2022-23
STUDENT PROJECTS

QIMR Berghofer
Medical Research Institute
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 programs: Cancer Research, Infection and Inflammation, Mental Health and Neuroscience, and Population Health. The Institute is home to more than 1000 scientists, staff, and students who consistently generate formidable, high-quality research. Each year, our work gives rise to more than 700 publications, around 40,000 citations, and more than $10 million in commercial income.

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 supported by a professional team who will help you 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 in this booklet can often be adapted to suit your particular skills and strengths, so I encourage you to talk to 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 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
# Table of Contents

Director's Welcome Message 3
Table of Contents 4
Quick facts about QIMR Berghofer 7
QIMR Berghofer Student Committee 8
Why study at QIMR Berghofer? 8
QIMR Berghofer Services
  Histology Facility 9
  Sample Processing 9
  Flow Cytometry and Microscopy 9
  DNA Sequencing 9
  Analytical Services 9
  Genome Informatics 9
QIMR Berghofer Facilities
  QIMR Berghofer Statistics Unit 10
  Q-Gen Cell Therapeutics 10
  GenomiQa 10
Medical Research Opportunities at QIMR Berghofer 11
Quick Admissions Guide for Students 12

## Cancer Research Program 13

### B-lymphocytes in Autoimmunity and Malignancies Group 14

- Investigating the therapeutic effect of a ketogenic diet in a xenogeneic (PDX) mouse model of chronic lymphocytic leukaemia 14
- Establishing a new experimental model of systemic lupus erythematosus 15
- Discovering novel immunoregulatory molecules underlying the pathogenesis of systemic lupus erythematosus 15
- Investigating the role of purinergic receptor signalling in the onset and progression of systemic lupus erythematosus 16

### Cancer Genetics and Genome Variation and Regulation in Disease Groups 16

- Identifying the causal genes at cancer risk loci 17
- Functional characterisation of breast cancer susceptibility loci 17

### Functional Cancer Genomics and Functional Genetics Groups 18

- Identifying new long-noncoding RNAs involved in Breast Cancer development 18
- Identification and evaluation of new melanoma risk genes 19
- Evaluation of new long-noncoding RNAs contributing to drug resistance in ovarian cancer 19

### Signal Transduction Group 20

- Repurposing an FDA-approved drug to treat mut-p53 cancers 20
- Decipher the role of a new epigenetic modulator, RLF, in replication stress response 20
- To understand mechanisms that mediate chemo-/radiosensitivity of breast cancer stem cells 21
- Expanding the scope of PARPi for treatment of high-grade serous ovarian cancers 21
- Targeting CEP55 in triple-negative breast cancer 22

### Conjoint Gastroenterology Group 22

- Colorectal cancer – from genetics to chemoprevention 23
- Genetic changes underlying colorectal cancer initiation and progression 23

### Medical Genomics Group 23

- Complex neoantigen prediction in cancers 23
- Genomic predictors of progestin response in endometrial cancer 24

### Translational Cancer Immunotherapy Group 24

- CAR T cells – redirecting T cells for cancer immunotherapy 24

### Cancer Precision Medicine Group 25

- Plasma protein biomarkers to predict immunotherapy response in lung cancers 25
- Novel approaches to augment immunotherapy response in cancers 25

### Epigenetics and Disease Group 26

- Determining the therapeutic efficacy of epigenetic drugs in ovarian cancer 26
Combining epigenetic drugs with immunotherapy in melanoma
27
Therapeutic opportunities targeting epigenetic-metabolism crosstalks in cancer
27

**Immune Targeting in Blood Cancers Group**
28
Targeting immuno-oncology molecules in blood cancers
28

**Cancer Genetic Susceptibility Group**
29
Screening of genetically identified compounds for endometrial cancer therapy
29
Identifying the regulatory targets of common endometrial cancer risk variants
29
Genetic epidemiology of endometrial cancer
30

**Transplant Immunology Group**
31
Targeting the gut and the microbiome therein to improve stem cell transplantation
31
Understanding infectious respiratory complications after stem cell transplantation
31

**Sid Faithfull Brain Cancer Group**
32
Improving survival for adult brain cancer patients by targeting “sleeping” cancer stem cells
32

**Population Health Program**
33

**Gynaecological Cancers Group**
34
Ovarian cancer risk factors for women with and without a pathogenic BRCA mutation
34
Green tea consumption and survival after a diagnosis of ovarian cancer
34

**Cancer Control Group**
35
QSKIN: the burden of skin cancer
35

**Cancer Aetiology and Prevention Group**
36
Reducing diagnostic delay in patients with pancreatic cancer
36

**Supportive Care in Cancer Group**
36
PROPCare: Practice Of supporting Partners and family Carers: They are not our patients – a system failure or not?
36

**PARTING: Psilocybin-Assisted suppoRtive psychoTherapy IN the treatment of complicated Grief**
37

**Mosquito Genomics Group**
37
Mosquito genomics for better control of mosquito-borne diseases
37

**Molecular Cancer Epidemiology Group**
38
Evaluation of variants in known or candidate high-risk cancer genes
38

**Statistical Genetics Group**
39
Genetics of skin cancer
39
Eye disease genetics
40

**Infection and Inflammation Program**
41

**Immunology and Infection Group**
42
Discovering novel immunoregulatory molecules that can be manipulated for clinical advantage.
42

**Inflammation Biology Group**
42
Establishing and characterising mouse models of long-COVID for intervention testing
42
Uncovering and characterising new alphavirus and flavivirus host co-factors
43

**Tumour Immunology Group**
44
Structural biology
44
Thinking outside the box: Novel strategies to treat viral infections and cancers
44
Adoptive T-cell therapy for HPV associated cancers
45
Improving the efficacy of T-cell therapy in vivo
45
Cellular immunotherapy – engineering “custom built” cells to treat cancer
46

**Molecular Parasitology Group**
47
Development of CRISPR based technology in schistosome bloodflukes
47
Development of new interventions including vaccines, DNA diagnostics and serological markers essential for ending neglected tropical diseases caused by schistosomes and intestinal worms in Asia and Africa 47

