2024-25
STUDENT PROJECTS

QIMR Berghofer
Medical Research Institute

Director's Welcome

By all measures, QIMR Berghofer is one of the leading medical research institutes in Australia. In fact, in 2023 QIMR Berghofer was ranked second in Australia for its success rate with National Health and Medical Research Council (NHMRC) research grants. Our mission is to deliver 'better health through impactful medical research', and we do that by developing new diagnostics, better treatments and more effective strategies to prevent disease. Research at the Institute is channelled through four clinically relevant programs: Cancer Research, Infection and Inflammation, Mental Health and Neuroscience, and Population Health (disease causation, prevention and control).

The Institute is home to more than 1000 scientists, staff and students who consistently generate formidable, high-quality research. In 2022-2023, QIMR Berghofer researchers published 621 unique publications that were cited 709 times, and income from commercial collaborations and contract research was over $12 million. The Institute also ranked number one in the Nature Index NPR/NGO for Australia in 2022-2023.

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

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

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

Professor Fabienne Mackay

Director and CEO

QIMR Berghofer Medical Research Institute

QIMR Berghofer
Medical Research Institute

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Quick facts about QIMR Berghofer

QIMR Berghofer Student Society

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

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

Attendees at the 12th QIMR Berghofer Biennial Postgraduate Student Conference – Mercure Clear Mountain Lodge, Spa & Vineyard, Brisbane Queensland

Why study at QIMR Berghofer?

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

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

Clinician scientists undertake a fundamental role in medical research translation, bridging the gap between research and clinical practice. They bring a valued perspective to QIMR Berghofer, with their research informed by their experiences in Queensland hospitals and other clinical settings.

Professor Elizabeth Powell is the Clinical Director at the Institute. She is overseeing the career development, professional development, academic training, and mentorship for clinician researchers. We hope to strengthen and improve the Institute's integration with hospitals, clinics and clinicians by cultivating opportunities for clinicians and researchers to work collaboratively together. If you are interested in these opportunities, please contact Professor Powell to discuss your interest further.

Clinical Director: Professor Elizabeth Powell

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Elizabeth.Powell@qimrberghofer.edu.au

PROFESSOR POWELL'S CAREER PROFILE:

Professor Elizabeth Powell, a Hepatologist and Senior Staff Specialist, Department of Gastroenterology, Princess Alexandra Hospital, is the Clinical Director at QIMR Berghofer. She is also Director of the network Centre for Liver Disease Research and Professor, School of Medicine, The University of Queensland. She leads a productive research program in chronic liver disease, bridging clinical research and basic science, and mentoring the career development of emerging researchers and clinicians. She has held three 5-year NHMRC Practitioner Fellowships, and a Queensland Health Clinical Research Fellowship. Her seminal work includes shaping two new paradigms in hepatology research: the importance of metabolic risk factors in the progression of chronic liver disease and proposing altered hepatic regeneration and the ductular reaction as a potential driver of hepatic fibrosis. Over the last 5 years she has led research of emerging themes in hepatology research, examining the role of injury-stratifying biomarkers and pathways of care for metabolic dysfunction-associated steatotic liver disease (MASLD) and chronic liver disease. A significant contribution has been to foster a multidisciplinary, collaborative approach to the field, involving hepatopathology together with molecular and clinical hepatology research.

QIMR Berghofer Services

HISTOLOGY FACILITY

The QIMR Berghofer Histology Facility provides expertise, technical services, and consultation on: routine paraffin and cryo histology; special stains; IHC (TSA) and antibody optimisation, FISH and CISH labelling, TMA preparation and high-resolution digitisation of histology slides (e.g. Vectra Imaging System). The facility caters to the needs of scientists and postgraduate students from QIMR Berghofer as well as external and international institutions.

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

SAMPLE PROCESSING

The Sample Processing Service provides expertise and service for the pre-analytical preparation of biological samples. The service works alongside researchers and clients, to design bespoke solutions for the collection, transportation, storage, aliquoting, blood fractioning and cell isolation, nucleic extraction (DNA and RNA extraction), sample QC, and PCR; designed to efficiently and economically meet requirements. Capacity for high throughput processing or single sample processing is accommodated. The service dovetails a range of other Scientific Services to provide a seamless product from sample collection to data and supports a range of other analytical and scientific services at QIMR Berghofer.

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

Immunophenotyping and profiling of different immune cell populations is crucial in immunology research, making flow cytometry an indispensable tool that enables large amounts of complex and comprehensive data to be acquired in a short period of time.

At QIMR Berghofer, our Flow Cytometry Facility consists of internationally recognized cytometry experts that provide world-class flow cytometry services for scientists in Australia and beyond. We work alongside researchers, ensuring up-to-date technology and analytical software to accommodate the applications required by our scientists, and these services are also available to external clients.

The facility is well equipped with a range of different flow cytometers (conventional, spectral, and image cytometers), cell sorters and data analysis software, as well as a dedicated space for the processing of clinical samples.

The Microscopy Facility at QIMR Berghofer is equipped with a comprehensive range of instruments for imaging both fixed or living cells and tissue. These include stereo microscopes, slide scanners, compound microscopes, confocal microscopes, intra-vital microscopes, a scanning electron microscope and various analysis stations and software. We are equipped to capture images of cells or tissue stained with colourimetric dyes or fluorescent dyes at various resolutions from macro to super resolution. We have recently expanded our capabilities to provide cyclic immunofluorescence using the Akoya Phenocycler and spatial molecular imaging (molecular transcripts and protein) with the CosMx and the Xenium microscopes.

We provide technical assistance and training on all instruments and software as well as full service on all instruments for researchers who wish to use the facility.

SEQUENCING AND ANALYTICAL SERVICES

The QIMR Berghofer Sequencing and Analytical Service employs both Next Generation and Sanger sequencing to deliver reproducible high quality genomics data. Services include:

- RNAseq using mRNA capture and rRNA depletion for library transcripts.
- Chromium 10X single cell barcoding for gene expression and antibody capture NGS.
- Human exome capture including TSO500 clinical exome panels and human exome panels.
- Verification of pcr amplicons and plasmids using capillary sequencing.

