infectious respiratory complications after stem cell transplantation

Multiple projects available to suit Honours or PhD students

Stem cell transplantation (SCT) remains the preferred treatment option for the majority of blood cancers providing alloimmunity to eradicate the disease and prevent relapse. However, this results in patients becoming critically immunocompromised after transplant such that infection with common respiratory viruses can be life threatening. Respiratory syncytial virus (RSV) in particular can result in pneumonitis, respiratory failure and death in up to 50% of infected patients. With no vaccines and a lack of efficacious antivirals, new treatment options are needed. Given the paucity of mechanistic data to guide clinical studies or define the basis of disease, we established a murine model of RSV infection after SCT using pneumonia virus of mice (PVM), the murine homologue of human RSV. Using this model, the aim of this research is to investigate fundamental immunological mechanisms, which underlie this post-transplant complication. This will lead to the delineation of critical mechanisms and identification of therapeutic targets to alleviate infection-driven post-transplant mortality. This project will involve animal work, high-parameter flow cytometry, single-cell transcriptomics, molecular and viral techniques, with the validation of findings in clinical samples.

### KEY PAPER

Varelias A, *et al.* Lung parenchyma-derived IL-6 promotes IL-17A-dependent acute lung injury after allogeneic stem cell transplantation. *Blood*. 2015. 125(15):2435-44. Transplant Immunology Group



## Cancer Neuroscience Group



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The **Cancer Neuroscience Laboratory** aims to translate insights from fundamental neuroscience research and apply these to brain cancer, with a particular interest in glioblastoma, which is the most common malignant primary brain tumour in adults and has a median survival of just 15-months after diagnosis. At the core of The Cancer Neuroscience lab is a focus on researching cellular quiescence, a reversible hibernation-like state, adopted by brain cancer cells to evade chemotherapy and radiotherapy. By targeting these quiescent cells, we might overcome treatment resistance and improve outcomes for persons with glioblastoma. To identify novel therapeutic approaches to target quiescence, the lab also focuses on understanding how quiescence is regulated in normal neural stem cells in the memory centres of our brains.

### Should I stay, or should I go? How brain stem cells decide to leave quiescence

Multiple projects available to suit Honours or PhD students

Quiescence is a type of reversible cell-cycle arrest displayed by many resident tissue stem cell populations, which helps to ensure we have a lifelong population of stem cells to maintain tissue homeostasis, respond to injury and other stimuli. One region where these stem cells exist is in the brain. In mice, a major model organism, there are two main stem cell niches in the adult brain. These are the subgranular zone of the hippocampus and the subventricular zone lining the lateral ventricles of the forebrain. When quiescent neural stem cells in these regions activate, they generate neurons that function in memory, spatial navigation and odour discrimination. Similar neural stem cell populations with similar functions exist in the human brain.

#### AIM

This project aims to uncover novel molecular regulators of brain stem cell quiescence. One prism through which this will be explored, is by interrogating how brain stem

cells enter deeper quiescence during the aging process. The project will employ a range of techniques using aged wildtype mice, genetically modified mice and primary neural stem cell cultures derived from the hippocampus and subventricular zone of postnatal/adult mice. The outcomes of this project are expected to shed light on how quiescence is regulated. The genes/cellular processes we identify as being important in quiescence can then be explored in the context of diseases where adult neurogenesis is disrupted, for example during aging and major depressive disorder. Likewise, these findings will also be of interest to brain cancer research, where quiescence is frequently co-opted by cancer stem cells to evade therapies.

Specifically, this project will:

- 1) Establish the role of a novel group of calcium-binding proteins in deciphering activation/proliferation cues using in vitro and in vivo models.
- 2) Determine if decreased expression of these proteins explains why quiescence deepens during aging.
- 3) Determine if these proteins are functionally important in the progression of brain cancers, with a specific focus on quiescence and treatment resistance.

### Improving survival for adult brain cancer patients by targeting 'sleeping' cancer stem cells

Multiple projects available to suit Honours or PhD students

Glioblastoma (GBM) is the most common malignant primary brain tumour in adults and is inevitably fatal, with a median survival of just 15-months after diagnosis. Standard treatment involves surgical resection, postoperative radiation and chemotherapy. Unfortunately, significant populations of resistant glioma stem cells remain after chemotherapy, these cells regrow the tumour, and patients ultimately succumb to the illness. Glioma stem cells resist treatment in part because they are in a state of cellular sleep, known as quiescence. The quiescence of glioma stem cells means they divide very rarely, whereas current chemotherapy preferentially targets fast-dividing tumour cells. A common strategy in cancer research is to combine chemotherapy with drugs that slow tumour growth. However, this approach often increases the resistance of tumours as it forces more cells into quiescence. The innovative research program Dr Harris is developing is to target quiescent GSCs by leveraging unique features of quiescence and turning them into therapeutic vulnerabilities.

## Gordon and Jessie Gilmour Leukaemia Research Laboratory



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The **Gordon and Jessie Gilmour Leukaemia Research Laboratory** is researching myeloid blood cancers that include acute myeloid leukaemia (AML), myelodysplastic syndrome (MDS) and myeloproliferative neoplasms (MPN) as part of its translational leukaemia research work. These very aggressive and rapidly fatal blood cancers are among the most common types of cancer affecting Australians.

The laboratory's efforts concentrate on understanding how leukaemia stem cells in AML and MPN are able to regenerate leukaemia (or cause relapse in patients), even after cytotoxic chemotherapy. Research has focused on generating robust models of leukaemia and dissecting the pathways of self-renewal in leukaemia stem cells and normal blood stem cells. The group aims to tailor treatments for individual patients, identify new drug pathways and explore repurposing existing drugs to target resistant leukaemia types.

### The role of additional mutations in treatment response and disease progression in MPN



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Can be adapted in scope for Honours, Masters or PhD project

MPNs are a group of disorders characterised by the excess production of mature myeloid cells. MPNs are driven by the constitutive activation of the JAK-STAT signalling pathway as a consequence of mutations in

either JAK2, MPL or CALR in haematopoietic stem cells (HSC). Pioneering work from our laboratory has demonstrated the efficacy of interferon alpha (IFN $\alpha$ ) in the preferential targeting of MPN stem cells. In addition to these MPN-driver mutations, patients often present with additional mutations that can alter disease presentation. It is currently unclear if and how the presence of additional mutations may alter treatment outcomes in MPN, particularly in response to IFN $\alpha$ , and what mutation combinations are sufficient to drive transformation to leukaemia.

In this project we will use our well-established murine model of mutant Jak2-driven MPN in combination with CRISPR engineering technology to generate additional mutation combinations observed in the human disease. By treating these genetically engineered mice with IFN $\alpha$  we will determine what additional mutations or mutation combinations confer resistance to therapy and how. By ageing these mice and monitoring their disease phenotype long-term we will determine what mutation combinations result in the emergence of leukaemia. These studies will primarily employ mouse procedural work, primary cell culture, flow cytometry and basic molecular biology. Mechanistic studies are likely to include the use of high content sequencing technologies like RNAseq and ATACseq at a bulk, and possibly single cell, level.

### The role of the immune system in disease evolution and treatment response in AML

Can be adapted in scope for Honours, Masters or PhD project

Acute myeloid leukaemia (AML) is an aggressive blood cancer characterised by the excessive production of immature myeloid elements. AML is a genetically heterogeneous disease in that it is known to be driven by an extensive list of somatic mutations and chromosomal re-arrangements. We have demonstrated that the endogenous immune system is only capable of mounting a sufficiently powerful anti-AML immune response in specific molecular subtypes of AML. Through these studies we have demonstrated that mutations that drive the constitutive activation of Nras result in the upregulation of antigen presentation machinery and immunostimulatory ligands. Of great interest is that the overexpression of the oncogene Myc is sufficient to inhibit multiple aspects of this pro-immunogenic mutant Nras-driven phenotype. Furthermore, we have also demonstrated that treatment of AML with the commonly used therapy Azacitidine results in the upregulation of immunogenic ligands on

the AML and changes in the composition of the immune microenvironment.

In this project we will use established models of mutant Nras-driven AML to determine how changes in Myc activity alter the expression of immunogenic ligands and if it also changes the composition of the immune microenvironment. We will also determine the dependency of Azacitidine treatment efficacy on the presence of a competent immune system, and how this relates to transcriptional and epigenetic changes that occur in the AML in response to treatment. These studies will primarily employ mouse procedural work, primary cell culture, flow cytometry and basic molecular biology. Mechanistic studies are likely to include the use of high content sequencing technologies like RNAseq, ATACseq and EMseq.

### Role of MYC in leukaemic cell differentiation



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Can be adapted in scope for Honours, Masters or PhD project with bioinformatics background

MYC is a pleiotropic transcription factor with a key role in controlling cell proliferation. Deregulation of MYC through amplification or genomic rearrangement is the oncogenic driver in many cancers of different tissue origin. Novel therapies that inhibit downstream effects of MYC activation have great efficacy and improve clinical outcome. In acute myeloid leukemia (AML) compared to other cancers, MYC is not subject to genomic amplification or rearrangement. However, it is highly expressed in majority of AMLs. We recently identified a novel role of MYC as regulator of the antigen presenting machinery but other than this little is known about its role in AML disease progression and therapy resistance.

### OBJECTIVE

The objective of this project is to study the effect of MYC expression in AML with different oncogenic drivers. The project involves the use of single cell RNA-Sequencing data of human AML patients to characterize the role of MYC expression in different stages of leukaemic cells. You will use dimension reduction, machine learning and novel RNA velocity estimation techniques to integrate data from AML with different genetic backgrounds.

The results of the projects will aid to understand the combined effect of MYC expression and different oncogenic drivers on cell phenotype and differentiation and to rationalize MYC downstream effect inhibition as a treatment for AML.

### What determines leukaemic stem cell maintenance and resistance to chemotherapy?

Can be adapted in scope for Honours, Masters or PhD project with bioinformatics background

Acute myeloid leukemia is a highly aggressive disease with the majority of patients still relapsing even after achieving remission from chemotherapy. It is hypothesized that relapse arises from residual leukaemic stem cells that are resistant to chemotherapy. To date transcriptional analysis of AML has focused on whole bone marrow or peripheral blood samples, which is mainly composed of leukaemic blasts, masking the transcriptional program of leukaemic stem cells. Data generated from AML samples using single cell RNA sequencing will enable the analysis of the leukaemic stem cell transcriptome.

### AIM

The aim of this project is to analyse single cell RNA Sequencing data of AML to determine potential mechanisms of resistance in leukaemic stem cells. These findings will be correlated with previously identified genome-wide CRISPR screen hits that conferred chemotherapy resistance in AML cell lines and other datasets of relapsed/refractory AML. In addition, you will characterize leukaemic stem cells compared with leukaemic blasts. You will use dimension reduction and machine learning approaches to integrate data of AMLs with different genetic background and prognosis. Findings from this project will inform further investigation of pathways involved in chemotherapy resistance and therapeutic strategies targeting chemoresistant leukaemic stem cells.

## Sid Faithfull Brain Cancer Laboratory



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The **Sid Faithfull Brain Cancer Research Laboratory** studies the most common and aggressive form of both adult brain cancer, Glioblastoma (GBM) and paediatric brain cancers, Medulloblastoma and Diffuse Midline Glioma (DMG). The focus of our research is on understanding the molecular mechanisms which are responsible for the initiation and recurrence of brain cancers and to develop and test new and effective therapies to treat these aggressive diseases.

Our ultimate objective is to offer a comprehensive pipeline from discovery to translation and into the clinic. We seek to harness our scientific and clinical collaborative networks to initiate better designed clinical trials state-wide and nationally. Better outcomes are urgently needed as overall survival for brain cancer sufferers has increased by months only in the last 50 years.