**Hepatic Fibrosis Group** 48

- MicroRNAs as anti-fibrotic agents to treat liver scarring, fibrosis and cirrhosis in chronic liver disease 48
- Anti-inflammatory small molecule inhibitor development to control liver inflammation associated with hepatic fibrosis in chronic liver disease 48

**Iron Metabolism and Molecular Nutrition Groups** 49

- Developing improved methods for assessing iron status 49
- The effect of iron supplements during pregnancy 50
- Targeting the ferroxidase hephaestin to treat iron loading disorders 50
- The regulation of body iron homeostasis 51

**Mucosal Immunology Group** 51

- Prevention of allergy development in neonates by manipulating the microbiome 51
- Hookworm-derived polypeptides for the treatment of chronic diseases 52

**Respiratory Immunology Group** 52

- Insights into the influence of maternal diet on the severity of infant viral bronchiolitis 52
- Microbiome and neonatal immune development in early life 53
- The role of prostaglandins in chronic respiratory diseases (e.g. COPD and asthma) 53
- Cell death pathways and the induction of type-2 inflammation 53

**Mental Health and Neuroscience Program** 55

**Psychiatric Genetics Group** 56

- Assessing the cost and impact of Attention Deficit Hyperactivity Disorder in Australia 56
- The role of genomics in understanding psychiatric and neurological disease 56

- Health and wellbeing in people with bipolar disorder 56
- Identifying risk factors for problematic internet use and video gaming in Australian adults 57

**Brain Modelling Group** 57

- Modelling brain dynamics across the lifespan 57
- Novel methods for monitoring brain activity in preterm babies 58
- Neonatal seizures as a biomarker of underlying pathology 58
- Regional maturation in developing brain function 58

**Translational Neurogenomics Group** 59

- The interplay between environmental and genetic risk factors in the aetiology of substance use disorders 59
- Integrating genomic data to characterise inherited risk factors for mental health disorders 60

**Genetic Epidemiology Group** 61

- Genetics of differences in symptomatology and treatment response in depression 61
- Cracking the genetic code of Parkinson’s disease 61
- Genetic and brain structure correlates of suicidal behaviour and mental illness 62
- Identifying individuals at high risk of Alzheimer’s disease 62

**Cellular and Molecular Neurodegeneration Group** 63

- Development of metal-based therapeutics for neurodegenerative diseases 64
- Generating patient-derived microglia to investigate neuroinflammation in MND 64
- Generating Alzheimer’s microglia for testing patient responses to immune-modulating compounds 64
- Olfactory stem cells for investigating the causes and progression of dementia 65
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 800 scientists (of which approximately 150 are students) in about 70 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.
Welcome Future Medical Leaders!

We are the QIMR Berghofer Student Committee, your gateway to social aspects of your time within the Institute. Our responsibilities include organisation of social and fundraising events for all QIMR Students through though the year, including Christmas Party, Easter Egg Hunt, BBQs, movie nights, coffee meet-ups, bake sales, and an International Food Day. We also organise development seminars and a conference-style student retreat where you can meet your fellow students and interact with industry representatives.

The Student Committee is one of the three committees representing students within QIMR, the other two are the Higher Degree Committee (HDC) and the Seminar Convenors.

The HDC student representatives provide feedback and concerns from students directly to the HDC panel, consisting of senior scientists from QIMR Berghofer. If you have any comments or questions, they are the ones to contact. They organise a range of workshops and orientation sessions, as well as an annual student symposium to enhance your presentation skills and network with other researchers within the Institute.

The Seminar Convenors are in charge of the Early Career Research Seminar Series hosted every Friday. This series allows you to practise your scientific communication abilities in a supportive environment and catch up with other students over food and drinks.

QIMR Berghofer is a fun, engaging, and supportive community and a hub for world-class research. What else could you ask for when considering your next career step?

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 RBWH and the Herston Campus 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 future desired 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 Services

HISTOLOGY FACILITY
The QIMR Berghofer Histology Facility is a fully equipped service and research laboratory. The facility caters to the needs of scientists and postgraduate students from QIMR Berghofer as well as external and international institutions. The unit provides technical services and also trains and consults on matters relating to:

- Routine paraffin and cryo histology.
- Special stains.
- Immunohistochemistry (Tyramide Signal Amplification) and antibody optimisation.
- FISH and CISH labelling.
- Tissue preparation and sectioning for transmission electron microscopy and high-resolution digitisation of histology slides (e.g. Vectra Imaging System).

The facility stocks a broad selection of commonly used primary antibodies and secondary detection antibodies to label mouse, rat, rabbit, hamster, guinea pig, and chicken primary antibodies with horseradish peroxidase, alkaline phosphatase, Alexa fluorescent or Tyramide (TSA) markers.

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.

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.

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).

ANALYTICAL SERVICES
QIMR Berghofer Analytical Services contain fully equipped service and research laboratories, enabling the delivery of high-quality and reproducible data. Analytical Services caters to the needs of scientists and postgraduate students from QIMR Berghofer as well as external and international institutions. The facility provides technical services and also trains and consults on cell line authentication, culture media services unit, glassware, and waste disposal.

GENOME INFORMATICS
The Genome Informatics Group works on the analysis of next-generation sequencing (NGS) data and its research and clinical applications, particularly with respect to cancer. Cancer is increasingly being viewed as a disease where the tissue of origin is less important therapeutically than the unique spectrum of mutations found in the individual patient’s tumour. NGS is the key technology used to catalogue mutations in both DNA and RNA and while it has been a research staple for over five years, it is only now starting to make inroads into the clinic. NGS is a high-throughput genomics technology with significant computational and storage requirements. The data for each tumour/normal sample pair can use up to half a terabyte of the disk to store and tens of thousands of CPU hours to analyse.
QIMR Berghofer Facilities

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 provides world-class facilities for the manufacture of cellular therapies to GMP standards. Our experienced team can support your research from discovery through to phase I clinical trials, phase II and beyond.