The use of contaminated and misidentified cell lines in biomedical research has proliferated to a point where high impact journals require diagnostic evidence that

cell lines are free from Mycoplasma contamination and authenticated as the correct cell line via Short Tandem Repeat DNA sequencing. We provide a service for the detection of viable Mycoplasma in tissue culture, requiring only 1mL of spent media, to detect as low as 50 cfu's. Our human cell line authentication service uses Short Tandem Repeats (STR) to validate cell line authenticity. A minimum of 10 markers are used to identify a cell line (conforms to ATCC ASN-0002 standard) from as little as 50ng of genomic DNA. Our experienced staff can also offer advice for problematic allelic spectral interpretations.

METABOLOMICS

Metabolomics investigations aim to achieve the comprehensive characterisation of the complement of metabolites in biological systems (i.e. the metabolome). They can provide an overview of the metabolic status and global biochemical events associated with a cellular or biological system, and can be used to deduce mechanistic understanding of the biochemical/ metabolic changes that occur during the onset, progression or as a consequence of disease, or as a result of treatment.

The Metabolomics Facility at QIMR Berghofer comprises two liquid chromatography-mass spectrometry (LCMS) systems and an automated liquid handler. These instruments provide the capability to perform quantitative analysis using triple quadrupole-based tandem mass spectrometry (QqQ-MS), or discovery analysis using quadrupole-time-of-flight mass spectrometry (Q-ToF-MS). Thus, the facility is equipped to undertake metabolomics analysis in both targeted and untargeted modalities.

We have longstanding expertise in metabolomics, from study design through analysis to data interpretation. We are able to provide this expertise to undertake service projects, or to provide training to users wishing to learn these skills to perform analyses themselves

PROTEOMICS

Mass spectrometry is a powerful analytical tool that currently represents the most comprehensive approach for profiling proteins, and allows for the identification and quantitation of thousands of proteins from a single analysis. Using mass spectrometry-based proteomic techniques, we can study how protein concentrations change across varying conditions, identify protein interaction partners, and uncover targets and off-targets of drugs, making it a valuable resource for biological scientists. Mass spectrometry is a powerful analytical tool that currently represents the most comprehensive approach for profiling proteins, and allows for the identification and quantitation of thousands of proteins from a single analysis. Using mass spectrometry-based proteomic techniques, we can study how protein concentrations change across varying conditions, identify protein interaction partners, and uncover targets and off-targets of drugs, making it a valuable resource for biological scientists.

The Proteomics Facility at QIMR Berghofer currently comprises two liquid chromatography-mass spectrometry (LC-MS) systems and an off-line LC-based fraction collector. These instruments provide the capability to perform both quantitative and qualitative/ discovery analysis, as well as to separate (fractionate) samples for a focussed analysis.

We have diverse expertise in proteomics and are able to provide this expertise to undertake service-based projects, or to provide training to users wishing to learn these skills to perform analyses themselves.

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.

HIGH PERFORMANCE COMPUTING (HPC)

The Genome Informatics group manages QIMR Berghofer's high-performance computer cluster which is available to all staff and students. The cluster has over 2000 CPU cores, 12 PB of disk and a growing number of GPU nodes to support artificial intelligence workflows. It has about 500 scientific software packages installed for general use in addition to thousands of packages for R and Python. New software is constantly being installed as requested by researchers.

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 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 Program

Through The University of Queensland, QUT, and Australian Catholic University, we offer vacation research experience. These are small projects carried out over a 4-8 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/

Projects Webpage:
https://www.qimrberghofer.edu.au/student-projects/

For Further Inquiries, 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 with.

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 Teams/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 applicable).

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/

Projects Webpage:
https://www.qimrberghofer.edu.au/student-projects/

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

Cancer Program

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

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

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

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

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

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

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

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

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

Laboratory of B-lymphocytes in Autoimmunity and Malignancies

Director and CEO, Group Leader: Professor Fabienne Mackay

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www.qimrberghofer.edu.au/our-research/cancer-research/b-lymphocytes-in-autoimmunity-and-malignancies/

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

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

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

Co-Supervisor: Dr M Arifur Rahman

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

BACKGROUND

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

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

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

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

AIMS

The aims of this project are to:

- Evaluate the therapeutic effect of diet in a patient derived xenogeneic (PDX) model of CLL.
- Identify the metabolites associated with the ketogenic diet-mediated protection against CLL in the PDX model.
- Test the anti-leukaemic function of the metabolites in-vitro.
- Understand the molecular function of these metabolites (such as receptors, target cells, and signaling).
- Evaluate the anti-leukaemic metabolites in mouse and PDX models of CLL.

The identification of anti-leukaemic metabolite/s will facilitate development of a new class of drugs, with a novel mechanism of action and minimal side effects. Through these studies, the student will gain significant expertise in mouse models of disease, cell culture, flow cytometry, immunohistochemistry, and metabolomics. This project has a high potential for translation and interaction with industry.

PROJECT POTENTIAL

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

Discovering novel immunoregulatory molecules underlying the pathogenesis of systemic lupus erythematosus

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

BACKGROUND

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

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

AIMS

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

This project will use a range of immunological techniques (mouse models of experimental SLE, flow cytometry, confocal microscopy, ELISA), metagenomic sequencing, microbiome analysis and metabolomics to characterise the immunological mechanisms of action. We will validate the research findings using clinical samples.

PROJECT POTENTIAL

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

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

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

BACKGROUND

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

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This project will use a range of immunological techniques (mouse models of experimental SLE, flow cytometry, confocal microscopy, ELISA), metagenomic sequencing, microbiome analysis and metabolomics to characterise the immunological mechanisms of action. We will validate the research findings using clinical samples.

PROJECT POTENTIAL

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

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

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

BACKGROUND

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

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

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

AIMS

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

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

PROJECT POTENTIAL

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

Can diet influence immune tolerance?

This project is suitable for an Honours or Masters student.

BACKGROUND

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

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

This project will explore the following hypothesis: can diet (eg. high fat) prevent negative selection and therefore promote autoimmunity? To explore this, the above two models of B cell tolerance described will be fed with

various diets and the impact of diet on the emergence of self-reactive B cells and their activation status will be investigated.