### Targeting novel receptors in GBM



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Can be adapted in scope for Honours or PhD project

### BACKGROUND

We have generated well-characterised monoclonal antibodies (mAbs) against two receptor proteins that are present on two discrete cell populations and propose to use these simultaneously to effectively target this devastating disease. By targeting two proteins specifically expressed on the tumour and not normal brain, we aim to reduce toxicity while effectively killing most of the tumour. We have conjugated the mAbs with a drug to make antibody drug conjugates (ADCs) and aim to test their killing efficacy *in vitro*.

### AIM

To validate dual targeting using ADCs as an effective therapeutic strategy for GBM *in vitro*.

### APPROACH

*In vitro* killing assays to determine GBM cell killing and IC50

Apoptosis/Cell death assays

Flow cytometry and Western blotting

Immunofluorescence and confocal microscopy.

### OUTCOME

Validation of novel ADCs that have anti-cancer effects in primary GBM cell line models which would then serve as a base for further validation in animal models. This would pave the way for translation into the clinic to improve outcomes for patients with GBM.

## Cancer Genetics Group



**Senior Scientist (Cancer Genetics):  
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The **Cancer Genetics Group** focuses on why some people get breast cancer, and how these cancers develop from a normal cell. Using genome-wide association studies (GWAS) we have identified over 200 breast cancer risk loci. We have successfully identified some of the target genes at several of these loci. The functional mechanism behind the associations usually involves perturbed regulation of target gene transcription by risk single nucleotide polymorphisms (SNPs) lying in regulatory elements positioned some distance from the target. The nearest gene to the GWAS 'hit' is not necessarily the target of the association, and for some loci, there are multiple gene targets. We have developed a pipeline for predicting target genes at GWAS hits but the challenge of functionally interrogating each risk locus to identify the target gene(s) is enormous.



## Genome Variation and Regulation in Disease Group



**Team Head:**  
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My team in the **Genome Variation and Regulation in Disease Laboratory** are interested in how human genetics contributes to disease and how we can use these discoveries to find better treatments. We integrate large-scale genetic and functional genomics data to guide computational analyses and laboratory experiments. We are using a diverse array of approaches including pooled functional genetic screens, multiplex reporter assays, and genome editing to pinpoint the causal genetic changes, their target genes and pathways, and the cell types in which they act.

### Joint project: Identifying the causal genes at cancer risk loci

#### Suitable for PhD or Honours students

Our laboratory is involved in genome-wide association studies (GWAS) to identify common variations underlying the risk of breast and ovarian cancers. The current challenge is in the functional interpretation of genetic association data. With this aim, we use a variety of computational approaches to define potential molecular mechanisms at GWAS loci and to generate specific hypotheses to guide further experimental work.

Specific areas of interest include:

- Analysis of high throughput sequencing data, such as ATAC-seq and HiChIP from primary breast samples and cultured cells.
- Integration of genetic and functional genomics data to predict target genes at GWAS loci.
- Mining of public epigenomic datasets such as those from the ENCODE and ROADMAP Consortia.

- Identification of candidates for drug repositioning.
- Analysis of CRISPR screen data.

The project would suit a bioinformatics student with an interest in gene regulation. Students would work closely with dry and wet lab scientists to identify cancer genes and pathways, which might represent targets for future drug development.

# Population Health Program

**Our Population Health team is dedicated to understanding the factors influencing the health and wellbeing outcomes of all Australians.**

Drawing on the expertise of our clinical scientists, epidemiologists, health economists, and specialist researchers, we examine the causes of disease, and identify patterns and changes in the health of the population. This knowledge is used to develop measures to control and prevent diseases, increase early detection and improve treatments to ensure the best possible health outcomes.

The research we do is diverse. It ranges from examining the role of vitamin D supplementation in health outcomes to reducing the incidence of mosquito-borne illnesses and from identifying environmental and genetic risk factors for disease to improving the wellbeing of those caring for cancer patients and evaluating the social and economic consequences of disease.

Our studies are helping develop treatment guidelines to ensure all patients receive the best possible care, prevent hospital admissions, improve well-being and reduce mortality.

The Population Health program is guided by the ultimate goal of preventing ill-health and improving patient care, quality of life, and survival rates, so that all Australians have the opportunity to enjoy good health.

## Gynaecological Cancers Group



**Group Leader:**  
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The **Gynaecological Cancers Group** primarily investigates all aspects of gynaecological cancer from aetiology to diagnosis, patterns of care, quality of life and survival. A particular focus is on the role of environmental (non-genetic) factors and the interaction between genetic and environmental factors in the causation and prognosis of ovarian and endometrial cancer. Much of this work is conducted within three national studies and two international consortia. The group is also leading the PROMISE study – a new hybrid effectiveness-Implementation trial evaluating the use of electronic Patient Reported Outcome Measures (PROMs) in routine cancer care.

About 1500 women are diagnosed with invasive ovarian cancer in Australia every year and five-year survival is still less than 50%. About 3000 women are diagnosed with endometrial cancer. Both the cancers and the treatment for them can affect a woman's quality of life. To reduce incidence we need better information about what causes the cancers and who is most at risk. To improve outcomes we need to ensure that all women get optimal care, increase understanding about the problems that women experience and identify factors that can improve prognosis.

The Australian Ovarian Cancer Study (AOCS) collected information about potential risk factors, quality of life and survival and the Ovarian Cancer Prognosis and Lifestyle (OPAL) study has followed a national cohort of women newly diagnosed with ovarian cancer for up to 8 years. Both of these studies also contribute data to the international Ovarian Cancer Association Consortium (OCAC). The Australian National Endometrial Cancer Study (ANECS) has similar data for endometrial cancer and is also part of the international Epidemiology of Endometrial Cancer Consortium (E2C2).

### Use of dietary supplements and outcomes after a diagnosis of ovarian cancer

*Suitable for a Masters (preferably part-time) or Honours student. Some experience in biostatistics and data analysis is essential and a background in epidemiology and/or an interest in cancer are highly desirable*

#### BACKGROUND

The use of dietary supplements by cancer patients is common but contentious, particularly during chemotherapy. Survivors often take supplements in the hope these will improve their wellbeing, alleviate chemotherapy side effects, boost immune function, and perhaps improve their long-term survival. There is, however, a growing body of evidence suggesting that supplements, particularly antioxidants, might interact with conventional chemotherapeutic treatments and thus be detrimental to health. In recent analyses of patients with breast cancer enrolled in a randomised clinical trial, there was a suggestion that those who used multivitamin supplements experienced less neurotoxicity during treatment while those who used supplements other than multivitamins had poorer survival.

#### AIM

To evaluate the relation between use of dietary supplements, particularly antioxidants, by women with ovarian cancer before diagnosis, during and after treatment, and (i) wellbeing and (ii) survival.

#### APPROACH

Analysis (linear and logistic regression/survival analysis) using individual-level data from women in the OPAL study who provided information about dietary supplement use before and after diagnosis (3-monthly for the first year then annually to 4 years).

### Use of complementary and alternative medicine and outcomes after a diagnosis of ovarian cancer

*Suitable for a Masters (preferably part-time) or Honours student. Some experience in biostatistics and data analysis is essential and a background in epidemiology and/or an interest in cancer are highly desirable*

#### BACKGROUND

The use of complementary therapies by cancer patients is common but contentious, particularly during chemotherapy. Survivors often use complementary medicine in the hope it will improve their wellbeing,

alleviate chemotherapy side effects, boost immune function, and perhaps improve their long-term survival. There is little information about the use of complementary and alternative therapies by women with ovarian cancer, if/ how this changes after their cancer diagnosis, what women use during treatment or how this might affect their wellbeing and, ultimately, their survival.

#### AIM

To document the prevalence of use of complementary and alternative therapies by women with ovarian cancer, changes in use after diagnosis, and the relation between use and wellbeing and survival.

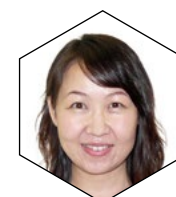
#### APPROACH

This project could include some/all of the following components:

- (i) A literature review of the current evidence.
- (ii) Descriptive analyses of what women use and how this changes from before diagnosis to during treatment, after treatment and after recurrence.
- (iii) Analysis of factors associated with use or that predict changes in use.
- (iv) Analyses of the relation between use, symptoms and side-effects, and wellbeing.
- (vi) Analyses of the relation between use and survival.

Analyses will use individual-level data from women in the OPAL study who provided information about complementary and alternative therapy use before and after diagnosis (3-monthly for the first year then annually to 4 years).

### Using Mendelian Randomisation to investigate the associations between dietary exposures and risk of ovarian and endometrial cancer



**Co-Supervisor:**  
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*Suitable for a Masters (preferably part-time) or Honours student. Some experience in biostatistics and data analysis is essential and a background in epidemiology and/or an interest in cancer are highly desirable*

#### BACKGROUND

Endometrial cancer and ovarian cancer are the most common gynaecological cancers other than cervical cancer among women in high-income countries. Observational studies have evaluated some potentially modifiable factors including physical activity and some dietary components (e.g. coffee, mono-unsaturated fatty acid, calcium, vitamin B/C, iron, selenium and zinc) in the causation and survival of these gynaecological cancers, but data have been either limited or inconsistent. However, observational studies may not provide robust evidence of causality as it is often vulnerable towards confounding bias, reverse causation and/or measurement error. Mendelian randomization (MR) is an analytic approach that can mitigate these problems using instrumental variables constructed from genetic variants to provide insights into causality. Subject to specific mathematical assumptions, analyses using germline genetic variants as instrumental variables are less susceptible to biases from confounding and reverse causation as the allocation of these germline variants cannot be influenced by later-year lifestyle and environmental factors. This property allows specific risk factors/exposures to be proxied via genetic predisposition (e.g. genetically predicted coffee intake can be estimated through the aggregation of alleles associated with increased daily coffee intake in large genetic studies) which can be used to infer causality between risk factors (e.g. coffee intake) and the outcome. Findings from MR can help re-prioritise resources toward trials of the most promising interventions. This project will apply various MR techniques in large population-based studies and biobanks to investigate the relationship between potentially modifiable factors and ovarian and endometrial cancer outcomes.

## Cancer Control Group



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Research undertaken by the **Cancer Control Group** is conducted with a view to reducing the burden from cancer through identifying risk factors, then translating



these research findings into policy and practice. This includes research to identify the environmental and genetic factors that cause cancer, as well as research into early diagnosis, treatment and survival.

The group has two major areas of research focus: melanoma and skin cancer, and upper gastrointestinal neoplasia.

### QSKIN: the burden of skin cancer



**Supervisor:**  
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#### Suitable for Masters and PhD students

The QSkin study is a longitudinal cohort study established with the primary aim of deriving measures of absolute and relative risk for basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and melanoma associated with phenotypic, genetic, clinical, and environmental factors. Secondary aims were to estimate the burden (treatments, hospitalisations, direct and indirect costs, mortality etc.) of skin cancer; quantify the effects of protective behaviours; and develop tools for predicting risk of melanoma and other skin cancers. The cohort was established in 2010 and comprises of 43,794 men and women aged 40-69 years sampled randomly (in strata of age and sex) from the Queensland Electoral Roll. Participants completed a baseline survey and gave consent for record linkage to the Queensland Cancer Registry (QCR), Medicare (MBS/PBS), pathology providers (private and public) and the Queensland Hospital Admitted Patient Data Collection. These linkages ensure virtually complete follow-up of all clinical events in the cohort. In 2015, 18,000 participants provided a saliva sample and these have been genotyped on the Illumina Global Screening array.

We are seeking highly motivated PhD students with experience in data analysis who are interested in undertaking a project related to skin cancer. These may include (but are not limited to):

- Health services research.
- Pharmaco-epidemiology.
- Mendelian randomisation (MR) analyses.
- The genetics of multiplicity (i.e., susceptibility to many tumours).