Q-Gen Cell Therapeutics is TGA-licensed for human cell and cellular product development and production, quality control testing, microbial contamination, endotoxin, mycoplasma, flow cytometry cell viability and identification, and regulatory documentation development.

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.
Medical Research Opportunities

Join one of the largest Medical Research Institutes in Australia.

The options for students to be part of QIMR Berghofer are:

A. 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.

B. Vacation Research Programs
   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.

C. 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.

General info: www.qimrberghofer.edu.au
University Students Webpage: www.qimrberghofer.edu.au/education/for-university-students/
For further enquiries, please contact: GraduateEducation@qimrberghofer.edu.au
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

University Students Webpage: www.qimrberghofer.edu.au/education/for-university-students/


For further enquiries, please contact: GraduateEducation@qimrberghofer.edu.au
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.

New cancer cases diagnosed per year are expected to increase to 185,000 in 2031 as Australia’s population ages. 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 to be more effective.

Our researchers are working on a number of projects which include investigating specific environmental and genetic factors that reduce a person’s risk of developing cancer. They are also developing better screening tests to detect cancer earlier and finding more effective treatments through clinical trials.

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.
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 laboratory 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.

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 leukaemia in adults, and typically occurs during or after middle age. The majority of the patients have an indolent form of CLL and remain stable for many years without treatment, while others develop aggressive disease hallmarks.

In CLL there are too many abnormal B lymphocytes present, along with poor responses to infections and low anti-tumour immunity. Infections are a major cause of death in CLL patients; existing 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 vital anti-microbial/tumoral immune functions in CLL patients is currently an unmet need, and new drugs and treatments are critical.

Using a mouse model of CLL, we have recently discovered that mice fed a ketogenic diet are protected against CLL development. However, the clinical relevance of this dietary intervention has not been tested. The protection provided by the diet against CLL was associated with the enrichment of a set of metabolites possibly with an 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 lacking T, B and NK cells that allows 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 metabolites associated with ketogenic diet mediated protection against CLL in the PDX model.
• Test the anti-leukaemic function of metabolites in-vitro.
• Evaluate anti-leukaemic metabolites in mouse and PDX models of CLL.

METHODS
The identification of anti-leukaemic metabolite/s will facilitate the 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.

Establishing a new experimental model of systemic lupus erythematosus
This project is suitable for an Honours or Masters student.

BACKGROUND
Systemic lupus erythematosus (SLE) is a chronic, debilitating autoimmune disease affecting millions of people worldwide. SLE is characterised by pro-inflammatory autoantibodies and immune-mediated damage, affecting multiple organs, and resulting in long-term morbidity and reduced life expectancy. There are very few treatments, and current therapies fail to prevent these outcomes and are associated with significant toxicity.

Levels of circulating B-cell activating factor of the TNF family (BAFF) are elevated in patients with SLE, and mice overexpressing BAFF (BAFF-Tg mice) develop SLE-like symptoms by 8 to 12 months of age. We have recently generated a new BAFF-overexpressing transgenic mouse using a liver-specific promoter. This strain also expresses the reporter protein td-tomato along with BAFF, allowing us to identify specific BAFF-expressing cells. Our preliminary analysis indicated an accelerated disease onset in these mice.

AIMS
• Functional characterisation of transgenic B cells ex-vivo in response to toll-like receptor and B cell receptor stimulation.

METHODS
This project will establish a new mouse model of SLE in the lab and facilitate testing of a novel therapeutic antibody against SLE. This project will use a range of immunological techniques (mouse models of disease, cell phenotyping using flow cytometry, histology, confocal microscopy, ELISA) and molecular biology techniques (RNA extraction, RT-PCR).

Discovering novel immunoregulatory molecules underlying the pathogenesis of systemic lupus erythematosus
This project is suitable for an Honours, Masters or PhD student.

BACKGROUND
The Mackay laboratory investigates 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).

The BAFF receptor TACI is highly expressed on memory B cells in SLE patients, and BAFF-TACI interactions lead to heightened autoantibody production driving the disease pathology. Importantly, genetic deletion of TACI protects against SLE, yet the underlying mechanism remains largely unknown.

AIMS
• To investigate the cellular mechanism by which TACI signalling leads to exaggerated autoantibody production in SLE.
• To investigate how altered gut microbiota (through the regulation of immunoglobulin A production by TACI) and metabolites are associated with SLE disease severity.

METHODS
This project will use a range of immunological techniques (mouse models of disease, 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.
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 are obtained from food or synthesised by the body. BAFF is a B cell survival factor, and overexpression of BAFF in BAFF-transgenic (BAFF-Tg) mice causes the expansion of autoreactive, pathogenic B cells leading to SLE. 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 was associated with a reduction in autoreactive B cell numbers and protection from SLE. We also found that supplementation protects BAFF-Tg 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
• To investigate the requirement of a purinergic receptor in the high-fibre diet-mediated protection against SLE.
• To investigate if metabolite-purinergic receptor signalling is critical for the protection against SLE.
• Characterise a novel metabolite therapy for SLE.

METHODS
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.

Cancer Genetics and Genome Variation and Regulation in Disease Groups

Senior Scientist (Cancer Genetics): Professor Georgia Chenevix-Trench
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The Cancer Genetics Laboratory 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.
**Identifying the causal genes at cancer risk loci**

Team Head (Genome Variation and Regulation in Disease): Associate Professor Jonathan Beesley

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Jonathan.Beesley@qimrberghofer.edu.au

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.

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**Functional characterisation of breast cancer susceptibility loci**

Suitable for PhD students only.

**BACKGROUND**

Through our collaboration with the international Breast Cancer Association Consortium, we have identified over 200 regions of the genome associated with breast cancer risk. The detected variants are generally in non-coding regions, so a major challenge is to now identify the target genes, which mediate risk. Knowledge of the functional mechanisms, genes and pathways is essential for the clinical translation of GWAS discoveries.