AIMS

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

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

PROJECT POTENTIAL

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

Functional Cancer Genomics & Functional Genetics Laboratories

Senior Group Leader: 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 cancer genome-wide association studies (GWAS). This includes identification of the functional risk variants, connecting these variants to their target genes and understanding how the new genes contribute to cellular phenotypes. Our research integrates genetics, chromatin and transcriptome profiling, computational genomics and molecular studies to unravel the complexity of cancer development. These discoveries have accelerated progress from genetic studies to biological knowledge that may ultimately guide preventative and therapeutic measures.

Senior Group Leader and Program Director (Cancer): 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.

Evaluation of new long-noncoding RNAs driving Breast or Ovarian Cancer development

This project is suitable for Honours or PhD students.

BACKGROUND

It is now clear 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 is still not well understood.

Genome wide association studies (GWAS) have identified thousands of common variants associated with an increased risk of breast and ovarian cancers. Large-scale genome sequencing projects have also identified regions of the genome that are frequently mutated in breast and ovarian cancers. Importantly, the majority of these disease-associated variants and mutations lie within intergenic regions and introns of protein-coding genes, suggesting that undiscovered RNA transcripts such as lncRNAs, may play a direct role in cancer development. We have recently used different RNA sequencing and bioinformatic approaches to identify hundreds of new breast and ovarian cancer-related lncRNAs.

AIMS

We have recently used RNA sequencing and bioinformatic approaches to identify hundreds of new cancer-related lncRNAs. We now want to understand how these lncRNAs modulate breast and ovarian cancer development.

METHODS

Projects will use multiple in vitro approaches to determine how the variants and mutations alter lncRNA function, including CRISPR-based lncRNA editing and reporter assays. We will link lncRNAs to their target protein-coding genes using HiChIP chromatin assays and CROP-seq experiments. We expect that some of the lncRNAs will have cancer-related biological functions. We will therefore overexpress or silence lncRNAs in breast and ovarian cancer cells and examine their effects on cell growth, response to DNA damage, apoptosis, migration and tumour formation. We will also assess the function of lncRNAs in tumour formation using an explant assays in mice. The discovery of novel regulatory lncRNAs influencing cancer development may reveal entirely new avenues for breast and ovarian cancer therapeutics.

Students will have access to unique expertise and reagents, and will acquire skills in tissue culture, CRISPR-based methods, RNA and DNA manipulation, confocal microscopy, FACS analyses and other molecular biology techniques.

Molecular Oncology Group

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

Re-sensitising treatment resistant metastatic ovarian cancer

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This project is suitable for honours or masters students.

High grade serous ovarian cancer is most often detected after it has moved away from the ovaries and fallopian tubes, where it is harder to treat and almost always becomes resistant to current treatments. Standard therapy relies on tumour cells being unable to accurately repair DNA damage due to mutations in common DNA damage response genes. Resistance to treatment occurs when tumour cells gain further mutations to bypass or repair mutated genes to re-enable accurate DNA repair.

The project will employ CRISPR screening, cell and molecular biology techniques to investigate mechanisms of resistance and identify novel strategies for re-sensitising ovarian cancer to therapy.

Translational Cancer Immunotherapy Group

Group Leader: Associate Professor Siok Tey

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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), which is the most established form of cancer immunotherapy, but it is 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

This project is suitable for Honours, Masters and PhD students.

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

FOCUS/AIMS

- To develop new CAR T cells that are directed at novel antigens or combination of antigens using novel gating strategies.
- To develop CAR T cells with different signalling functionality to enable their evasion of the immunosuppressive tumour microenvironment.
- To examine the fate of CAR T cells and the bystander immune compartment in clinical CAR T cell therapy.

APPROACH/ METHOD

- Molecular biology approaches to design and clone new CAR constructs and the generation of CAR T cells using viral vectors.
- Functional testing of CAR T cells in vitro and in vivo using immunological techniques, including flow cytometry, live cell imaging and small animal models.
- Analysis of clinical samples and correlation with clinical data.

Understanding the immunobiology of bone marrow transplantation

Co-supervisor: Dr Andrea Henden

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This project is suitable for Honours or Master students.

BACKGROUND

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

FOCUS POINTS/AIMS

- To examine the impact of the gastrointestinal microbiome on T cell function and GVHD.
- To examine the fate of T cell and non-T cell immune populations after BMT and the impact of viral infection and cytokines on immune reconstitution.

APPROACH/ METHOD

- Immunophenotyping including flow cytometry and spectral cytometry.
- Measurement of soluble immune mediators.
- Correlation with clinical outcome data.

Cancer Genetic Susceptibility Laboratory

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

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Identifying the regulatory targets of common endometrial cancer risk variants

This project 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

This project is 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, 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 randomization. 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.

Transplantation Immunology Laboratory

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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.

Research conducted by the Transplantation 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.

Harnessing the gut microbiome to improve stem cell transplantation

Aspects of this project would be suitable for Honours, Masters, MPhil, MD and PhD students. Email the supervisor to discuss suitability.

BACKGROUND

Haematopoietic stem cell transplantation (HSCT) is considered the gold standard procedure for the treatment of high-risk blood cancers. However, graft-versus-host disease (GVHD) remains a barrier to the success of this life-saving immunotherapy. GVHD occurs in 50-70% of transplanted patients, of which 20% will develop severe GVHD which is unresponsive to therapy and is eventually fatal. Thus there is an urgent need for new treatments. Systemic exposure to gut microbes (and their derivatives) which are normally sequestered in the lumen, are initiated by chemotherapy/radiation treatment prior to transplant and can have profound effects on GVHD severity. Antibiotic-based approaches to deplete the microbiome and prevent acute GVHD have been partially successful, however increasing antibiotic resistance and the realization that many bacteria have important anti-inflammatory properties severely limits this approach.

AIM

This project aims to improve our fundamental understanding of microbial-host interactions which regulate protective and pathogenic mechanisms after transplant.

METHODS

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

PROJECT POTENTIAL

This research will generate new knowledge and lead to the identification of novel strategies to prevent and/or treat acute gastrointestinal GVHD.

Understanding infectious respiratory complications after stem cell transplantation

Aspects of this project would be suitable for Honours, Masters, MPhil, MD and PhD students. Email the supervisor to discuss suitability.