- Gene/environment interactions in the aetiology of skin cancer.
- Dietary/lifestyle factors in the aetiology/prevention of skin cancer.

## Cancer Aetiology and Prevention Group



**Group Leader:**  
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The **Cancer Aetiology and Prevention Group** focuses primarily on understanding the health benefits of vitamin D supplementation, balancing the risks and benefits of sun exposure and reducing the impact of pancreatic cancer.

### Reducing diagnostic delay in patients with pancreatic cancer

#### Suitable for Masters and PhD students

Pancreatic cancer is difficult to diagnose and many patients describe diagnostic delay. However, the extent, causes and consequences of diagnostic delay in Australia are not well understood. This project will involve interviews with patients and their families, along with analyses of linked data, to explore this issue and devise potential methods to optimise the diagnostic journey for Australian patients.

### Understanding variability in management of patients with pancreatic cancer

#### Suitable for Masters and PhD students

Patients with pancreatic cancer have poor outcomes, and there is evidence that some patients do not receive optimal care. We have established a data linkage platform that will enable students to examine variability in care, factors associated with suboptimal care, and associations between care and survival.

### Balancing the risks and benefits of sun exposure: communicating a complex message

#### Suitable for Honours, Masters and PhD students

The sun has risks and benefits for health. It causes skin cancer and eye diseases, but also produces vitamin D and has other benefits. Finding the balance is challenging, and it is not the same for all people. This project will work with communications experts and implementation scientists to develop methods to help people make informed decisions about their sun exposure.

## Supportive Care in Cancer Group



**Team Head: Associate Professor**  
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The **Supportive Care in Cancer Group** conducts research aimed at improving the management and quality of life of cancer patients and their family carers. Our work spans across many tumour streams with a focus on more vulnerable groups including those people affected by pancreatic, ovarian and brain cancers as well as parents of children with cancer. We use person-centred approaches to determine the supportive care requirements of patients and carers across all phases of the care continuum, from diagnosis to death or bereavement. We also conduct comprehensive evaluations to identify the most promising interventions and models of care, and trial new innovative support interventions.

### PROPCare: Practice Of supporting Partners and family Carers: They are not our patients – a system failure or not?

#### The project would be suitable for an Honours, Masters Dissertation or PhD student

In hospitals, patients are the focus of care, they have a UR number and hospitals can bill for their care; this is not the case for carers. Family carers of patients with pancreatic cancer are confronted with the need to assist in the management of complex physical symptoms. Additionally, they face the impending loss of their loved one and are twice as likely to experience anxiety as the patients they cared for. Best practice supportive care delivery for cancer carers includes having a protocol for supportive care needs assessment and referral pathways, conducting needs assessment periodically using carer-specific validated questionnaire, and developing a supportive care plan. This project will involve interviews with oncology staff and/or primary care practitioners to gain insights into supportive care screening and the support interface between acute and primary care of this population.

### PARTING: Psilocybin-Assisted supportive psychotherapy IN the treatment of complicated Grief

#### The project would be suitable for an Honours or PhD student in the field of psychology or psychiatry

While grief is a normal reaction to loss, 30% of cancer carers are reported to experience prolonged grief disorder. Patients with prolonged grief require grief-focused intervention in addition to the depression-focused treatment. Several landmark double-blinded randomised controlled trials have shown one or two doses of the psychedelic drug psilocybin administered along with supportive psychotherapy can produce profound, rapid and enduring mental health benefits in terminal cancer patients with anxiety and people with treatment-resistant depression. This will be the first trial specifically looking at psilocybin-assisted psychotherapy for prolonged grief. The aim is to determine whether this new treatment is acceptable to and safe for participants and to establish an initial impression of its effectiveness in treating people with prolonged grief. The project collects both qualitative and quantitative data on a range of outcomes and can be tailored to the students' interest and skills. It will involve analysis and write-up of publications, and potentially some qualitative interviewing.

## Molecular Cancer Epidemiology Group



**Group Leader: Associate Professor Amanda Spurdle**

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The **Molecular Cancer Epidemiology Group** studies breast and ovarian cancer, endometrial cancer, colon cancer and prostate cancer, with a focus on identifying molecular signatures of normal and tumour tissue that can point to the genetic and environmental causes of these cancers. The laboratory covers a range of projects with the themes of cancer epidemiology and molecular pathology.

### Evaluation of variants in known or candidate high-risk cancer genes



**Co-Supervisor: Dr Aimee Davidson**

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Can be adapted in scope for Honours or PhD

### BACKGROUND

Panel gene testing is increasingly applied to identify the underlying genetic cause of cancer in patients with suspected hereditary cancer. Identification of a pathogenic variant directly influences clinical management for patients and their at-risk relatives, setting the path for preventative and increasingly chemotherapeutic options. Unfortunately, such testing often identifies variants with uncertain impact on function and clinical phenotype. Such variants of uncertain clinical significance create considerable difficulties for counselling and clinical management. A range of methods can be useful for assessing variants, including bioinformatic analysis, assays of mRNA and protein function, and also investigating association with clinical features such as segregation in families, age at onset /phenotype in case-control studies and tumour pathology.

### AIM

To use statistical and laboratory methods to assess the clinical relevance of rare cancer gene sequence variants identified by clinical genetic testing of patients with suspected hereditary cancer, identified in Australia or through the international consortia such as ENIGMA.

### APPROACH

This project will assess the effect of variants on gene/protein function using a variety of bioinformatic predictions, molecular biological assays and/or statistical analyses. Techniques may include RNA analyses using LCLs and/or constructs, protein assays in collaboration with other laboratories, pedigree analysis and simple statistical analyses of clinical factors predictive of pathogenic variant status, to develop calibrated measures of association with disease for use in multifactorial likelihood analysis.

### OUTCOME

Analysis of specific variants will provide evidence regarding their pathogenicity for translation in the clinical setting. Comparison of assay results with risk will form the foundation for improving bioinformatic prediction tools and incorporating predictions and/or biological assay results in statistical models of risk prediction.

### Evaluation of pharmacogenomics variants from genome sequencing data

Honours and/or flexible for clinical students

Despite demonstrated clinical utility and continual decreases in sequencing costs, pharmacogenomics testing in Australia is limited. Although carrier rates vary, it is estimated that up to 99% of individuals tested will carry at least one actionable pharmacogenomics variant. The project will aim to identify pharmacogenomics variants from the next-generation sequencing data of predominantly individuals presenting for clinical genetic testing relating to their cancer diagnosis. This project will also make use of large public repositories such as: ClinVar, gnomAD, LOVD. Candidate variants may include those affecting human leukocyte antigen (HLA) sensitivity, drug metabolism, and/or drug targets. A basic understanding of R and/or Python is preferred.

## Genetics & Computational Biology Department

### Statistical Genetics Group



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The **Statistical Genetics Group** studies the role that genetic variation plays in determining risk of disease and its risk factors. The laboratory develops and applies statistical genetic methods to gene mapping studies across a wide range of traits and diseases.

One major focus is understanding genetic and epigenetic variation in various cancers. Cancers studied include melanoma, ovarian cancer, breast cancer and oesophageal cancer. Ultimately, this work will lead to a better understanding of why particular individuals are affected by cancer or why they respond poorly to a cancer treatment.

Another major interest is ophthalmological genetics, with work ongoing to identify the specific genes involved in both eye disease and in underlying quantitative risk factors.

### Evaluating the present state of genetic research in diverse populations



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This project is suitable for PhD students only. Some experience in biostatistics and data analysis is essential, and a background in epidemiology, health economics, and/or public health is highly desirable. It is important to note that this project involves communicating research findings to external stakeholders and people from different cultural backgrounds. Therefore, demonstration of strong interpersonal skills will be highly desirable.

### BACKGROUND

Genomics research is an important field that can provide insights into the genetic underpinnings of human diseases and inform personalized treatments. However, there is a growing recognition that genomics research has not been conducted equitably across diverse populations. The historically Eurocentric bias in genomics research has resulted in a lack of representation of non-European populations in important genetic discoveries. This has significant implications for health equity and precision medicine, as genetic variations can impact disease susceptibility and response to treatment differently across populations. Therefore, it is crucial to address the factors that drive disparities in genomics research on diverse populations.

### AIMS

This project aims to examine the opportunities and challenges for conducting human genetic research on age-related disorders in diverse ancestries. This includes identifying factors related to the implementation of state-of-the-art statistical genetics, understanding the dynamics of data transfer versus knowledge transfer in genomic research, and identifying common as well as unique challenges generating disparities in research capacity in various communities with diverse ancestries.

### APPROACH

The candidate will be trained to work on multi-ancestry genetic data through various applications in age-related human diseases using readily available datasets and upcoming resources. They will then examine both technical and non-technical aspects (perception of utility, culture, policy, and people) influencing the adoption of genetic research in various regions, using a wide range of research methodologies. This project is highly collaborative in nature and will involve working with other stakeholders of science, including health economists, policymakers, patients, and healthcare professionals, to validate research assumptions and derive equitable solutions. One tangible goal of this project is to develop a framework to guide capacity building for genetic research in communities of diverse ancestries.



## Genetics of skin cancer



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Suitable for Masters and PhD students. The post is suited to someone with an undergraduate or Master's degree in genetic epidemiology, epidemiology, statistics or bioinformatics. Experience in the analysis and manipulation of large datasets and a good knowledge of computing is desirable. Experience in cancer genetics and/or molecular biology is advantageous but not essential. Non-statistical applicants must be able to demonstrate some knowledge of statistics. For applicants with a background solely in statistics, some knowledge of genetics is desirable.

### BACKGROUND

Genetics, together with sun exposure, play an important role in the development of skin cancers. Our lab studies both melanoma and the keratinocyte cancers basal cell carcinoma and squamous cell carcinoma. Melanoma is the deadliest skin cancer and is responsible for >1,900 deaths a year in Australia. While keratinocyte cancers are rarely deadly, their high incidence still results in ~600 deaths a year, and that same high incidence means overall they are the most expensive cancer in Australia (> \$500 million p.a.). The goal of this project is to dissect the genetics of skin cancers and work out how we can use this information to improve health outcomes.

Our resources include large cohort studies based at QIMR Berghofer, including the Queensland Study of Melanoma: Environmental and Genetic Associations [1], the Queensland Twin Registry [2], and the QSkin Sun and Health Study [3] with genetic data on over > 40,000 people across the cohorts. Through access to large public datasets like the UK Biobank and international collaborations, we have data linking genetics to skin cancer risk for over 800,000 people [4,5]. Through this large resource, we are able to dissect the genetics of skin cancer and their risk factors like pigmentation, tanning ability, and mole count.

### AIMS

- To use computational statistics approaches to dissect the genetics of melanoma, keratinocyte cancers, and their risk factors.

- To use this genetic information in risk prediction models and to identify factors important for outcome and prognosis.
- To use this genetic data to understand how genetic differences cause skin cancer.

### APPROACH

The project will focus on characterising the role of germline genetic variation in skin cancer. Genome-wide genetic information will be married with data on cancer susceptibility traits and cancer outcomes<sup>4,5</sup>. The overlap of skin cancer and its risk factors will be used to identify new genetic risks common to all traits<sup>6</sup>. Fine-mapping, bioinformatics, and post-GWAS approaches (e.g., gene-based tests) will be used to fully interpret identified genetic variants<sup>5</sup>. The resulting genetic data will be used to develop prediction models and these models will be calibrated against in house datasets such as QSkin to determine how they can best help predict risk of skin cancer<sup>7</sup>. Mendelian randomisation will be used to determine if potential risk factors associated with skin cancer are causal<sup>8</sup>.