**AIM**

Identify target genes at breast cancer risk loci, which modulate specific hallmarks of cancer.

**METHODS**

We are using high-throughput CRISPR functional screens to test candidate genes for effects on cancer phenotypes, such as proliferation and immune responses. These screens nominate candidate functional genes for which we aim to test the hypothesised link between the risk variants and gene regulation. We use data from RNA-seq, ATAC-seq, and HiChIP (publicly available or in-house) to guide experimental approaches such as high-throughput reporter assays and generation of isogenic cellular models using CRISPR base editing in order to evaluate allele-specific effects.

This project would suit students with an interest in wet lab experimental work, allowing the development of skills in molecular biology techniques, the use of CRISPR, tissue culture, and animal models. Students will work closely with computational and other wet lab scientists to identify cancer genes and pathways, which might represent targets for future drug development.
**Functional Cancer Genomics and Functional Genetics Groups**

**Group Leader: Associate Professor Stacey Edwards (Functional Cancer Genomics Group)**

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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.

**Group Leader: Associate Professor Juliet French (Functional Genetics Group)**

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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 project.

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 IncRNA expression and identify allele-specific chromatin interactions. We expect that some of the IncRNAs will have cancer-related biological functions. We will therefore overexpress or silence IncRNAs 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 IncRNAs 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.

**Identification and evaluation of new melanoma risk genes**

**Suitable as a PhD project.**

Genome-wide association studies (GWAS) have successfully uncovered new risk genes and new biology for complex diseases resulting in a major push to translate these findings to improve drug development. We want to realise the promise of this approach in cutaneous melanoma (CM), the deadliest form of skin cancer. In the last two years, GWAS have identified single nucleotide polymorphisms (SNPs) across 56 regions associated with an increased risk of CM. Importantly, the majority of these risk SNPs lie within noncoding regions of the genome such as introns and intergenic regions. Therefore, despite the significance of the genetic analyses, additional functional studies are required to identify the key genes targeted by the risk SNPs. Recent studies indicate that cancer risk SNPs are enriched in DNA regulatory elements such as enhancers. Enhancers can be located hundreds of kilobases from their target genes and regulate transcription through long-range chromatin interactions. The noncoding genome also serves as a template for the transcription of long noncoding RNAs, some of which are mutated in cancer initiation and progression.

In this project, we will use a combination of high-throughput methodologies to comprehensively identify all CM risk-associated enhancers and their target protein-coding and noncoding RNA genes. These include targeted RNA sequencing, chromatin conformation-based techniques, eQTL analyses and reporter assays. We will generate isogenic cell lines using CRISPR technology, which will be used to measure enhancer expression, identify allele-specific chromatin interactions and assess transcription factor binding. We will also examine the function of the enhancer genes in cancer-related pathways. Melanoma cells will be engineered to overexpress or silence target genes, then assayed for cell proliferation, apoptosis, response to DNA damage and tumour formation using explant assays in mice. The outcomes of this project will represent a major breakthrough as the products of these genes may provide new drug targets for future CM prevention or therapy.

Students will have access to unique expertise and reagents, and will acquire skills in tissue culture, CRISPR/Cas9, DNA/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 project.**

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.

Decipher the role of a new epigenetic modulator, RLF, in replication stress response

Suitable for Honours or PhD students.

Uncontrolled cell proliferation, a hallmark of tumour cells, leads to high levels of replication-related lesions and double strand breaks (DSBs). As a survival strategy, some cancers have elevated activity of the Homologous Recombination (HR) pathway, the main pathway repairing DSBs arising from replication stress, or promote other error-prone repair pathways capable of compensating defective HR. Thus, thorough understanding of the mechanisms by which cancer cells alleviate the ongoing replication stress and endogenous DNA lesions will unravel novel therapeutic targets and opportunities.

Rearranged L-myc fusion (RLF), an epigenetic modifier, is found to be amplified/gained in a significant proportion of ovarian (50%) and other cancers. A previous study has shown that RLF interacts with components of DNA damage sensing complex, MRN, a tricomplex critical for HR pathway (Harten et al, 2015, BMC Biology). Using a murine-derived knockout cell model, we have further established that RLF is required to modulate cellular replication stress. We will conduct further investigations using this established cell model to analyse the role of RLF in HR mediated DNA repair during replication stress and extrapolate its function in ovarian cancer tumorigenesis. Scholars will gain skills extensively in cell culture, molecular biology techniques including western blotting, immunofluorescence, immunoprecipitation and FACS.
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 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.

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

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Suitable for Honours or PhD students.

In Australia, approximately 1600 women are diagnosed with ovarian cancer each year and the majority have high-grade serous ovarian type (HGSOC). The five year 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 have 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 majority of patients who do not carry BRCA1/2 mutation.
Targeting CEP55 in triple-negative breast cancer

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Breast cancer in females has now passed lung cancer as the most common diagnosed cancer. It affects over 10% of women before the age of 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.

This project 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. 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.

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.

**Genomic predictors of progestin response in endometrial cancer**

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The project is available for Honours or Masters students, full time.

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 analysed 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.

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**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 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 but many challenges remain. These include cancer relapse due to loss of CAR T cells; antigen escape and other yet undefined mechanisms; life-threatening neurological toxicity and cytokine release syndrome; and lack of significant success to date with CAR T cells targeting other cancers. This project involves developing and testing new concepts in CAR T cell engineering to improve their effectiveness, safety and applicability.
Cancer Precision Medicine Group

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The Cancer Precision Medicine Laboratory employs a multi-disciplinary approach involving genomics, proteomics and bioinformatics to characterise molecular alterations associated with various cancers. These alterations provide insights into mechanisms underlying molecular pathogenesis of cancers. They can also serve as biomarkers for identification and stratification of patient sub-groups that can benefit from targeted therapeutic intervention strategies. In addition, the lab works on delineating mechanisms of acquired resistance to kinase inhibitors and devising novel strategies to combat therapeutic resistance.