BACKGROUND

Respiratory viral infections are a major global public health problem. RSV-induced bronchiolitis and pneumonia are the leading cause of hospitalization in infants and young children worldwide, while in adult allogeneic hematopoietic stem cell transplant (HSCT) recipients the incidence of progression from upper to lower respiratory tract infection is 40-60%, with mortality rates as high as 80%. With the 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, to address the knowledge gaps in the field.

AIM

This project aims to investigate fundamental immunological mechanisms which underlie the RSV-mediated post-transplant complication.

METHODS

This project will involve animal work, high-parameter flow cytometry, single-cell transcriptomics, spatial transcriptomics, proteomics, digital PCR and histopathology; with the validation of findings in clinical samples.

PROJECT POTENTIAL

This research will lead to the delineation of critical mechanisms which underpin fatal pneumonitis, and the identification of potential therapeutic targets to ameliorate RSV-driven HSCT transplant mortality.

Identifying novel MAIT cell expansion strategies to mitigate graft-versus-host disease

Aspects of this project would be suitable for Honours, Masters, MPhil, MD and PhD students. Email the supervisor to discuss suitability.

BACKGROUND

Mucosal-associated invariant T cells (MAIT cells) are an important regulatory subset which possess potent anti-microbial functions, primarily due to their rapid, diverse and expansive cytokine production. Initially, MAIT cells were shown to respond to vitamin B-derived microbial metabolites presented by the MHC class I-like molecule MR1, however increasing evidence now shows activation via MR1-independent mechanisms such as cytokine-mediated pathways. We have shown recipient MAIT cells control gut barrier function, in part via interleukin-17A, to attenuate pathogenic T cell responses in the colon and protect against the development of acute graft-versus-host disease.

AIM

This project aims to validate newly identified candidates that expand MAIT cells in vivo.

METHODS

This project will involve ex vivo murine and human PBMC functional assays, high-parameter flow cytometry, cellular metabolism assays, gut organoid cultures and immunofluorescence microscopy.

PROJECT POTENTIAL

This translationally-focused research builds on strong preclinical findings and is pertinent for the development of MAIT cell-based immunotherapeutic approaches to treat gut GVHD in the clinic.

In situ immune cell profiling using spatial transcriptomics in gastrointestinal graft-versus-host disease

Aspects of this project would be suitable for Honours, Masters, MPhil, MD and PhD students. Email the supervisor to discuss suitability.

BACKGROUND

Acute gastrointestinal graft-versus-host disease (GVHD) is a common, life-threatening complication following allogeneic haematopoietic stem cell transplantation. Gut GVHD occurs when donor-derived T-cells traffic to host GI tract tissue in response to cytokine release during conditioning chemotherapy, resulting in T cell mediated apoptosis of GI tract mucosa. Early identification of patients at greatest risk of gut GVHD would allow for trials of early escalation of immune-suppressing treatment to prevent gut GVHD onset or ameliorate its severity. Currently, there is a lack of predictive tools for the early detection of acute gut GVHD. Although blood based biomarkers are relatively easily obtained, they are often less informative compared with tissue-based biomarkers.

AIM

This project aims to examine the feasibility of applying spatial transcriptomics in the diagnosis and prognostication of acute gut GVHD.

METHODS

This project will involve spatial transcriptomics, computational analysis, histopathology and microscopy techniques.

PROJECT POTENTIAL

This research will generate tissue specific cellular transcriptomic signatures that may serve as potential biomarkers to improve early acute gut GVHD diagnosis and prognostication.

Cancer Neuroscience Laboratory

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

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

Multiple projects available to suit Honours or PhD students.

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

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

Specifically, this project will:

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

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

Multiple projects available to suit Honours or PhD students.

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

Gordon and Jessie Gilmour Leukemia Research Laboratory

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

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

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

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

MPNs are a group of disorders characterised by the excess production of mature myeloid cells. MPNs are driven by the constitutive activation of the JAK-STAT signalling pathway as a consequence of mutations in either JAK2, MPL or CALR in haematopoietic stem cells (HSC). Pioneering work from our laboratory has

demonstrated the efficacy of interferon alpha (IFNα) in the preferential targeting of MPN stem cells. In addition to these MPN-driver mutations, patients often present with additional mutations that can alter disease presentation. It is currently unclear if and how the presence of additional mutations may alter treatment outcomes in MPN, particularly in response to IFNα, and what mutation combinations are sufficient to drive transformation to leukaemia.

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

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

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

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

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

Role of MYC in leukaemic cell differentiation

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

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

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

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

What determines leukaemic stem cell maintenance and resistance to chemotherapy?

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

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

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

Leukaemia Metabolism Laboratory

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The Leukaemia Metabolism Laboratory investigates topics at the interface of oncology, immunology and biochemistry with a focus on Acute Myeloid Leukaemia (AML), a very aggressive and rapidly fatal disease. A major aspect of its research program is the development of humanised mouse models using patient samples, normal cord blood or bone marrow-derived stem cells and recently engineered, improved recipient mouse strains to model systemic disease. We apply integrated omics profiling and single cell sequencing in combination with CRISPR/Cas9-mediated gene editing to characterise the molecular responses to standard and novel therapies. Specifically, the lab investigates the role of lipid desaturation and ferroptosis in leukaemic stem and immune cell compartments, and aims to identify metabolic vulnerabilities that can be exploited to develop novel, effective therapies for AML.

Metabolism-Focused Preclinical Development of Therapies for Acute Myeloid Leukaemia

This project is suitable for Honours and PhD students.

BACKGROUND

Acute myeloid leukaemia (AML) is an aggressive and lethal blood cancer with a 5-year overall survival of less than 45% for patients younger than 60 years of age, or less than 10% for older patients. In Australia, about 1,000 patients are newly diagnosed with AML each year, and about 60,000 new AML patients per year are estimated for the developed world in total. Most patients initially respond to chemotherapy but ultimately relapse and die from disease. Relapse is mediated by leukaemia stem cells (LSCs) that initiate, maintain and serially propagate AML. The development of therapeutic strategies to target leukaemia stem cells is therefore a promising approach and key priority.