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## Eye disease genetics



**Co-Supervisor: Associate**  
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PhD students only. Suited to someone with an undergraduate or Master's degree in genetic epidemiology, epidemiology, statistics or bioinformatics. Experience in the analysis/ manipulation of large datasets and a good knowledge of computing is desirable. Experience in ophthalmic genetics advantageous but not essential. Nonstatistical applicants must be able to demonstrate some

knowledge of statistics. For statistical applicants, some knowledge of genetics is desirable.

### BACKGROUND

Glaucoma is the leading cause of irreversible blindness worldwide. While there is no cure once visual loss occurs, progressive visual loss and blindness can usually be prevented by timely treatment. This means early detection is vital. Unlike many other common complex diseases, the heritability of glaucoma is very high (70%) and traditional epidemiology studies have not identified any means by which risk can be decreased (e.g. via modifiable risk factors). The major role of genetic factors in glaucoma make understanding the molecular mechanisms fundamental to improve screening and develop better therapies. Although we have developed genetics based risk prediction tools for glaucoma, we have shown there is scope to improve them.

### AIM

To develop improved risk prediction tools for glaucoma based on genetic data. To translate these genetic findings into improved screening for the disease. Particular sub-aims of interest include examination of population subgroups where risk is unusually high due to for example family history and/or the presence of high penetrance rare risk variants. The project may also consider gene-mapping and prediction analysis for other eye diseases.

### APPROACH

We already have custody of very large-scale genetic data sets (genome wide association studies, exome/genome sequencing), with further data nearing completion. The student will employ a range of statistical genetic approaches to interrogate these data and to determine the genes and pathways underlying glaucoma and use these in prediction models.

# Infection and Inflammation Program

**Our world-leading Infection and Inflammation Program develops drugs and vaccines, along with prevention and education strategies to tackle globally important diseases caused by viruses, bacteria and parasites, as well as systemic chronic inflammation.**

We have a distinguished history studying viruses, gained over many decades, and use this knowledge to develop and deliver new treatments as well as cellular therapies for cancer and diseases of the central nervous system.

Our specialist labs have an international reputation in malaria volunteer infection studies and test new anti-malaria drugs for deployment in the developing world.

We have a strong record in vector control and work on innovations in mosquito surveillance and measures to interrupt pathogen transmission, and deliver a strong helminth control program resulting in major public health gains.

Our research programs have been adapted to rapidly respond to the COVID-19 pandemic with the Institute establishing a highly secure facility to grow the SARS-CoV-2 virus and test new drugs, vaccines and treatment options.

The Institute has a dedicated scabies lab which does vital work into the skin infestation that largely effects our indigenous population.

New drugs have been developed by our researchers using tissue organoids that can prevent and/or reverse the effects of chronic inflammation on the heart, lung, brain and skin.

There is also a focus on new treatments for liver disease and gut health, particularly its relationship to childhood diseases.

## Immunology and Infection Group



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The **Immunology and Infection Laboratory** studies host immune responses during malaria and leishmaniasis. Its aim is to distinguish anti-parasitic host immune responses that control infection from those that cause disease.

The laboratory uses experimental models, as well as samples from patients and human volunteers deliberately infected with parasites for their research. Particular interest is on understanding how T cells influence anti-parasitic immune responses.

The long-term goal of research is to develop better vaccines and therapies to prevent and treat infectious diseases.

### Characterising CD4+ T cell responses during parasitic infections

**Suitable for PhD or Honours students**

Inflammation is a complex biological response of the body to injury, infection or other harmful stimuli. It is a protective mechanism that helps to remove the cause of injury and initiate the healing process. Immune regulation refers to the mechanisms that control inflammation to ensure that it functions properly and does not cause damage to the body's own tissues. The immune system has a delicate balance between being responsive to pathogens and harmful invaders, while also avoiding overreaction or autoimmunity.

CD4+ T cells play critical roles in coordinating immune responses and differentiating into functional subsets best suited to control pathogen growth, as well as controlling resulting inflammation. We hypothesise that the composition of anti-parasitic CD4+ T cells subsets that develop during parasitic infection determines the outcome of disease. Furthermore, CD4+ T cell subset composition can be manipulated to improve vaccine and drug efficacy to establish long-term immunity.

## AIMS

To test this hypothesis, we will address the following aims:

1. Define CD4+ T cell molecular and phenotypic signatures associated with parasite control.
2. Develop strategies to modulate CD4+ T cells to improve their anti-parasitic functions.
3. Test host-directed strategies in pre-clinical disease models and primary human CD4+ T cells.

## Inflammation Biology Group



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The **Inflammation Biology Group** has developed, refined and characterised a number of mouse models used to gain new insights into the factors that regulate viral infection and inflammatory disease. The models are also exploited for collaborative research and development with industry to test potential new interventions (e.g., vaccines, anti-inflammatory drugs, anti-viral agents).

The group has over 25 years of activity in improving our understanding of the immunopathogenesis of the diseases caused by arthritogenic alphaviruses such as chikungunya virus and Ross River virus. We have also developed mouse models of Zika virus (foetal brain infection and testes damage) and Yellow fever virus liver pathology, which have been used in the development of vaccines and characterisation of pathogenic determinants.

Very recently, we repurposed a PC3 laboratory and have started to undertake research into SARS-CoV-2 and COVID-19 using transgenic hACE2 mice.



## Establishing and characterising mouse models of long-COVID for intervention testing



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Suitable for Honours or PhD students

### BACKGROUND

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has sparked an unprecedented global quest for vaccines and treatments. Key to such efforts are animal models of SARS-CoV-2 infection and COVID-19 disease. We have recently refurbished a state-of-the-art PC3 facility at QIMR Berghofer MRI for SARS-CoV-2 research and have established a number of mouse models of infection and acute disease. Long-COVID is now well recognised, with a range of sequelae described that are primarily associated with pulmonary, neuropathic, and cardiac symptoms. While long-COVID is well-recognised, immune mechanisms are less understood, and there remains a lack of targeted therapies.

### AIM

The project will involve establishing and characterising several different mouse models of long-COVID, and exploiting them to determine viral and immune mechanisms of disease. Once mouse models of long-COVID are established and characterised, the project will involve collaborations with academics and possibly industry partners to evaluate a range of potential interventions. Risk factors, such as obesity, diabetes, and iron deficiency, will also be investigated.

### METHOD

The project will involve animal handling, virological assays, histology and RNA-Seq and will be supported by a team of virologists and bioinformaticians. QIMR Berghofer requires and arranges that all staff working in the physical containment 3 (PC3) facility on SARS-CoV-2 are vaccinated.

## Uncovering and characterising new alphavirus and flavivirus host co-factors

Suitable for Honours or PhD students

### BACKGROUND

The global range of mosquito-borne diseases is already expanding, with climate change likely to exacerbate this trend. Over 10 million cases of chikungunya virus (CHIKV) infection have been recorded globally, and often manifests as debilitating polyarthralgia/polyarthritis (pain/inflammation in multiple joints) that can last months or years. The only available treatment targets pain and inflammation and there are no specific anti-viral treatments or vaccines approved for human use. CHIKV belongs to a group of globally distributed arthritogenic alphaviruses that include the Mayaro virus (MAYV), Getah virus (GETV), and Ross River virus (RRV) which records ~4600 annual cases in Australia.

### AIM

The project will focus on identifying new human co-factors for CHIKV replication, by exploiting a recent finding of a cell line where CHIKV replication fails. High-throughput technologies such as CRISPR/Cas9 and Whole Human Genome Lentivirus Open Reading Frame Pools will be exploited to identify new crucial CHIKV host factors. Follow up investigations including knockout mice, chimeric/mutant viruses, structure determination (i.e., cryo-EM, crystallography), antiviral screening etc. would be envisaged to fully characterise new virus-host interactions. A similar approach could be taken for Japanese Encephalitis Virus (JEV), the virus recently causing outbreaks in Australia.

### METHOD

The project will involve molecular biology, virological assays, and animal handling, and will be supported by a team of virologists and bioinformaticians. QIMR Berghofer requires and arranges that all staff working in the physical containment 3 (PC3) facility on JEV are vaccinated.

## Translational and Human Immunology Group



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Adoptive cell therapy (ACT) has become one of the most powerful immunotherapy tools for the treatment of cancer and infectious diseases. ACT is often used as a last-line therapy but has expanded in recent decades to encompass the use of highly specific targeting strategies, such as chimeric antigen receptor (CAR) T cells in addition to the more traditional expansion of highly specific endogenous T cell clones. Globally, ACT has revolutionised the treatment of blood cancers and is now approved for clinical application in multiple countries.

The **Translational and Human Immunology Group** is focused on identifying novel targets for disease and transitioning this research into novel therapies that target a range of viral diseases in humans. A major goal is to increase our understanding of what T cell attributes contribute to improved control of cancers and infectious disease in the body. We then aim to translate these findings into the provision of adoptive T cell therapies with better efficacy and potency to ultimately enhance patient outcomes in the clinic.

### Modeling viral-associated diseases to improve adoptive T cell outcomes



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This project would be highly suitable for a motivated PhD candidate. However, aspects of this project work could also be refined for a full-time Honours or Masters student project

Epstein Barr Virus (EBV) infects around 95% of the global population and establishes lifelong persistence in

patients through the latent infection of otherwise healthy B cells. While this persistent infection is asymptomatic in most people, EBV has been linked to a range of human cancers and in addition, has an aetiological role in the development of the autoimmune disease, Multiple Sclerosis.

In recent years we have developed a humanized animal model of EBV-driven disease that enables us to examine the infection, trafficking and therapeutic targeting of human EBV-infected B cells within a functional murine in vivo setting. Here, we are particularly interested in the ongoing development of laboratory techniques that expand our understanding of the interplay between ACT and the control of disease burden in vivo, including the development of new strategies to interrogate whether specific T cell signatures facilitate the preferential homing of ACT to distinct anatomical sites in the body.

The scope for this project is broad and will provide ample opportunity for the development of laboratory techniques including microscopy and/or live cell imaging, T cell sequencing and viral transduction.

## Tumour Immunology Group



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The major goal of the **Tumour Immunology Laboratory** is to obtain a deeper understanding of the mechanisms by which an immune response to tumours may be generated, augmented and applied to the inhibition of tumour growth. The members of this laboratory share the expectation that such insight will be applicable to the treatment and/or prevention of cancer.

## Structural biology



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### Suitable for Honours and Masters students

Understanding the molecular mechanisms underpinning disease is crucial to the development of diagnostics, treatments and cures for diseases including cancer, immune disorders and infectious diseases.

In the Tumour Immunology laboratory, we utilise state-of-the-art structural biology techniques, including X-ray crystallography and cryogenic electron microscopy (cryoEM). This allows us to observe atomic-level detail of proteins and molecules of viruses and the immune system. It furthers our understanding of how viruses develop cancer-related sequelae and allow us to effectively design and tailor vaccines and treatments against these diseases.

Two main focuses of my research are: 1) to characterise novel, recombinant viral fusion proteins for use in vaccines for human cytomegalovirus (HCMV) and 2) characterisation of antibody binding to glycoproteins of Epstein-Barr virus (EBV) for use in immunotherapy against EBV and EBV-associated lymphomas.

Prospective students will learn a wide range of protein technology and structural biology techniques, including protein expression and purification techniques, chromatography, multi-angle light scattering, mass photometry, small-angle X-ray scattering, X-ray crystallography, negative-stain electron microscopy and cryogenic electron microscopy.

## Thinking outside the box: Novel strategies to treat viral infections and cancers



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### This project is suitable for Master or PhD students

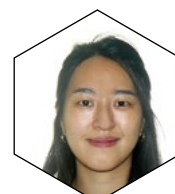
The control of viral infections and cancers is reliant on a functioning and organised immune system. However,

uncontrolled virus replication and cancer growth result in immune dysfunction and lead to disease progression. This project aims to identify new targets, which have the potential to activate or rescue dysfunctional immune cells and increase their ability to fight the disease.