**Plasma protein biomarkers to predict immunotherapy response in lung cancers**

Suitable for PhD Students.

**BACKGROUND**

Immunotherapy has revolutionised cancer treatment in recent years. It has been successfully used to treat several melanoma and lung cancer patients. It is reasoned that the efficacy of immunotherapy in melanoma and lung cancers is due to high mutation burden, which potentially results in high load of cancer neo-antigens on the surface that can be recognised by immune cells. However, not all lung cancer patients with high mutation burden respond to immunotherapy. There is a clinical need for biomarkers that can identify lung cancer patients that are most likely to benefit from immunotherapy. In this project, we will employ mass spectrometry-based proteomics approaches to carry out plasma proteomic profiling of samples from lung cancer patients that undergo immunotherapy. The plasma proteome profiles of patients who respond to immunotherapy will be compared with those that do not respond to immunotherapy, to identify biomarkers of response. These markers will be useful to stratify lung cancer patients that are most likely to benefit from immunotherapy, from those that are unlikely to benefit.

**AIM**

Identification of protein biomarkers in plasma to predict immunotherapy response in lung cancers.

**HYPOTHESIS**

Lung cancer patients who respond to immunotherapy have a distinct plasma proteome profile compared to patients who do not respond.

**APPROACHES**

- High abundant protein depletion from plasma.
- Fractionation of plasma proteins using HPLC.
- Proteolytic digestion and sample preparation for plasma proteome profiling using mass spectrometry.
- Global proteomic profiling using mass spectrometry and data analysis.
- Targeted mass spectrometry and ELISA based methods to validate potential biomarkers.

**Novel approaches to augment immunotherapy response in cancers**

Suitable for PhD Students.

**BACKGROUND**

Immunotherapy has revolutionised cancer treatment in the last decade. This is exemplified by the success of checkpoint inhibitors in treating various cancers. T cells mount immune response by recognising peptide antigens presented by MHC complex on the cell surface. The nature of specific antigens recognized by T cells remains ill understood in cancers. Mutant proteins that harbor cancer specific coding variations are thought to be the primary source of cancer neo-antigens recognized by T cells. However, immunopeptidomics studies have shown that the number of mutant peptides from coding variations that are presented by MHC complex is extremely low. Mass spectrometry based immunopeptidomics studies from our lab indicates that aberrant expression of proteins from non-coding regions of the human genome is a major source of tumour neo-antigens. Enhancing the expression of these proteins in cancer cells can potentially increase the load of MHC class I presented neo-antigens.

We are investigating potential ways to enhance the expression of these non-canonical proteins by cancer cells. This strategy in combination with checkpoint inhibitors has the potential to augment immunotherapy responses in cancers.
AIM
To develop novel approaches to enhance expression of cancer neo-antigens and identification of antigens that can trigger T cell response in cancers.

HYPOTHESIS
Proteins encoded by non-coding regions in the human genome is a major source of cancer neo-antigens.

APPROACHES
• Mass spectrometry based immunopeptidomics.
• Transcriptomics and proteomics studies to identify proteins encoded by ‘non-coding’ regions in the human genome.
• Pharmacological inhibition and siRNA-based studies to identify targets to enhance neo-antigen production in cancer cells.
• Assays to identify neo-antigens that trigger T cell response.
• Animal studies to determine immunotherapy response in vivo.

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 Epigenetics and Disease 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 the 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.

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Determining the therapeutic efficacy of epigenetic drugs in ovarian cancer

BACKGROUND
Because cancer and many diseases arise from a combination of genetic propensity and the response of cells to external factors mediated through changes to the expression of key genes, it is important to understand epigenetic regulation. The epigenome is crucial to the changes of gene expression and there is now strong evidence that epigenetic alterations are key drivers of cancer progression. However, very few drugs targeting epigenetic modifiers have been successful, in part due to the lack of effective means to select the patient group in which they will be most effective. This highlights an urgent need to understand the molecular basis of epigenetic changes in aggressive cancer. Therefore, understanding the role of these enzymes in cancer progression using patient-derived samples will aid in improving existing therapies and potentially identify new targets for treatment.
HYPOTHESIS
1. Deregulation of epigenetic modifiers is responsible for cancer progression and metastasis.
2. Inhibiting the activity of epigenetic modifiers will allow re-expression of genes that may improve outcome of cancer patients.

AIM
The overall goal of this study is to develop a novel therapy targeting epigenetic modifiers and validate the epigenetically-suppressed gene signature that predicts outcome in aggressive cancer patient samples to generate a signature-based diagnostic tool that can identify cancer patients at high risk of recurrence and metastasis.

APPROACHES
• Cellular models and treatments.
• Characterisation of the epigenetic modifier change by RNA-seq.
• Promoter methylation analysis.
• Protein complex purification and proteomics.
• Immunoprecipitation assays.
• Characterisation of putative target genes by ChIP-seq.

Combining epigenetic drugs with immunotherapy in melanoma

BACKGROUND
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. In addition, prohibitive cost of immunotherapy can be overcome by therapy that uses relatively inexpensive small molecules. Patients suffer considerable side effects and these may be alleviated by changed drug doses when used in combination with other drugs. Thus, investigation of alternative approaches is essential. Recent studies have shed light on the importance of epigenetic regulation in cancer biology including overexpression of histone methyltransferases in cancers. Combining inhibitors of epigenetic modifiers may either enhance the efficacy of immunotherapy or treat those patients that have become resistant to therapy.

HYPOTHESIS
Combining epigenetic modifier inhibitors with immunotherapy will be more effective compared to using one drug alone.
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.

APPROACHES

• 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.

METHODS

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

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Screening of genetically identified compounds for endometrial cancer therapy

Can be adapted in scope for Honours or PhD.