We have previously identified a specific vulnerability of LSCs to genetic telomerase inhibition, and subsequently performed comprehensive, randomised, Phase II – like preclinical trials of imetelstat in AML patient-derived xenograft (PDX) models. Using extensive mutational, transcriptional and lipidomic profiling techniques in combination with functional genetics (genome-wide CRISPR/Cas9 knockout screens), we have identified molecular driver candidates for resistance and response to imetelstat therapy, and discovered lipopagy-induced ferroptosis as unexpected mechanism of action of imetelstat in AML.

AIM

The aim of this project (Honours component) is to better characterise imetelstat-mediated lipophagy-induced ferroptosis in AML. These findings will reveal critical insight into the mechanism of action of imetelstat, facilitating the development of effective combination

therapies and selection of AML patient subgroups that will respond best to this treatment.

This Honours project is not limited to but will involve cell culture techniques, molecular biology, immunoblotting, metabolomics and flow cytometry.

The project suitable for a PhD student will aim to:

1. Define metabolic biomarkers of resistance and response to imetelstat.
2. Identify metabolic vulnerabilities of therapy-resistant AMLs.
3. Evaluate the effectiveness of sequential combination therapies that target putative metabolic vulnerabilities of AML cells to effectively combat AML relapse.

This PhD project involves a breadth of wet and dry lab techniques, prior experience with small rodent work is highly desired but not essential.

SELECTED PUBLICATIONS

» Bruedigam C, Porter AH, Song A, Vroeg In de Wei G, Stoll T, Straube J, Cooper L, Cheng G, Kahl VFS, Sobinoff AP, Ling VY, Jebaraj BMC, Janardhanan Y, Haldar R, Bray LJ, Bullinger L, Heidel FH, Kennedy GA, Hill MM, Pickett HA, Abdel-Wahab O, Hartel G, Lane SW. Imetelstat-mediated alterations in fatty acid metabolism to induce ferroptosis as a therapeutic strategy for acute myeloid leukemia. *Nature Cancer* 2023.

» Waksal JA, Bruedigam C, Komrokji RS, Jamieson CHM, Mascarenhas JO. Telomerase-targeted therapies in myeloid malignancies. *Blood Advances* 2023.

» Bruedigam C, Bagger FO, Heidel FH, Paine Kuhn C, Guignes S, Song A, Austin R, Vu T, Lee E, Riyat S, Moore AS, Lock RB, Bullinger L, Hill GR, Armstrong SA, Williams DA, Lane SW. Telomerase inhibition effectively targets mouse and human AML stem cells and delays relapse following chemotherapy. *Cell Stem Cell* 2014.

Cancer Genetics and Genome Variation and Regulation in Disease Laboratories

Distinguished 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.

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

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

Identifying the causal genes at cancer risk loci

This project is 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.

Cancer Metabolism Group

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Google Scholar: https://scholar.google.com/citations?user=DvDo86sAAAAJ&hl=en

These projects can be adapted in scope for Honours or PhD students.

The Cancer Metabolism Group is keenly interested in how the physiological state of a person affect cancers. Over a person's lifetime somatic cells will accumulate spontaneously occurring gene mutations, the majority of which do not cause disease. The global incidence of cancer has more than doubled over the past 30 years – primarily due to increasing living standards, modern lifestyles and an ageing population. The common denominator for these is alterations to the physiological homeostasis of the individual at risk rather than a change in mutational burden. This strongly implies that the interaction of physiological conditions with cells harbouring oncogenic mutations govern cancer risk. The main focus of the lab has so far been obesity – however going forward, we plan to incorporate exercise and fasting in our research program.

Mechanistic understanding of how obesity causes cancer

Obesity increases the risk of developing thirteen types of cancer that normal weight individuals may not develop despite of harbouring the same cancer risk loci. Globally, overweight/obesity may account for 544 300 cancer cases every year and is currently implicated in 15-20% of cancer-related mortalities. This places obesity second only to smoking as the most prevalent preventable cause of cancer.

Research project #1: What are the properties of cancer cells adapted to aberrant physiological environments?

We have previously demonstrated that obesity is not associated with additional oncogenic genetic alterations that could explain the increased cancer risk. Instead, we demonstrate that cancer cells undergo adaptive

epigenetic remodelling and gain tumour initiating properties when exposed to prolonged periods of obese conditions. This interaction between metabolic, epigenetic, and tumorigenic events currently represents significant knowledge gaps.

AIMS

- Uncover the relationship between systemic metabolic challenge as induced by physiological stressors and intracellular metabolite dynamics in cancer cells.
- Identification of the metabolites that are sufficient to drive tumour initiation – and how this is achieved.
- Determine how metabolite-driven epigenetic changes can display loci specificity.
- Discover the epigenetic, transcriptional and translational machinery required to that link physiological stressor to tumour initiation.

Key methodologies for this project are in vivo CRISPR loss- and gain-of-function screens, single cell transcriptomics and epigenomics, in vivo tumour modelling and metabolomic tracer studies.

Research project #2: How do physiological stressors affect the tumor ecosystem?

We know that stem cells are intrinsically connected to the cellular niche in which they reside and that these cellular interactions are particularly important and instructive for stem cell plasticity. In this project we ask if an obese environment instructs the cancer stem cell niche to govern cancer cell dedifferentiation and enhanced stemness features.

AIMS

- To develop a comprehensive cellular spatial map of the cancer stem cell niche in obese and non-obese cancer patients.
- To comparatively extract obesity-dependent deregulated cell abundancies and cellular interactions within such niches.
- To mechanistically dissect the causal importance of the obesity-dependent niche composition.

Key methodologies for this project are spatial interrogation of the tumour microenvironments (sequencing and proteome-based), in vivo tumour modelling and antibody-based therapeutics.

Research project #3: How does physiological stressors affect somatic fully differentiated cells of the body?

This project address two areas that we believe are currently severely understudied: 1) How does the obese phenotype affect male and female germ cells and thereby the intergenerational metabolic health and 2) How does a history of obesity affect future possibilities of cancer risk (epigenetic memory).

AIMS

- Uncover the relationship between systemic metabolic challenge the epigenetic landscape of both male and female germ cells.
- Demonstrate how efficiently the obese phenotype is transferred between generations in mice.
- Conduct generational cancer studies.