This work will utilise genetically modified mouse strains to study the role of specific molecules in regulating the function of immune cells (T cells and natural killer cells) and determine how they affect viral and tumour control. Promising molecules will be further studied in blood samples from patients as well as humanised mouse models, which are mice engineered to carry human immune cells. These molecules may be exploited for the development of novel immunotherapies or the improvement of existing immunotherapies to treat viral infection and cancer.

During this project, students will learn techniques in pre-clinical drug development, including animal handling and therapeutic avenues for drugs or adoptive cell therapy. They will also develop expertise in immunology methods, including cell culture, immune cell proliferation/activation/killing assays, flow cytometry and immunohistochemistry, in addition to molecular biology methods (e.g., PCR and RT-PCR). For PhD students, the project will also involve verifying immune mechanisms using humanised mice or patient blood samples.

## Adoptive T-cell therapy for HPV associated cancers



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### Suitable for PhD or Honours students

Long-lasting infections with high-risk human papillomavirus-16 (HPV16) can cause epithelial cancers, which include squamous cell carcinomas (SCC) and adenocarcinomas of the cervix, oropharynx, anus, vulva, vagina, and penis. Oncogenic HPV virus accounts for approximately 600,000 cases worldwide every year and advanced HPV-associated cancers are generally incurable and resistant to chemotherapy. However, T cell receptor (TCR)-based adoptive T cell therapies (ACT) hold great promise for the treatment of HPV associated cancer, targeting viral antigens which are absent in healthy tissues, making them attractive targets for genetically engineered T-cell therapy. We have been working on the oropharyngeal cancer patient's samples and identified

HPV16 antigens specific high-avidity CD4+ and CD8+ TCRs directed against different HPV16 antigens by single cell TCR sequencing.

### AIMS

- Functional characterisation of HPV specific transgenic TCR T cells, which involves assessing the in vivo efficacy by real time killing assay (Xcelligence assay) and flow cytometry and ex vivo efficacy using HPV xenograft mice model.
- Adoptive therapy with ex vivo-expanded genetically modified antigen-specific T cells, which can induce remissions in patients with relapsed/refractory cancer. The clinical success of this therapy depends upon efficient transduction and expansion of T cells ex vivo and their homing, persistence and cytotoxicity following reinfusion. This focuses on the use of different cytokines and metabolic checkpoint inhibitor or epigenetic regulator in ex vivo culture to further enhance the efficacy and quality of genetically modified HPV-specific T cells.

This project involves characterisation of HPV16 specific transgenic TCR T cells and standardisation of culture conditions to further improve their effectiveness and applicability.

## Cellular immunotherapy – engineering “custom built” cells to treat cancer



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This project is suited for a Master's or PhD work and is flexible for clinical students.

### BACKGROUND

Current standard approaches for the treatment of human cancers typically employ broad acting radiotherapeutic and chemotherapeutic approaches. There has been growing interest in approaches using immunotherapy with adoptive cell transfer (ACT): using patient's immune cells to treat their cancer. A specific type of ACT uses chimeric antigen receptors (CARs). These are genetically engineered molecules, which are custom built to specifically target protein antigens expressed on malignant cells. There are three FDA-approved CAR T cell-based therapies targeting CD19 on certain B-cell malignancies. CAR19 treatment, of children with relapsed

or refractory acute lymphoblastic leukaemia (ALL), and of adults with advanced lymphomas, has demonstrated remarkable success and complete remission in some patients. Although approved therapies are limited to blood cancers, a growing number of CAR T-cell therapies are being developed and tested in clinical studies in multiple solid tumours. There are promising clinical data targeting tumour-associated antigens in melanoma, lung, liver, breast, and brain cancers.

There are major differences between CAR therapies, mostly at the tumour-antigen recognition site, but CARs share similar components known as signalling domains that can affect the cells' overall function, such as their ability to produce more cells after infusion into the patient (expansion), and to survive longer in circulation (persistence). The ability to manipulate these domains to custom build CAR T cells to specifically target certain tumours, and avoid toxicity, is critical for the success of CAR T cell therapy.

### AIM

The CAR T cell program at the Tumour Immunology Laboratory aims to design and test novel CAR T cell therapies for virus-associated cancers. We have designed a CAR T cell, which targets a glioblastoma (GBM)-specific antigen A3 that is being tested for the treatment of GBM, an aggressive form of brain cancer. In our clinical trial of ACT to treat GBM (1) we identified a distinct T cell expression signature associated with potency and favourable long-term survival in GBM patients. This project will use this knowledge and expand the potential of the A3-specific CAR T cell product. We will customise the signalling domains to engineer a CAR with a similar expression signature to that of T cells with known GBM-killing potential. We will ultimately build a CAR better suited for the treatment of GBM.

### METHOD

The student will learn *in vitro* molecular and cell biology techniques involving gene cloning, non-viral transfections, lentiviral transductions, cell phenotyping using flow cytometry and NanoString technology. For a PhD student the work will also involve in vivo study in murine xenograft models of GBM to test the efficacy of the custom-built CAR T cells.



## Hepatic Fibrosis Group



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The **Hepatic Fibrosis Laboratory** investigates the cellular and molecular mechanisms of liver injury, scar tissue formation (fibrosis) and regeneration in chronic liver disease. If left untreated, uncontrolled fibrosis leads to cirrhosis and liver cancer in adult liver diseases such as haemochromatosis, viral hepatitis and non-alcoholic fatty liver disease, and in children in diseases such as cystic fibrosis and biliary atresia.

### MicroRNAs as anti-fibrotic agents to treat liver scarring, fibrosis and cirrhosis in chronic liver disease

Project can be adapted to suit Honours, PhD, or clinical students

Virtually all biological processes in eukaryotic cells are regulated by microRNAs that control protein-coding gene expression. Our laboratory has identified a number of different microRNAs that regulate the expression of collagen in liver disease and that can be manipulated to control liver scarring or fibrosis. This project is designed to generate novel, chemically modified microRNAs that can be used as anti-fibrotic therapeutics to treat hepatic fibrosis and thus control the development of cirrhosis and liver cancer in patients with chronic liver disease.

### Anti-inflammatory small molecule inhibitor development to control liver inflammation associated with hepatic fibrosis in chronic liver disease

Project can be adapted to suit Honours, PhD, or clinical students

Inflammation is integral in driving early liver scarring (fibrogenesis). The association between hepatic inflammation and circulating ferritin levels in chronic liver disease is well known. However, rather than simply acting as a marker of inflammation, our research has demonstrated that the H-subunit of Ferritin (FTH),

released upon hepatocellular injury, actually mediates inflammation. This project will utilise state-of-the-art molecular modelling techniques to identify FTH binding sequences on cell surface receptors we have identified on liver fibroblasts that signal to the nucleus to proinflammatory cytokines. Therapeutic small molecule inhibitors will then be developed to treat chronic liver disease-inducing hepatic inflammation.

## Iron Metabolism and Molecular Nutrition Groups



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The **Iron Metabolism Laboratory** studies a wide spectrum of iron-related issues from basic mechanisms of iron homeostasis to disorders of iron metabolism. We are particularly interested in iron nutrition, diseases of iron loading (haemochromatosis, thalassaemia) and the effects of iron on other conditions. To do this, we integrate genetic and molecular studies with biochemical and physiological approaches. Much of our recent research has been based on understanding mechanisms of cellular iron transport and the way in which these processes are regulated. The ultimate goal of our work is to improve the diagnosis and treatment of iron related disorders. A second major interest of our group is the use of nanotechnology to deliver drugs to treat iron loading disorders and other conditions, such as cancer.



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In the **Molecular Nutrition Laboratory**, we are working hard to understand the molecular basis of iron-related conditions such as iron deficiency and the iron loading

disorder hereditary haemochromatosis, both of which affect a surprisingly high number of Australians. We want to develop better treatments for affected individuals. Iron is a nutrient that is essential for the growth and development of infants and children. It is necessary for healthy red blood cells, which move oxygen from the lungs throughout the body. Iron deficiency during development can leave a permanent, life-long burden. Not only does it stunt growth and leave the child with a lack of energy, but also it can permanently impair brain function. Having too much iron in the body can create another set of problems. One of the unexpected symptoms of haemochromatosis is early-onset arthritis.

### Developing improved methods for assessing iron status

Projects can be adapted to suit Honours or PhD student

#### BACKGROUND

An adequate supply of iron is essential for normal health, and disturbances in iron metabolism represent a significant class of human diseases. Biochemical tests for measuring iron status are among the most frequently requested by doctors, but current methods for measuring body iron levels are far from ideal. The main limitation is that the tests for measuring body iron are also influenced by inflammation. A good example of this is the serum ferritin test. As the incidence of obesity rises in our population, we are seeing more and more instances of high serum ferritin that are not related to high body iron. This is because obesity is an inflammatory condition. While correction of iron status markers for inflammation can be carried out, this is not always reliable and requires multiple tests to be conducted.

#### AIM

The major goal of this project is to seek one or more robust and reliable markers of iron status that are not influenced by inflammation. A secondary goal is to develop a point of care assay based on this (or these) molecules.

#### APPROACH

This project will consist of two main components. The first will be the discovery phase and will be carried out using mice. This will enable us to precisely control conditions so that we can distinguish between iron-related effects and those caused by inflammation. Plasma samples will be collected and analysed using a contemporary proteomics approach to seek differences between the various conditions. Depending on the initial results, we may also extend this to analyse the plasma metabolome. We will

identify molecules that are influenced by iron status, but show little or no variation in response to inflammation. In the second part of the project, we will validate our findings by developing assays (likely immunoassays) for the molecules of interest and test them against a bank of human plasma samples taken from individuals whose iron status has been well characterised using conventional tests. If time permits, we will optimise the assay for the most promising molecule with a view to developing a low-cost point of care assay for iron status that requires only very small volumes of blood.

### The effect of iron supplements during pregnancy

Projects can be adapted to suit Honours or PhD student

#### BACKGROUND

Adequate dietary iron intake is vitally important during pregnancy as the consequences of iron deficiency at this time can be severe. Complications can include pre-term delivery, intrauterine growth restriction and irreversible neurological damage in the developing infant. With a recent study suggesting that, a staggering 60-70% of pregnant women in Australia are iron deficient, it is not surprising that oral iron supplements are widely consumed. What is surprising, however, is that the effects of such supplements has not been well studied. While the benefits of supplementation on maternal iron stores and haemoglobin levels are well accepted, any benefit to pregnancy outcomes and foetal development is less evident. Many studies have shown little or no improvement in a range of parameters, including prematurity and birth weight. In addition, the supplementation of iron replete pregnant women has been shown to be detrimental to both maternal and infant health, increasing the risk of both preterm delivery and small for gestational age births. With iron deficiency affecting so many pregnant women, it is critical that we determine the cause of these effects so that optimal supplementation regimens can be implemented to reduce the prevalence of iron deficiency and maximise the health and safety of both mother and infant.

#### AIM

To investigate the effects of iron supplementation during pregnancy, with particular emphasis on the placenta and foetus.

**APPROACH**

Most of the studies to be carried out will use the mouse as a model, but some of the work will utilise human placental samples. Initial studies will use time mated mice to assess the response of the placenta and foetus to oral iron supplements based on ferrous iron. The effect on the offspring after birth will also be investigated. Subsequent studies will examine the potential benefits of alternative forms of iron supplementation.