BACKGROUND
There is promising evidence that genetic studies of cancer will advance the development of new therapies. For example, clinically approved drugs are more likely to target proteins that have been linked to disease traits through genome-wide association studies (GWAS) than proteins with no such links. Indeed, several drugs already used to treat endometrial cancer are known to target proteins that have been linked to genetic variation associated with endometrial cancer risk. To discover genes regulated by endometrial cancer GWAS variants, and hence potential drug targets, we have performed functional genomic analyses of endometrial cancer. These analyses revealed candidate targets tractable to small molecule inhibition. Three of these candidates are now undergoing a virtual small molecule screen, using artificial intelligence to prioritise compounds. Additionally, we have performed bioinformatic analysis of GWAS data, revealing existing drugs that may have efficacy for endometrial cancer.

AIM
To screen compounds, selected by artificial intelligence, for activity against candidate protein targets identified from endometrial cancer GWAS and assess the anti-cancer effects of prioritised compounds and existing drugs for anti-cancer effects.

APPROACH
We will use commercially available and previously reported assays to screen for the effects of compounds on the activity of candidate protein targets. Compounds with the strongest effects in protein assays will be prioritised for assessment of anti-cancer effects in novel endometrial organoid models. Existing drugs identified through bioinformatic analysis will also be tested in organoid models.

OUTCOME
Identification of novel compounds or existing drugs that have anti-cancer effects in organoid models would provide the necessary evidence for further development of these molecules, with the ultimate aim of conducting clinical studies of endometrial cancer.

Identifying the regulatory targets of common endometrial cancer risk variants

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.

**AIMS**

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.

**APPROACHES**

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 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, 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


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.

REFERENCES

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Brain Cancer Group

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Improving survival for adult brain cancer patients by targeting ‘sleeping’ cancer stem cells.

There are three distinct projects. Each of these are suitable for PhD students but can be considered in a revised format for Honours or Masters.

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, post-operative 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.
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.
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).

**Ovarian cancer risk factors for women with and without a pathogenic BRCA mutation**

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**

Women who carry a pathogenic BRCA gene variant are at greatly increased risk of developing ovarian cancer. While factors that affect ovarian cancer risk in the general population also appear to affect risk in BRCA carriers, this is not always the case and some factors have not been evaluated.

**AIM**

To evaluate whether factors known or suspected to affect risk of ovarian cancer differ between women with and without a pathogenic BRCA gene mutation.

**APPROACH**

A pooled analysis using individual-level data from the international Ovarian Cancer Association Consortium.

**Green tea consumption and survival 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**

Existing data suggest a potential relation between more green tea consumption and better survival after a diagnosis of ovarian cancer; however most studies that evaluated this have been restricted to information about tea consumption prior to diagnosis. The one study with information about consumption after diagnosis was conducted in China where patterns of green tea drinking are very different from Australia.

**AIM**

To evaluate the relation between tea and green tea consumption before and after a diagnosis of ovarian cancer and survival.

**APPROACH**

Survival analysis using individual-level data from women in the OPAL study who provided information about tea consumption before and after diagnosis (3-monthly for the first year then annually to 4 years).
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.

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.

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QSKIN: the burden of skin cancer

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.
Cancer Aetiology and Prevention Group

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The Cancer Aetiology and Prevention Laboratory 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.

Supportive Care in Cancer Group

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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, 40% of cancer carers are reported to experience complicated grief or prolonged grief disorder. Treatment-resistant depression often accompanies complicated grief; however, patients with complicated grief require grief-focused intervention in addition to the more usual depression-focused treatment. Three landmark double-blinded randomised controlled trials have shown a single dose 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, depression and existential distress. This will be the first trial specifically looking at psilocybin for complicated grief. The aim is to assess feasibility and acceptability of psilocybin as an addition to an existing counselling trial for 15 bereaved carers of patients with pancreatic cancer and to establish an initial impression of its efficacy. The project will involve qualitative interviews and analysis of participants’ data to evaluate their experience post intervention.

Mosquito Genomics Group

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Mosquito genomics for better control of mosquito-borne diseases

Projects can be adapted to suit Honours, Masters and PhD level students.

New technologies to control mosquitoes and diseases they transmit are developing rapidly – from the natural pathogen-blocking symbiotic bacteria to the engineered ‘selfish genes’. In creating and assessing new mosquito control technologies, we take the approach ‘from the field – to the lab – back to the field’. This means that we study natural mosquito populations, do laboratory experiments, and aim to produce practical solutions for field deployment. In doing so, we generate and analyse genomic data from a single mosquito cell to a system of mosquito populations.

We welcome students who are interested in using genomics to understand:

- How mosquitoes move and mate in different environments, before and after a control campaign (landscape genomics).
- How different genes affect mosquito development (identifying new targets for genetic control).

If these are not your cup of tea, but you are passionate about (hating or loving) mosquitoes and think you have good research ideas – get in touch – we might be able to help you pursue your dream mosquito project!
Molecular Cancer Epidemiology Group

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The Molecular Cancer Epidemiology Laboratory 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

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.
The **Statistical Genetics Laboratory** 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.

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**Genetics of skin cancer**

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 Medical Research Institute, including the Queensland Study of Melanoma: Environmental and Genetic Associations, the Queensland Twin Registry, and the QSkin Sun and Health Study 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. 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.
APPROACHES
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\(^4\).\(^5\). The overlap of skin cancer and its risk factors will be used to identify new genetic risks common to all traits\(^6\). Fine-mapping, bioinformatics, and post-GWAS approaches (e.g., gene-based tests) will be used to fully interpret identified genetic variants\(^5\). 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\(^7\). Mendelian randomisation will be used to determine if potential risk factors associated with skin cancer are causal\(^8\).

REFERENCES

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Eye disease genetics
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.

AIMS
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.

APPROACHES
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.
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.

Discovering novel immunoregulatory molecules that can be manipulated for clinical advantage

Suitable for PhD or Honours students.

Diseases caused by intracellular protozoan parasites that cause malaria and leishmaniasis require the generation of CD4+ T (Th1) cells that produce pro-inflammatory cytokines. These molecules stimulate dendritic cells (DCs) and macrophages to expand CD4+ T cell responses and activate phagocytes to kill captured or resident pathogens. However, the inflammatory cytokines produced by Th1 cells also damage tissues, and as such, need to be tightly regulated. A downside of this regulation is that it can allow parasites to persist and cause disease.