Key methodologies for this project are single cell transcriptomics and epigenomics, metabolomics, mouse in vitro fertilization and advanced mouse cancer models (genetic and viral based).

Cerebellum & Neurodegeneration Group

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The Cerebellum & Neurodegeneration Research Group uses human neuroimaging and behavioural assessment approaches to investigate the expression and progression of brain changes in people with degenerative neurological conditions, with a primary focus on rare inherited movement disorders. We focus on translational application of cutting-edge imaging, biofluid, and digital technologies and analysis approaches to develop disease biomarkers and provide new insights into disease manifestation.

Human neuroimaging and blood biomarkers for inherited neurodegenerative diseases

This project is suitable for PhD students.

BACKGROUND

Can new human brain imaging techniques allow us to better understand, track, and treat neurodegenerative diseases?

Can blood-based proteomics/metabolomics help us to better define and predict heterogeneity in the onset and progression of neurodegeneration?

Can machine learning be applied to complex, multi-domain clinical and biological data to identify disease subtypes?

These are some of the burning questions that are at the forefront of research in our lab. Hereditary cerebellar ataxias (HCAs) are inherited neurodegenerative diseases that are associated with motor, cognitive, and neuropsychiatric impairments. These diseases result in profound disability and mortality. There are currently no cures, but the field is on the precipice of gene therapies, stem cell interventions, and targeted pharmaceuticals. Next-generation magnetic resonance imaging (MRI) and proteomics/metabolomics approaches offer powerful new methods to characterise the onset and progression of disease, to define disease subtypes, and to optimise clinical trial design by improving patient selection (stratification) and outcome monitoring (sensitive endpoints).

AIMS

Multiple projects are available to undertake one or more of the following in cohorts of individuals with hereditary cerebellar ataxias:

1. Application of novel quantitiative MRI approaches to assess changes in myelination, iron metabolism, inflammation, and tissue microstructure.
2. Determine the proteomic and metabolomic profile of disease expression and progression.
3. Machine learning approaches to define disease clusters (subgroups) and predictive models of disease progression using clinical, imaging, and biological data.

PROJECT POTENTIAL

These projects will improve biological understanding, treatment targeting, and outcome monitoring for debilitating, fatal, and currently intractable neurodegenerative diseases.

Neuroimaging big data in rare neurodegenerative diseases: an international collaboration

This project is suitable for Honours, Masters, MD, or PhD students.

BACKGROUND

Hereditary Cerebellar Ataxias (HCAs) are rare neurodegenerative diseases that are associated with profound and extensive motor control impairments, predominantly affecting the cerebellum and brainstem. Neuroimaging provides a powerful tool to investigate the functional and structural alterations occurring in HCAs, and ultimately advance our understanding of these diseases. However, current studies of these diseases usually rely on small samples and are therefore limited in there scientific and clinical significance.

Our lab has teamed up with clinicians and researchers from around the world to overcome these barriers by establishing international consortia (such as the ENIGMA-Ataxia working group) and multisite research studies (including TRACK-FA and the RFC1 Natural History Study). Combined with new tools for multi-site image harmonisation (COMBAT, SynthSeg), these initiatives provide unprecedented power to define the profile, evolution, and heterogeneity of rare neurological diseases.

AIMS

This study will undertake the large-scale analyses of structural and connectivity changes in HCAs using data from international consortia of clinical research sites. This work will include functional and structural MRI methods including resting state fMRI and diffusion tensor imaging (DTI) to examine cerebellar anatomical, microstructural, and connectomic changes in these diseases.

PROJECT POTENTIAL

This project will define the profile of anatomical, functional, and connectivity changes that occur in the brain and spinal cord of individuals with hereditary cerebellar ataxias, improving efforts to define sensitive markers of disease progression (biomarkers) and characterise inter-individual variability in disease expression.

Medical Genomics Group

Senior Group Leader: Professor Nic Waddell

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The Medical Genomics Team analyses next generation sequence data to address clinical challenges in a variety of diseases. The approaches we take include:

- Characterising cancer genomes with short and long read sequencing.
- Classification of tumours into significant subtypes.
- Identification of mutational processes that underlie tumour development.
- Determining genomic and transcriptomic features associated with immune response.

Ultimately, we aim to take steps towards 'personalised medicine' to enable the diagnosis, management and treatment of patients.

Somatic changes to mitochondria DNA in cancer development

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

BACKGROUND

Mitochondria are membrane-bound cell organelles that are critical for energy production and cell metabolism. Mitochondria are located in the cytoplasm of cells and have their own DNA that is circular and approximately 17 kb. Aberrant mitochondrial function is a key component of cancer. 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, an area that is understudied is the prevalence of somatic mutations in mitochondria and their association with cancer development.

AIMS

1. Analyse whole genome sequencing from multiple cancer types to quantify mitochondria and characterise somatic mutations.
2. Develop computational approaches to study mitochondrial genomes using long read DNA sequencing. This will involve mutation calling, quantification, assembly and methylation profiling.
3. Determine how heterogenous mitochondria populations are within cancer samples and how they change overtime.

METHOD

This project will be conducted within the Medical Genomics group at QIMR Berghofer, and will work closely with the Genome Informatics group and have opportunities to collaborate with clinical collaborators. This is a bioinformatics project that will involve the analysis of large cancer genomic datasets, therefore knowledge of python and R is preferable.

PROJECT POTENTIAL

This work will provide insights into how mitochondria contribute to cancer development. This is an exciting project that is expected to result in significant new knowledge. We anticipate this work will lead to multiple publications and conference speaking opportunities.

Sid Faithfull Brain Cancer Laboratory

Group Leader: Professor Bryan Day

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https://www.qimrberghofer.edu.au/our-research/cancer-research/sid-faithfull-brain-cancer-laboratory

The Sid Faithfull Brain Cancer laboratory focuses on Glioblastoma (GBM) which is the most common and aggressive form of adult brain cancer. GBM kills approximately 1200 people per year in Australia. Survival rates are very poor with a median survival of approximately 15 months. Meaningful advancements in patient treatment and survival have not changed for decades. New and better treatment therapies are urgently needed.