**Targeting the ferroxidase hephaestin to treat iron loading disorders**

Projects can be adapted to suit Honours or PhD student

**BACKGROUND**

Iron overload diseases represent one of the largest groups of inherited disorders worldwide. The primary iron overload disorder HFE-related haemochromatosis is the most common autosomal recessive disease in humans, affecting 1 in 180 Australians and leading to liver cancer, dementia, diabetes and arthritis if untreated. Iron loading anaemias such as  $\beta$ -thalassaemia have equally devastating effects and are prominent in southern European, Middle Eastern and Southeast Asian populations. These two forms of iron loading share the common features of increased dietary iron absorption and macrophage iron recycling, both of which are secondary to reduced levels of the iron regulatory hormone hepcidin. Hepcidin acts by binding to the iron export protein ferroportin, reducing the amount of iron it delivers to the plasma. Ferroportin in turn requires a copper-dependent ferroxidase to export iron efficiently. It is this hepcidin/ferroportin/ferroxidase axis that is critical for body iron intake and distribution. While both hepcidin and ferroportin are being investigated as potential therapeutic targets for iron loading disorders, the essential ferroxidase component of this pathway has received little, if any, attention.

**AIM**

The goal of this project is to test the hypothesis that disrupting the activity of hephaestin, the main ferroxidase involved in dietary iron absorption, will alleviate the iron loading that occurs in haemochromatosis and  $\beta$ -thalassaemia.

**APPROACH**

Initial experiments will involve knocking out hephaestin in mouse models of haemochromatosis and  $\beta$ -thalassaemia to determine whether this enzyme is a suitable pharmacological target for treating these

disorders. Subsequent studies will involve establishing a high-throughput *in vitro* assay to allow the screening of compound libraries for potential inhibitors of hephaestin activity. Any “hits” will then be validated in tissue culture prior to testing in our animal models of disease.

**The regulation of body iron homeostasis**

Projects can be adapted to suit Honours or PhD student

**BACKGROUND**

Human conditions with disrupted iron homeostasis are very common and most centre around the inappropriate production of the peptide hormone hepcidin, which regulates body iron metabolism. Hepcidin is produced by the liver and secreted into the bloodstream where it acts as a negative regulator of intestinal iron absorption and storage iron release. Prominent examples of conditions associated with altered hepcidin production are hereditary haemochromatosis, the anaemia of inflammation and  $\beta$ -thalassaemia.

**AIM**

To investigate the pathways by which hepcidin production is regulated and to investigate ways to manipulate these pathways with the aim of treating diseases of iron homeostasis.

**APPROACH**

A range of techniques and models will be used to examine the regulation of hepatic hepcidin expression. The *in vivo* role of soluble forms of HFE and TFR1 will be determined using adenovirus-mediated overexpression in mice, as each of these molecules has the potential to modulate hepcidin production. Knockdown of hepatocyte SMAD6 and SMAD7 will be achieved using siRNA in mouse models of haemochromatosis and  $\beta$ -thalassaemia to determine whether inhibition of these molecules can modulate disease progression. Studies will also be carried out in cells in culture, including an in-depth analysis of the binding of soluble TFR1 to membrane bound HFE and factors affecting this interaction.

**Mucosal Immunology Group**

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The overarching theme of the **Mucosal Immunology Group** is to promote immune regulation in order to control inappropriate immune responses responsible for allergy and autoimmune diseases. We utilise experimental, preclinical, and computational approaches to develop novel therapeutic strategies that translate into preventative or therapeutic interventions.

**Prevention of allergy development in neonates by manipulating the microbiome**

This project is suitable for a PhD student.

Nearly one billion people globally suffer from allergies responsible for significant morbidity and reduced quality of life. Our group has discovered a process during the neonatal ‘Window of Opportunity’ that prevents allergy from developing later in life. We propose to understand the mechanisms that allow neonates to become resistant to allergen sensitisation. This project will allow us to develop a novel and revolutionary approach to the management of allergic diseases. We will use a combination of experimental and clinical resources to address the role of the immune cells populating the gut and gut-associated tissues, which will be visualised by flow cytometry and fluorescence imaging. We will use techniques like metagenomic sequencing, metabolomics and proteomics to determine the interaction between the microbiome – intestinal epithelium – immune cells.

**Hookworm-derived polypeptides for the treatment of chronic diseases**

This project is suitable for a Master, Honour or PhD student

We have discovered hookworm proteins and peptides able to modulate the immune response and protect against allergic and autoimmune diseases (like IBD and colitis). We are interested in developing these novel compounds into the clinics and determine how the proteins alter cellular function. Gut-resident dendritic cells are the primary target and epigenetic modifications are likely to occur. This project will use a range of immunological techniques (experimental models, flow cytometry, fluorescence imaging), proteomics approaches (mass spectrometry), and single cell sequencing / metabolomics to characterise the mechanism of action.

**Respiratory Immunology Group**

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The **Respiratory Immunology Laboratory** focuses on identifying pathogenic pathways that underpin the onset, progression, and exacerbations of asthma and chronic obstructive pulmonary disease. To achieve this, high-fidelity preclinical models of disease are developed that recapitulate key gene-environment interactions and allow for elucidation of cellular and molecular mechanisms. Where possible, scientific findings are translated with *ex vivo* model systems using primary human cells and by analysing clinical material.

**Insights into the influence of a maternal high-fat diet on infant susceptibility to severe lower respiratory tract infections**

This project is suitable for a Master, Honour or PhD student

Viral bronchiolitis is an infection of the small airways (bronchioles) characterised by the infiltration of



neutrophils, oedema, and shedding of the epithelial cells that line the airway. A recent population study found that the offspring of mothers who ate a poor diet in the third trimester were predisposed to severe viral bronchiolitis. We have modelled this association in mice, and established that the maternal diet affects the nascent microbiome in the offspring and associated immune development. This project will explore the cellular and molecular mechanisms by which the microbiome affects immune development and susceptibility to infection in the lungs.

**Understanding the mechanisms by which the assembling neonatal microbiome promotes neonatal immune development**

This project is suitable for a Master, Honour or PhD student

The microbiome is known to affect immune development. For example, germ-free mice have fewer Peyer's patches in the gut wall, suggesting that the gut microbiome regulates the formation of this lymphoid tissue. Other studies have shown that germ-free mice have fewer natural killer T cells. Both the microbiome and the immune system develop postnatally (predominantly if not exclusively), and there is considerable bi-directional crosstalk. In this project, we will study this relationship, with a focus on the seeding of innate lymphoid cells in mucosal tissues such as the gut and the lungs.

# Mental Health and Neuroscience Program

**Our Mental Health and Neuroscience research program is making a meaningful difference to thousands of Australians.**

The research is critical with about half of all Australians experiencing mental ill-health at some stage in their lives. It focuses on a range of mental health areas including anxiety, depression, ADHD, Autistic Spectrum Disorder, bipolar disorder, eating disorders, and schizophrenia.

Our neuroscientists, geneticists, epidemiologists and clinical researchers are devoted to developing treatments, finding the causes, and working out how to prevent these conditions.

This includes investigations into innovative neuro-stimulation and psychopharmacological interventions for people with serious mental disorders. Our understanding in the areas of psychiatric genetics, neuroimaging and neuroscience will inform novel strategies for prevention, early intervention and the treatment of complex syndromes.

Neurological conditions such as Parkinson's disease, multiple sclerosis (MS), motor neuron disease, epilepsy and dementia including Alzheimer's disease are a growing health issue in Australia, often with limited treatment options. Our researchers are providing a broad interdisciplinary expertise in advancing understanding of this area from infancy to the elderly.

## Psychiatric Genetics Group



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The **Psychiatric Genetics Group** focuses on investigating the genetic and environmental factors that influence mental health conditions and the impact of non-psychiatric conditions on mental health across the lifespan. The group also have a strong focus on the genetics of brain structure and on women's health.

### Assessing the cost and impact of Attention Deficit Hyperactivity Disorder in Australia

Project is suitable for PhD students only. The project will require a strong background in statistics and research methodology. Applicants with backgrounds in Psychology/Psychiatry, Statistics or Public Health are preferred.

#### BACKGROUND

ADHD (defined as an inability to focus, high levels of impulsivity and age-inappropriate hyperactivity) is the most prevalent childhood psychiatric disorder (affecting around 5% of children), with ~50% of those affected continuing to experience symptoms into adulthood. There is a high level of comorbidity with other psychiatric disorders and increased risks of incarceration, death and disability from suicide, car accidents and misadventure. Using data from the census ADHD study a new richly-phenotyped nationwide cohort of children with ADHD, this project will examine the cost and impact of ADHD on families and the community.

#### POTENTIAL PROJECTS

Potential sub-projects include

- Assessing the health service usage and financial costs of ADHD.
- Assessing the impact of ADHD on individual and family level psychological and social functioning.
- Assessing the level and types of side effects associated with ADHD medication.

Please note this is a dry lab analysis focused project.

### The role of genomics in understanding psychiatric and neurological disease

Project is suitable for PhD students only. Applicants with backgrounds in Psychology, Psychiatry, Statistics or Public Health are preferred.

Over the past decade, large-scale collaborative projects have significantly increased our knowledge and understanding of the genetic risk factors for mental health and neurological conditions across the lifespan.

Translation of genetic findings is usually conceptualised as a process involving the characterisation of implicated loci, identification of treatment targets, drug development and clinical trials. However, the accurate communication of the promises and limitations of new research findings is an essential part of research translation as is examining the utility of analytic techniques such as polygenic risk scores.

This project will focus on examining the ways genomic data could be used in clinical practice and the accuracy and specificity of these techniques. The project will require a strong background in statistics and research methodology.

Please note this is a dry lab analysis focused project.

### Health and wellbeing in people with bipolar disorder

Project is suitable for PhD students only.

Bipolar disorder is a lifelong and severe psychiatric illness characterised by recurrences of episodes of depression and hypomania or mania. Lithium is the first option in the pharmacotherapy of bipolar disorder. However, only one third of patients have a good response to this treatment, i.e., they often recover and remain well as long as they continue taking Lithium. The rest have a partial or deficient response.

QIMR Berghofer is part of an international effort to identify individual differences in Lithium response. We are collecting data across Australia on mental health, wellbeing and treatment response on bipolar disorder. We offer a project to analyse Lithium response in bipolar patients, comorbidity with other disorders and quality of life.

Please note this is a dry lab analysis focused project.

### Exploring the genetic basis of depression



**Co-supervisor:**  
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PhD or Honours project. Seeking a motivated student with experience in psychology, genetics, epidemiology or statistics for dry lab analysis focused project.

#### BACKGROUND

One in five Australians will be diagnosed with depression in their lifetime, and approximately one third of those will not respond to treatment. While some progress has been made in understanding the role genetics plays in risk of depression, there is still much more understanding needed to elucidate the biology of disorder. We are particularly interested in exploring whether genetics plays a role in how people experience depression and the extent to which genes may play a role in how people respond to treatment. This will encompass exploring depression features, such as age of onset, recurrence, and the differences in depression risk factors between males and females as well as treatment response variables such as medication efficacy and side-effects.

#### AIM

- Better understand how genes play a role in depression risk as well as depression features such as age of onset, recurrence etc.
- Assess whether depression treatment response traits are heritable.
- Identify genetic variants influencing these traits.

#### METHOD

We already have access to national and international large-scale genetic data sets (N=20,000 and N=500,000 respectively) which collected data on depression risk, features, medication response including efficacy, tolerability, and adverse side-effects as well as psychotherapy response. The student will employ a range of statistical genetic approaches such as, genome-wide association studies and polygenic risk scoring, to interrogate these data and to determine the genes and pathways underlying depression-related traits as well as explore the relationships between depression and other phenotypes.