We identified unique gene signatures associated with regulatory CD4+ T cell subsets and will test if molecules associated with these signatures can be manipulated to improve responses to drug treatment and/or vaccines.

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

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.
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.

**METHODS**
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.

**METHODS**
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.
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.

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Structural biology

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.

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

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

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.

Improving the efficacy of T-cell therapy in vivo

Suitable for Masters or Short-term clinical Students.

BACKGROUND

Adoptive T-cell therapy (ACT) has shown good promise in the treatment of a range of virus-associated diseases and haematological cancers. However, it faces a number of barriers to efficacy against solid cancers, as the tumour microenvironment (TME) and disease burden play a critical role in regulating the clinical outcome of ACT. Cancer-intrinsic pathways alongside tumour heterogeneity dictate the hostility of the TME, enable immune escape, and facilitate adaptive resistance to ACT. These pathways involve receptor tyrosine kinase, anti-apoptosis, cancer metabolism, epigenetic and cell cycle pathways, which are the hallmarks of tumour progression and survival. We postulate that cancer-intrinsic pathways heavily contribute towards compromising anti-tumour immune responses and promote network rewiring that enables adaptive resistance against ACT. Therefore, molecular targeting of these pathways in combination with ACT forms a rational approach for the treatment of aggressive solid cancers.

AIM

This project will delineate the functional role of multiple cancer-intrinsic pathways in augmenting resistance to ACT, using a platform developed by our laboratory against Epstein–Barr virus (EBV)-associated solid cancers. In addition, the project will characterise the synergism of novel therapeutic strategies that include the combination of EBV-specific ACT and targeted therapy against cancer intrinsic pathways using small molecule inhibitors. The innovative aspect of this project comprises of the strategically targeting cancer-intrinsic pathways regulated by the EBV-associated latent genes using the respective small molecule inhibitors (SMI) to enhance the efficacy of T-cell therapy against solid cancers in the clinic. Importantly, these pathways are known to facilitate network rewiring upon challenge with anti-cancer therapeutics; hence characterising their function in supplementing resistance against T-cell therapy is of high significance. As a stand-alone, SMIs used for targeted therapy have shown low response rates with poor clinical outcome. The project will emphasise the concept of “repurposing” the use of SMIs to overcome a hostile TME and overcome cancer-imposed resistance as a rationale of combining with ACT. The creativity of this project stems from broadening the clinical applicability of SMI to enhance immune cell function and sensitise a hostile TME to a favourable TME, by overcoming adaptive
resistance; hence endorsing the rationale of formulating novel molecular-cellular therapies.

METHODS
The study will enable students to gain expertise in performing molecular techniques involving gene cloning, cell survival and killing assays, flow cytometry, immunofluorescence, and immunohistochemistry to generate in vitro data. It will also provide the opportunity to learn use of in vivo murine xenograft models to test the efficacy of the combination strategy, which in future might lead to a manuscript to be submitted in a highly reputed journal.

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

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. The CAR T cell program at the Tumour Immunology Laboratory aims to design and test novel CAR T cell therapies for virus-associated cancers.

AIM
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 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.

METHODS
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.
The Molecular Parasitology Laboratory researches the biology and epidemiology of parasitic worms of humans and works on developing new interventions and diagnostic procedures that will lead to their elimination.

The lab researches parasitic worms of humans, particularly schistosome blood flukes, which are responsible for the potentially debilitating disease schistosomiasis (Bilharzia), and dog tapeworms (Echinococcus), which are the cause of hydatid disease.

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Development of CRISPR based technology in schistosome bloodflukes

Suitable for PhD, Masters and Honours students.

Schistosomiasis is a serious global problem and the second most devastating parasitic disease after malaria. Currently, there is no effective vaccine available and treatment is entirely dependent on praziquantel chemotherapy, which raises significant potential threat to public health should drug resistance develop. The paucity of molecular tools to manipulate schistosome gene expression has made an understanding of genetic pathways in these parasites difficult, increasing the challenge of identifying new potential drug and vaccine candidates.

In this project, we aim to develop a CRISPR-mediated gene editing system in schistosomes for better understanding gene function, providing a powerful approach in the identification of new drug and vaccine targets and the unravelling of potential drug resistance mechanisms. We will perform CRISPR-Cas9-mediated gene editing in different life cycle stages of schistosomes and test/validate the gene modification efficiency by next generation sequencing and further phenotypic studies. This CRISPR-Cas9 system in schistosomes will significantly improve the ability to manipulate the schistosome genome. In addition, by using CRISPR-Cas12/13 based system, we will develop fast, accurate and portable diagnostic tools for the diagnosis of schistosomiasis. This research has the potential to be extended for diagnosing other neglected tropical diseases in the future.

Development of new interventions including vaccines, DNA diagnostics and serological markers essential for ending neglected tropical diseases caused by schistosomes and intestinal worms in Asia and Africa

Suitable for PhD or Honours students.

The Neglected Tropical Diseases (NTDs) are a group of parasitic/bacterial diseases that cause substantial morbidity for more than one billion people globally. Afflicting the world’s poorest people, NTDs cause severe disability, hinder growth, productivity and cognitive development, and often end in death. Children are disproportionately affected. Asia is a NTD hot spot claiming some of the highest infection rates in the world, second only to that of sub-Saharan Africa. Approximately one-third of the world’s parasitic worm infestations occur in this region. Our laboratory focuses on understanding the biology and epidemiology of NTDs caused by parasitic worm infections due to the Schistosoma blood flukes (schistosomiasis), the Echinococcus (hydatid) tapeworms (echinococcosis) and soil transmitted helminthiases – diseases of the world’s poorest people that result in both major suffering and economic loss.