The laboratory also studies a number of paediatric brain cancers including medulloblastoma and an incurable form of brain stem glioma called diffuse intrinsic pontine glioma (DIPG). Our goal is to design therapies that specifically treat the tumour while keeping the healthy developing brain intact.

Targeting novel receptors in GBM

Co-supervisor: Dr Rochelle D'souza

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This project can be adapted in scope for Honours or PhD.

BACKGROUND

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

AIM

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

Approaches used include

- In vitro killing assays to determine GBM cell killing and IC50.
- Apoptosis/Cell death assays.
- Flow cytometry and Western blotting.
- Immunofluorescence and confocal microscopy.

OUTCOME

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

Cancer Drug Mechanisms Laboratory

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The Cancer Drug Mechanisms Laboratory combines expertise in cell biology with understanding of drug mechanisms to treat cancers and other chronic diseases. The group's cancer biology work currently focuses on understanding the development and progression of cancers of the skin and oral cavity. Specifically, the laboratory is investigating the molecular mechanisms involved in the progression and metastasis of melanoma, head and neck cancer, as well as cutaneous squamous cell carcinoma. These mechanisms also affect drug resistance of cancers. The identification and understanding of pathways in these cancers is crucial prior to the design or identification of suitable treatments. The group also uses its cell biology knowledge to assist in the development process for novel agents targeting cancer and other chronic disorders.

Molecular Immunology Laboratory

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The Molecular Immunology Laboratory works on the immunology of malaria, cancer and autoimmunity. In 2016, the laboratory discovered Programmed cell death1 Ligand 2 (PD-L2) was contrary to dogma, not a "brake" on the immune system, but actually an essential activator of immunity. The laboratory has since then

used this finding to develop multiple immunotherapies and diagnostics for the treatment of cancer and autoimmunity. The first immunotherapy for cancer was licensed to Merck KGaA in 2020. However, the laboratory continues to also undertake basic immunological research to dissect the reason for loss of immunity during malaria and cancer or hyper-responses during autoimmunity.

Conjoint Gastroenterology Laboratory

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The Conjoint Gastroenterology Laboratory studies the 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 programme. Collaboration with gastroenterologists, surgeons, pathologists and oncologists is a key aspect of its research.

Population Health Program

Our Population Health Program and its team is dedicated to understanding the factors influencing the health and wellbeing outcomes of all Australians and our regional neighbours.

Drawing on the expertise of our clinical scientists, epidemiologists, health economists, and specialist researchers, we examine the causes of disease, their transmission, 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 other tropical diseases; 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 in communities and improving patient care, quality of life, and survival rates, so that all Australians and our regional neighbours have the opportunity to enjoy good health.

Gynaecological Cancers Group

Distinguished Scientist: Professor Penelope Webb

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www.qimrberghofer.edu.au/our-research-population-health/gynaecological-cancers/

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.

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

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

Co-supervisor: Dr Nina Na

BACKGROUND

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

AIM

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

METHODS

Analysis (linear and logistic regression/survival analysis) using individual-level data from a cohort of 900 women with ovarian cancer women who provided information about dietary supplement use before and 3, 6, 9, 12 and 24 months after diagnosis.

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

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

Co-supervisor: Dr Nina Na

BACKGROUND

The use of complementary therapies by cancer patients is common but contentious, particularly during chemotherapy. Survivors often use complementary medicine in the hope it will improve their wellbeing, alleviate chemotherapy side effects, boost immune function, and perhaps improve their long-term survival. There is little information about the use of complementary and alternative therapies by women with ovarian cancer, if/how this changes after their cancer diagnosis, what women use during treatment or how this might affect their wellbeing and, ultimately, their survival.

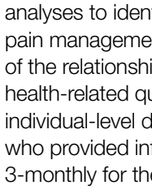
AIM

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

METHODS

This project could include some/all of the following components: (i) a literature review of the current evidence; (ii) descriptive analyses of what women use and how this changes from before diagnosis to during treatment, after treatment and after recurrence; (iii) analysis of factors associated with use or that predict changes in use; (iv) analyses of the relation between use, symptoms and side-effects, and wellbeing; and (vi) analyses of the relation between use and survival. Analyses will use individual-level data from women in the OPAL study who provided information about complementary and alternative therapy use before and after diagnosis (3-monthly for the first year then annually to 4 years).

Ovarian cancer pain management



Primary Supervisor: Dr Nina Na

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

BACKGROUND

In Australia in 2022, around 1,815 women were diagnosed with ovarian cancer and more than 1,000 lives were lost to the disease. Pain is the most common symptom experienced by ovarian cancer patients but there are limited data on the prevalence of pain and analgesic (non-opioid and opioid) use, and the relation between pain and quality of life, especially after cancer recurrence and towards the end of life.

AIM

To examine the prevalence of pain and analgesic use among women with ovarian cancer, changes in prevalence over time after completion of treatment to the end-of-life period, and the relation between pain, analgesic use and health-related quality-of-life and survival.

METHODS

This project could include some/all of the following components: (i) a literature review of the current evidence; (ii) descriptive analyses of the prevalence of pain and analgesic use from diagnosis to the end-of-life period; (iii) analyses to identify factors associated with inadequate pain management (persistent severe pain) and (iv) analyses of the relationship between pain, analgesic use and health-related quality-of-life and survival. Analyses will use individual-level data from participants in the OPAL study who provided information about pain and analgesic use 3-monthly for the first year after diagnosis then annually to 4 years.

Genomics, Imaging, and AI Laboratory

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The Genomics, Imaging, and AI Laboratory at QIMR Berghofer is part of the Population Health Program. With a primary focus on neurodegenerative disorders of the eye and brain, particularly glaucoma, macular degeneration, dementia, and Parkinson's disease, the lab employs statistical genetics and machine learning methodologies to advance gene discovery and improve risk prediction for these diseases. The lab also boasts exciting collaborations with industry partners in both clinical and machine learning analytical domains.

Early detection of neurodegenerative disorders using artificial intelligence

Suitable for full-time PhD students with expertise in artificial intelligence and data analysis.

Research studies focused on neurodegenerative diseases affecting the eye and brain, such as glaucoma, dementia, and Parkinson's disease. Early detection and intervention play a crucial role in managing the risks for developing these conditions.