### Statistical Genetic Analyses of Psychotic and Mood Disorders

PhD or Honours project. Seeking a motivated student with experience in psychology, genetics, epidemiology or statistics dry lab analysis focused project

#### BACKGROUND

Psychiatric disorders rank fifth in global causes of disease, contributing nearly 20% to non-fatal disease burden. Schizophrenia and bipolar disorder are associated with a substantial genetic risk, with genetic estimated to explain 60-80% of variability in these disorders. Although depression is less heritable, there are significant overlaps between these three disorders, with bipolar disorder often considered the intermediary between depression and schizophrenia. Schizophrenia, bipolar disorder, and depression have been shown to share genetic and biological factors that contribute to their development and course but as of yet the biological aetiology of these disorders is not clearly known.

#### AIM

This research project aims to further develop our understanding of psychotic and mood disorders through the lens of genetic analyses. By utilising a range of statistical techniques, this project can develop towards triangulating evidence from a variety of sources and explore biological mechanisms that are both shared and unique between these disorders.

#### METHOD

This project aims to use a variety of statistical genetic analyses, such as genome-wide association studies, polygenic risk scores, Mendelian randomization, pathway analysis and biological annotation. This project will utilise recent data from Australian medication-based recruitment studies conducted at QIMR Berghofer including the Australian Genetics of Depression Study (N=22,000), Australian Bipolar Genetics Study (N=5,000) and the currently recruiting Clozapine Study (schizophrenia). In addition, this research group are active collaborators within the Psychiatric Genetics Consortium (PGC) and have access to the largest available GWAS summary statistics for all three disorders.



## Identifying risk factors for problematic internet use and video gaming in Australian adults



**Co-supervisor:**  
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Suitable for Honours students only. This project is most suitable for students with a strong background in Psychology/Psychiatry and statistical analysis

The proliferation of computers, gaming consoles and widespread use of the internet in the last 15 years has resulted in the emergence of behavioural addictions to digital technology, namely the internet and video games, and the rise of cyberbullying. Pathological internet use and video gaming have been associated with mental health issues (such as anxiety and depression), increased rates of obesity, introversion, a high degree of loneliness, disrupted family relationships and academic problems. Similarly, victims of cyberbullying can experience significant emotional and physical harm as well as social isolation.

I have previously recruited a cohort of Australian adults who completed an online questionnaire in order to (i) identify risk factors associated with these behaviours, (ii) investigate the emotional and educational or occupational impacts of these behaviours, and (iii) examine the co-occurrence of these behaviours with other personality characteristics and psychopathologies such as substance use and mental health disorders.

I offer a project to analyse the collected online questionnaire data, and to provide the Honours student access to the online questionnaire in order for them to potentially recruit a second cohort.

## Clinical Brain Networks Group



**Group Leader:**  
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With the goal of progressing knowledge on brain disorders and evidence-based psychiatric therapies, the **Clinical Brain Networks Group** focuses on understanding how the structural and functional wiring of the brain underpin health and pathology. The lab uses a variety of neuroimaging, brain stimulation, and computational techniques. We are associated with the department of Genetics & Computational Biology at QIMR Berghofer. Our research is supported by philanthropic and government bodies including the National Health and Medical Research Council (NHMRC).

### Unravelling the secrets of the prefrontal cortex



**Co-supervisor:**  
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Suitable for PhD and Honours students

This project would suit students with a background in psychology, computer science or a related discipline, and an interest in computational neuroscience, with some experience in programming (e.g., in Python). The prefrontal cortex, located at the front of the brain, is responsible for various advanced cognitive processes observed in humans such as reasoning, problem-solving, and planning. Impairment in these abilities is observed across multiple psychiatric disorders, with impacts on day-to-day functioning of individuals. This project utilizes various tools including brain imaging (fMRI), brain stimulation, and brain modelling (artificial neural networks). By utilizing these tools, this project aims to gain deeper insights into the complex workings of the prefrontal cortex and its relationship to behavioural outcomes in individuals with psychiatric disorders.

There will be multiple applications depending on interests and abilities, for example:

- How does prefrontal cortex structure predict brain activations?
- How does brain stimulation perturb prefrontal cortex activity while performing a complex behavioural task?
- Can brain activations predict human intelligence?
- What are the limits of human reasoning behaviour?
- Can neural networks solve reasoning puzzles like humans can?

## Brain Modelling Group



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The **Brain Modelling Group** models and analyses brain structure and dynamics in health and disease. This work currently follows two major themes: developing new diagnostic methods for neonatal brain health and modelling large-scale brain activity across the lifespan.

In neonates, the group uses techniques from physics and machine learning to extract more information than ever before from intensive care monitoring of babies born prematurely. The goal is to enable early detection of injuries and early prognosis of developmental outcomes, so that clinicians can optimise care with personalised markers of brain health, potentially opening the window for new treatments.

On the modelling side, the group is harnessing the rapid developments in neuroimaging technology and connectomics to develop new mathematical models of brain activity, in particular at the spatial scales most relevant to human health. The goal is to fill in some of the large gaps in our knowledge of how neuroimaging brain signals emerge from brain structure, on how this relationship varies as we grow and age, and how things can go wrong leading to neurological and psychiatric disorders.

## Modelling brain dynamics across the lifespan

Suitable for PhD or Honours students. This project would suit students with a background in physics, maths, or a related discipline, and an interest in computational neuroscience, with some experience in programming (e.g., in MATLAB)

A major challenge for neuroscience is to understand how the brain's densely interconnected network of neurons—the “connectome”—gives rise to the rich repertoire of brain activity. The overarching aim of this project is to reveal how complex patterns of neural activity emerge from the connectome across the lifespan. This will entail using a novel combination of cutting-edge large-scale modelling of brain dynamics and state-of-the-art neuroimaging data (both structural and functional).

There will be numerous applications depending on interests, examples include:

- How ageing brain structure changes our brain activity.
- How non-invasive brain stimulation perturbs brain network activity.
- How disorders such as epilepsy, schizophrenia, or ADHD may emerge from biologically-plausible changes to model parameters.
- Modelling sleep dynamics
- Developing novel analysis methods for complex spatiotemporal dynamics.

## Novel methods for monitoring brain activity in preterm babies



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Suitable for PhD or Honours students. This project would suit students with a background in physics, maths, statistics, machine learning, engineering, or a related discipline, with some experience in programming (e.g. in MATLAB)

A major challenge in neonatal intensive care is timely and efficient bedside monitoring of the preterm brain to guide optimal individual care. The overarching aim of this project is to clinically validate novel methods to noninvasively detect acute brain injury and form a prognosis for long-

term outcome as early as the first hours after preterm birth. Electroencephalography (EEG) is widely used to monitor preterm brain health, but its diagnostic utility is limited by the need for subjective visual assessments of raw signals or simple trends. These are also prone to the many recording artefacts in intensive care units. We recently developed new metrics for analysing preterm brain activity that enable the detection of injuries and prediction of neurodevelopment, earlier than had been possible before. This project will take the crucial next steps toward taking our new technology to the clinic. This will involve validating and refining our existing metrics using a newly collected, large, multicentre dataset of preterm EEG with full clinical follow-up. There are also numerous technical challenges to solve so that our methods can work smoothly in the real-world intensive care environment. The outcome will be a validated brain monitoring toolbox for neonatal intensive care, ready for immediate implementation in brain monitors.

### Physiological signal analysis from infancy to adolescence

#### Suitable PhD, Masters or Honours students

The advent of precision medicine demands better tools for measuring human structure and function. A particularly important period of development where this lack of diagnostic and prognostic tools is felt in earnest, is the period from infancy to adolescence. We measure the function of the brain, heart and lungs during sleep to reveal important information on human health in this cohort. By taking advantage of advances in data analysis and computation, we develop tools that can track developmental trajectories more accurately, leading to improved patient stratification. In this project, we will implement head models that mature with a patient to convert electroencephalogram signals into source space for improved assessment of brain connectivity and network/graph analysis to discover the interplay between brain, heart and lung function. The resultant tools will be evaluated as developmental biomarkers as well as diagnostic tools to detect disease and monitor the response to interventions.

## Translational Neurogenomics Group



**Group Leader:**  
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The **Translational Neurogenomics Laboratory** investigates the role of genetic factors in a range of psychiatric conditions, including schizophrenia, addiction, anxiety disorders and compulsive disorders. By researching a wide variety of symptoms that are typical of patients with a particular psychiatric condition, they can use newly developed statistical methods to discover associations between the condition and genetic variants.

To fully identify and understand the biological processes that result in a psychiatric condition, the lab:

- Studies genetic variation.
- Identifies differences in gene expression levels observed in brain and non-brain tissues.
- Finds associations between genetic risk and brain anatomy.

Translational Neurogenomics refers to two topics that are equally important in the study of psychiatric disorders:

- The translation of genetic code to RNA and proteins.
- The translation of research findings to the clinic (from bench to bed).

### The interplay between environmental and genetic risk factors in the aetiology of substance use disorders



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Honours or PhD project. We are seeking a highly motivated student with a strong interest in statistics and quantitative studies.

### BACKGROUND

Mental health disorders (e.g., depression, anxiety, and substance use) are the leading cause of global disease burden in the young adult population. Twin and family studies show that both genetic and environmental factors play a large role in the aetiology of these disorders. The Translational Neurogenomics group aims to identify genetic risk factors for a range of mental health and substance use disorders, and investigate the interplay between genetic and environmental risk factors.

UK Biobank is a major national and international health resource with the aim of improving the prevention, diagnosis and treatment of a wide range of serious and life-threatening illnesses. UK Biobank recruited 500,000 people aged between 40-69 years in 2006-2010 from across the country to take part in this project. They have undergone measures, provided blood, urine and saliva samples for future analysis, and detailed information about themselves and agreed to have their health followed. Over many years, this will build into a powerful resource to help scientists discover why some people develop particular diseases and others do not. Extensive information on mental health has been collected from a subset of 150,000 individuals.

### POTENTIAL PROJECTS

1. Substance use and substance use disorders (SUDs) are explained by a combination of genetic and environmental factors. Exposure to traumatic experiences, particularly in childhood, has been linked with both substance abuse and dependence. Is this link stronger in people with a genetic predisposition to SUDs? This project will investigate the interaction between genetic liability to substance use and traumatic experiences in the UK Biobank.
2. A network approach to psychopathology is an alternative way of conceptualising mental illness. A disorder is conceptualised as a system of interacting relationships between symptoms, rather than the set of symptoms resulting from a single latent factor (the disorder). This project will conduct a network analysis of substance use disorders (SUDs) using symptom-level data from the UK Biobank. Networks will be estimated for groups with a high vs. low genetic predisposition for substance use in order to determine whether genetic risk is associated with differences in psychopathological network structure

### WHAT WE OFFER

- A position in a dynamic research environment and the opportunity to conduct high-quality studies.

- Access to large-scaled datasets through (inter)national collaborations.
- Being a part of a successful research team.

### Integrating genomic data to characterise inherited risk factors for mental health disorders

PhD or Honours project. We are seeking a highly motivated student with a strong interest in statistics and quantitative studies.

### BACKGROUND

Mental health disorders, including depression, anxiety, and substance abuse disorders, afflict around half of the individuals at some point in their lives and account for a substantial proportion of the global burden of disease. Recently, significant progress has been made in identifying genetic (i.e., inherited) risk factors associated with mental health disorders through genome-wide association (GWA) studies of large, population-based cohorts.

Although these GWA studies have implicated many genetic risk factors for mental health disorders, identifying the exact causal genes remains challenging. This is due in part to complex interactions between multiple cellular data types in specific tissues that are likely to mediate susceptibility. Integrated studies of multiple cellular data, such as DNA sequence variation, gene expression, and DNA methylation, in relevant tissues are therefore required to understand the impact of genetic risk factors on mental health.