Our laboratory has research projects suitable for PhD study in:

- Schistosomiasis epidemiology, surveillance and response with a focus in China.
- Schistosomiasis vaccine development/deployment.
- Epidemiological studies and research to eliminate echinococcosis in China through integrated control approaches.
- “Magic Glasses” Asia: Testing a video-based health educational intervention package for its impact on intestinal parasitic worm incidence, knowledge and hygiene behaviour in primary school children in Asia.
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 diseases such as cystic fibrosis and biliary atresia.

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

Projects 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. 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**

Projects 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.

AIMS
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.

APPROACHES
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 persists, 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.

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

APPROACHES
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 ß-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.

AIMS
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 ß-thalassaemia.

APPROACHES
Initial experiments will involve knocking out hephaestin in mouse models of haemochromatosis and ß-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 β-thalassaemia.

AIMS

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.

APPROACHES

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 β-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**

**Group Leader: Associate Professor Simon Phipps**

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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.

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**Insights into the influence of maternal diet on the severity of infant viral bronchiolitis**

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.
**Microbiome and neonatal immune development in early life**

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.

**The role of prostaglandins in chronic respiratory diseases (e.g. COPD and asthma)**

Prostaglandin D2 is a lipid mediator generated from the metabolism of arachidonic acid. We recently discovered (Werder et al, Science Translational Medicine) that PGD2 can enhance or suppress the production of type III IFN, a potent antiviral cytokine. This contrasting effect is dependent on the receptor subtype that is activated. In both COPD and asthma, acute exacerbations (or ‘attacks’) are associated with a respiratory infection, and in the setting of a viral infection, this has been associated with impaired production of type I and III IFNs. Here we will use clinical samples and a preclinical model of COPD to investigate whether PGD2 levels are elevated and whether this mediator contributes to the loss in viral control. We will also explore the molecular mechanism by which DP1 agonism promotes the production of innate IFNs.

**Cell death pathways and the induction of type-2 inflammation**

It is now recognised that there are several different types of cell deaths. Importantly, the mode of cell death affects the ensuing immune response. We have recognised an important role for necroptosis in the induction of type-2 inflammation and immunity, which is the predominant module of immunity that underpins allergic diseases such as asthma. In this project, we will employ experimental mouse models and in vitro culture models of primary airway epithelial cells to elucidate the molecular processes that initiate and regulate necroptosis.
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 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.

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.

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

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.

Brain Modelling Group

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.
- How flashing lights can drive nonlinear brain responses with application to migraine.
- Developing novel analysis methods for complex spatiotemporal dynamics.

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Novel methods for monitoring brain activity in preterm babies

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 neurodevelopmental outcome, 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.

Neonatal seizures as a biomarker of underlying pathology

Suitable for Honours students only.

Neonatal seizures are a common emergency in the neonatal intensive care unit. They are independently associated with poor neurodevelopmental outcome and are aggressively treated with an array of anti-seizure medications. The diagnostic utility of seizures is less well studied. In this project, we aim to characterise the spatial patterning, temporal behaviour and morphology of seizures to find differences with respect to the underlying aetiology of seizure generation.

Regional maturation in developing brain function

Suitable for Honours students only.

The brain develops at an astounding rate at, and around, birth. Structural and functional imaging with MRI and EEG shows clear changes at a resolution of weeks. In this project, we will investigate the functional maturation of the brain in preterm infants using EEG at the level of brain region. Regional maturation in the presence of diffuse neurological injury will then be studied to determine the clinical utility of maturational assessments (growth charts).
Translational Neurogenomics Group

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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

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 DO 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 DO 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**

**Senior Scientist:**
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The Genetic Epidemiology Laboratory 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.

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**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 in 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.

**Cracking the genetic code of Parkinson's disease**

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 in coding, analysing and plotting data using R/Python.

**BACKGROUND**

Parkinson’s disease (PD) is a genetically complex disease that affects >100,000 Australians, and the number of patients worldwide is estimated to be around 10 million. PD is the second most common neurological disorder, the second most common cause of dementia, and the fastest-growing neurodegenerative disease in Australia, with approximately 32 newly diagnosed patients every day. PD is a progressive condition, and the onset, intensity and progression of its motor and non-motor symptoms vary significantly from patient to patient.

**AIM**

To advance understanding of the environmental and genetic factors contributing to differences in Parkinson’s disease risk, susceptibility, treatment response and progression.
APPROACH
As part of the Australian Parkinson’s Genetics Study (APGS), we collected patient-reported measures on a range of sociodemographic, clinical and lifestyle variables from thousands of individuals with PD from all over Australia. The student will conduct statistical and computational analyses to identify risk and protective factors (including genetic biomarkers) for Parkinson’s disease and its associated variables.

OUTCOME
The characterisation of risk and protective factors may provide essential insights into the pathological mechanisms of PD development throughout the lifespan, leading to preventative and therapeutic interventions, including disease-modifying therapies.

Genetic and brain structure correlates of suicidal behaviour and mental illness

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
Suicide is a leading cause of death worldwide, taking the lives of more than 800,000 people annually. The aetiology of suicidal behaviour is complex and multifactorial and is influenced by genetic factors. Despite decades of research, there are currently no tools available for accurately predicting suicide risk and identifying individuals at increased risk. Together with the International Suicide Genetics Consortium, we have recently identified genetic markers for suicide attempt risk.

AIM
The proposed project aims to disentangle the biological basis of suicidal behaviour and other mental health disorders by combining large datasets with clinical, psychometric, clinical, neuroimaging and genetic data.

APPROACH
The student will conduct statistical and computational data analyses to characterise molecular and neuroimaging biomarkers, pathways and mechanisms implicated in the aetiology of suicidal behaviour and mental illness. The student will be actively engaged as part of international consortia such as the ENIGMA Suicidal Thoughts and Behaviour working group and the International Suicide Genetics Consortium.

OUTCOME
Understanding the biological basis of suicidal behaviour and mental illness is essential to devise new screening, intervention, and therapeutic strategies to fight the leading preventable cause of death worldwide.

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Identifying individuals at high risk of Alzheimer’s disease

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.

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 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.

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

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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