This project will use high-quality gene expression and DNA methylation data measured in whole blood to characterise genetic risk factors underlying mental health disorders. Analyses will then be conducted across tissues using several publicly available multi-tissue genomic compendia. This study will provide a unique resource to identify and characterise novel genetic factors underlying susceptibility to mental health disorders. The identification of such causal genes is the next crucial step in elucidating the complex molecular pathways of mental health disorders and may help in the development of diagnostic tests and more rational treatment strategies.

### AIM

- To characterise genetic risk factors for psychiatric disorders in a large population-based sample.
- To prioritise causal tissues and mechanisms using independent multi-tissue genomic compendia.



## WHAT WE OFFER

- A position in a dynamic research environment and the opportunity to conduct high-quality studies.
- Access to large-scaled datasets through (inter)national collaborations.

# Genetic Epidemiology Group



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The **Genetic Epidemiology Group** seeks to identify the particular genes involved in complex disease aetiology. It performs longitudinal studies with twins on a wide range of complex traits of medical and behavioural interest. Particular research over recent years has moved to genome-wide association studies (GWAS) to locate genes influencing complex traits including anxiety, alcoholism, and dizygotic twinning. Most recently, the laboratory initiated projects to recruit large patient samples for GWAS of anorexia, depression and other psychiatric disorders.

## Genetics of differences in symptomatology and treatment response in depression

The scope of the project can be adapted PhD, MPhil, or Honours. A background (or strong interest) in genetics, pharmacy, psychology, medicine, neuroimaging, data science, statistics, computer science, mathematics or bioinformatics is preferred. Previous research experience coding, analysing and plotting data using R/Python

### BACKGROUND

Depression is a common yet very heterogeneous mental disorder. Patients experience different onset, symptoms, and severity, present with different comorbidities, and respond to antidepressant treatment differently. Genetic factors contribute to these differences, but there is little evidence of specific genes, pathways and mechanisms implicated in such heterogeneity.

## AIM

To characterise the genes, pathways and mechanisms that underlie variation in symptom profiles, treatment response and other outcomes among patients with major depressive disorder (MDD).

### APPROACH

The student will apply statistical and computational approaches to analyse data collected as part of the Australian Genetics of Depression Study (AGDS), which comprises more than 20,000 genotyped volunteers diagnosed with major depressive disorder. Collaboration with other groups in Australia and abroad and within international consortia such as the Psychiatric Genomics Consortium will be an integral part of this project.

### OUTCOME

Understanding the molecular basis of clinical and treatment response heterogeneity in depression is necessary to enable precision psychiatry: the tailoring of treatment according to one's genetic background.

## Identifying individuals at high risk of Alzheimer's disease



**Co-Supervisor: Associate Professor Michelle Lupton**

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Suitable for a PhD or Honours student with a background in genetic epidemiology, statistics and bioinformatics. Experience in working with neuroimaging, DNA methylation or whole genome/exome sequence data is also desirable

### BACKGROUND

Dementia affects an estimated 353,800 Australians, with up to 80% being diagnosed with Alzheimer's disease (AD). Despite a major research effort, an effective treatment is not available. The pathogenic process of AD begins decades prior to the clinical onset, so treatments likely need to begin early in the disease process to be of benefit.

## AIM

To use known genetic and epigenetic risk factors to identify those at a high risk of developing AD, where a high proportion of individuals will be in a prodromal stage of AD.

## APPROACH

To build on our current work using genetic risk prediction to identify individuals who are at high risk of AD, a subset of which will be in a prodromal disease stage. To investigate both common and rare AD genetic risk factors and test for associations with extensive phenotypic data including neuroimaging and blood-based methylation markers. Our group has access to large highly phenotyped cohorts spanning different ages and stages of dementia, including PISA (the Prospective Imaging Study of Ageing: Genes, Brain and Behaviour) based at QIMR Berghofer.

### OUTCOME

The identification of individuals at high risk of Alzheimer's disease will provide: 1) important insights into mechanisms of AD development throughout the life span; 2) the opportunity to investigate prodromal markers and allow selection of individuals for early treatment strategies.

## An investigation of the relationship between fire smoke exposure and age-related cognitive decline and dementia

Suitable for Honours or Masters project

### BACKGROUND

Exposure to bushfire smoke is a major health concern in Australia, which is only set to increase due to fluctuating weather patterns because of climate change. Particulate matter (PM) present in bushfire smoke has adverse effects on health causing premature mortality and the exacerbation of cardio-respiratory conditions. In vitro studies have identified unique detrimental effects of bushfire smoke on brain cells, compared to that of traffic air pollution. Previous work has shown an association between air pollution and dementia, but there have been limited studies investigating the effect of bushfire smoke on cognitive decline and dementia risk.

## AIM

To identify dementia-related health and cognitive factors associated with bushfire smoke exposure in middle aged and older individuals.

### APPROACH

Using data (including cognitive testing, self-report and medical records) from our large-scale cohort study (PISA: the Prospective Imaging Study of Aging) together with the latest mapping of fire smoke exposure we will investigate the association of exposure to bushfire smoke with health and cognitive outcomes. This work is in collaboration

with the Cellular and Molecular Neurodegeneration Group (led by Professor Anthony White).

### OUTCOME

Understanding the potential consequences of exposure to bushfire smoke to dementia risk will be imperative in informing public health protection approaches as the incidence of bushfire events increase.

# Cellular and Molecular Neurodegeneration Group

## Group Leader:

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## The Cellular and Molecular Neurodegeneration Laboratory

investigates the cause and potential treatments for brain diseases including dementia (Alzheimer's disease), motor neuron disease (amyotrophic lateral sclerosis) and Parkinson's disease. These disorders (collectively known as neurodegenerative diseases) are a growing health issue in Australia and worldwide, with few treatment options available. In order to gain a better understanding of these diseases and develop new therapeutic approaches, the research team is currently developing new human brain cell culture methods.

A major focus of this research is the development of a 3D human 'brain on a chip' cell culture platform that combines different human brain cell types into a 3D microfluidic culture plate. The advantage is that the 3D system provides a far better model of the actual human brain while still allowing manipulation and experimentation in a culture plate.

The cells used in the 3D brain on a chip include neurons, astrocytes and microglia (resident brain immune cells) and are generated from human induced pluripotent stem cells, natural olfactory stem cells, and blood-derived cells from normal people and those with brain disease. This 3D platform is being used to build new models of the brain for dementia and motor neuron disease research, in

particular, to understand the role of the immune system in brain diseases and develop new therapeutic compounds targeting the immune cells of the brain.

### Development of metal-based therapeutics for neurodegenerative diseases

PhD project but may also be considered for an Honours project.

Biological trace elements, also known as trace mineral or biometals. include copper, zinc, iron, selenium and manganese. These and other biometals have essential roles in many areas of brain function including energy metabolism, transcription factor activity, antioxidant regulation and synaptic signalling. During ageing and brain disease, regulation of biometals is dramatically altered with changes to cellular and subcellular handling and localisation. This leads to impairment of brain cell function, in both neurons and surrounding cell types (astroglia and microglia) and contributes to neuronal cell death in disorders such as Alzheimer's, Parkinson's and motor neuron diseases, as well as in lysosomal storage disorders such as Batten disease (childhood brain disorder). Our research has uncovered some of the processes involved in the loss of biometal regulation and found this to be an early event in many disorders. We are also developing compounds that can help restore biometal stasis in the brain.

This project involves the investigation of new metal-based compounds as potential therapeutic or diagnostic agents for Alzheimer's disease and other brain disorders. These compounds have unique properties including modulation of brain cell signalling, control of anti-oxidant function, and regulation of neuro-immune responses. The project examines the action of the compounds on a range of cell types including animal and human neurons, astrocytes and/or microglia, and we aim to understand the molecular pathways that contribute to therapeutic action. Longer-term projects will involve the examination of the compounds as therapeutics in specific animal models of brain disease to determine if they are suitable for further therapeutic or diagnostic development towards the clinic.

The wet lab project will utilise a range of tools and techniques including brain cell culture, analysis of immune

response (cytokine analysis), phagocytosis assays, anti-oxidant assays, X-ray analysis of biometal distribution and metalloproteomic studies on metal-protein interactions.

### Generating patient-derived microglia to investigate neuroinflammation in MND

This project is suitable for a PhD or Honours student

This project will build important new tools for understanding the role of the immune system in amyotrophic lateral sclerosis (ALS), a form of motor neuron disease (MND). Inflammatory responses by the resident brain and spinal cord immune cells (microglia) have an important role in ALS/MND and are key targets for therapy. Until now, research on microglia has been largely restricted to cells of animal origin. We now have new techniques to generate microglia directly from ALS/MND patients to help understand the disease and test patient-specific drugs to modulate the immune response in the brain and spinal cord. This project will provide a new approach to investigating and treating inflammation in MND.

### Generating Alzheimer's microglia for testing patient responses to immune-modulating compounds

This project is suitable for a PhD or Honours student

Alzheimer's disease is anticipated to affect 100 million patients with an annual cost of US\$1 trillion by 2050. Promising amyloid-clearing therapies have failed to translate to clinical outcomes, and new approaches targeting the underlying molecular pathways of Alzheimer's disease are urgently required. There has been a 're-awakening' to the critical role of microglia in Alzheimer's disease pathology. However, our ability to translate abnormal microglial biology into clinically relevant advances has been greatly impaired by inadequate cell models. Microglia-like cells can now be routinely generated from human peripheral blood monocytes. The approach is cost-effective and rapid, and these induced microglia reveal a remarkably close relationship to mature human microglia in terms of cell surface marker expression, functional assays, and gene expression.

In this project, we will generate microglia-like cells from blood samples collected from Alzheimer's patients, and people who are considered at high risk for Alzheimer's disease. We will compare the cultured microglia to identify patient-specific immune abnormalities using a range of assays currently established in our lab. We will then screen individual patient microglia for the efficacy of immune-modulating compounds to identify effective patient-specific neurotherapeutics in 'real-time'. This

project will produce highly significant advances in patient-specific drug targeting for neuroinflammation in Alzheimer's disease, leading to the development of real-time, individual therapeutic approaches with major clinical benefits, including identifying patient-specific drugs, selecting suitable patients for clinical trials, and monitoring drug efficacy during trials.

### Olfactory stem cells for investigating the causes and progression of dementia

This project is suitable for a PhD or Honours student

#### BACKGROUND

With no clinical success yet achieved from amyloid-targeting strategies, there is an urgent need to gain new insights and develop effective treatments for people who have dementia. New stem cell-based approaches have generated much excitement in dementia research with the potential to study patient-derived neurons and supporting cells. However, the commonly used 'pluripotent' stem cells are artificially generated and do not possess all needed cell types, which makes them unsuitable as tools to understand the disease process in the majority of late-onset (sporadic) cases of dementia.

Olfactory (nasal) tissue contains a unique population of naturally occurring stem cells that renew the nasal receptor neurons and supporting cells in the nose throughout life. These exceptional stem cells can be collected through a routine procedure with local anaesthetic and readily grown in a culture dish in a laboratory to produce neurons and other key brain cell types that accurately reflect the same types of brain cells that occur in the patient of origin. These cells provide a unique tool to study patient-specific disease processes and develop therapeutics for personalised dementia medicine.

#### OBJECTIVE

Our plan is to collect nasal tissue from people with dementia and from people who are at high risk for dementia (together with matching control samples). The olfactory stem cells will be grown in our lab and studied using a range of molecular approaches to provide unique insights into the early disease changes in a person's brain cells. We are also attempting to grow brain organoids from stem cells. These are 'mini-brains' that represent the 3-dimensional structure of a small part of a human brain and allow a much more accurate understanding of how brain cells work (or fail to work) in dementia. This will enable us to understand how brain cells are affected by dementia differently for each patient (i.e., derived neurons

will retain patient-specific epigenetic markers) and will allow the screening of potential therapeutic drugs on an individual basis.



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