Our ongoing studies utilise machine learning and statistical methods to analyse existing ocular and neuroimaging data. We aim to enhance the prediction of risks associated with these conditions.

Cancer Control Group

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https://www.qimrberghofer.edu.au/our-research/population-health/cancer-control/

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

QSKIN: the burden of skin cancer

Supervisor: Associate Professor Catherine Olsen

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This project is suitable for Masters and PhD students.

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

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

- Health services research.
- Mendelian randomisation (MR) analyses.
- The genetics of multiplicity (i.e., susceptibility to many tumours).
- Gene/environment interactions in the aetiology of skin cancer.
- Lifestyle factors in the aetiology/prevention of skin cancer.

Cancer Aetiology and Prevention Group

Group Leader: Professor Rachel Neale

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https://www.qimrberghofer.edu.au/our-research/population-health/cancer-aetiology-and-prevention/

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.

Understanding variability in management of patients with pancreatic cancer

This project is suitable for Masters and PhD students.

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

Psychedelic Medicine and Supportive Care Group

Team Head: Associate Professor Vanessa Beesley

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https://www.qimrberghofer.edu.au/our-research/population-health/supportive-care-in-cancer

The Psychedelic Medicine and Supportive Care Group is dedicated to advancing psychedelic medicine and developing supportive care interventions for cancer and mental health. Our research aims to maximise quality of life by:

- Using population and person-centred approaches to assess supportive care needs.
- Identifying the most promising interventions and models of care.
- Embracing innovation and using cost-effectiveness and implementation trial designs.
- Championing equity and inclusivity for culturally safe, responsive and accessible care.
- Fostering interdisciplinary partnerships with clinicians, consumers and healthcare providers to facilitate translation.

Our current projects target cancer-related supportive care, adjustment disorders, prolonged grief and PTSD in disaster-affected communities.

Investigating the impact of structured counselling for carers of people with pancreatic cancer on patient and carer outcomes

This project is suitable for an Honours student starting as early as Q3 2024 or could expand for a PhD student.

BACKGROUND

Pancreatic cancer is rare and deadly. Patients and their families have little time to adjust to this devastating diagnosis. Family carers of patients are confronted with the need to assist in the management of complex physical symptoms and provide emotional, financial, and spiritual support, typically with minimal support or guidance.

AIM/S

The Pancreatic cancer Relatives Counselling and Education Support Service or PRoCESS trial aims to determine whether talking to a trained nurse-counsellor via video or phone is helpful for carers and whether it may also affect patient outcomes.

METHOD

The trial involved 176 families affected by pancreatic cancer, randomised to either receive up to 10 structured counselling and education sessions over four months, with the option for monthly booster sessions, or to receive usual care.

PROJECT POTENTIAL

The student may assess the effect of the counselling intervention compared with the control on various outcomes including patients' emergency department presentations, time spent in hospital, time to specialist palliative care referral and overall survival. Additionally, thematic analysis of qualitative (video) data from intervention participants' final counselling sessions and their unsolicited feedback may be used to provide insight into consumers' perceptions of the support service. The student will be responsible for writing up the findings for scientific publication.

The PEACE (Psychedelic Experiences And Cancer Evaluation) study

This project is suitable for an Honours student starting in Q1 2025 or could expand for a PhD student.

BACKGROUND

After receiving a cancer diagnosis, many patients and their caregivers live with emotional distress, often lacking access to meaningful psychosocial interventions. One potential avenue to bridge this gap in care is psychedelic-assisted therapy. This therapeutic approach involves the use of psychedelic drugs in conjunction with talk therapy in a safe setting to treat mental health issues such as depression, anxiety, existential distress, or post-traumatic stress disorder. Despite the growing body of evidence suggesting potential therapeutic benefits of psychedelics for cancer-related adjustment disorders and pain, there is a lack of population-based data on cancer patients' and carers' attitudes and experiences with these substances.

AIM/S

The aim of this study is to investigate cancer patients' and carers' beliefs, interest, patterns of use, and perspectives on the health effects of psychedelics substances and other novel supportive therapies.

METHOD

This mixed-methods study will entail a naturalistic survey of a registry-based sample of Queensland cancer patients and their caregivers, complemented by qualitative interviews with a subset of participants.

PROJECT POTENTIAL

This project offers an opportunity for the student to engage in the design and analysis of quantitative cross-sectional data, as well as qualitative interviews and analysis. The student will play a pivotal role in synthesising the findings for scientific publication.

Investigating MDMA-Assisted therapy for treatment-resistant PTSD related to natural disasters

This project is suitable for a PhD student starting in Q2 2025.

BACKGROUND

The escalating frequency and severity of extreme weather events due to climate change have led to increasingly complex mental health challenges. In February 2023, the Therapeutic Goods Administration (TGA) reclassified MDMA for therapeutic use in treating PTSD. MDMA, as a medicinal agent, primarily influences trauma processing by mitigating avoidance and fear-based responses in the amygdala while fostering social connection.

AIM/S

This project aims to examine the impact of group-based MDMA-assisted therapy on individuals affected by treatment-resistant PTSD resulting from the 2022 Lismore and northern NSW floods.

METHOD

The trial adopts a randomised stepwise parallel group trial design. Step 1 (low intensity) is a parallel-group RCT for 200 people with PTSD. Step 2 (high intensity) is for 84 eligible participants who continue to experience treatment-resistant PTSD. They will be assigned either to group-based MDMA-AT or wait-list control (6 months) as the comparator.

PROJECT POTENTIAL

The trial is assessing the effect of the intervention on various outcomes including PTSD, posttraumatic growth, depression/anxiety, social connectedness, self-compassion, climate change anxiety and health-related quality of life. The student will delve into relevant literature concerning the high-intensity intervention and may explore innovative analyses of the psychological processes likely to yield the most significant impact in a post-disaster context. The student will produce 4-5 scientific publication from this body of work.

Molecular Cancer Epidemiology Group

Group Leader: Professor Amanda Spurdle

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https://www.qimrberghofer.edu.au/our-research/population-health/molecular-cancer-epidemiology/

The Molecular Cancer Epidemiology Laboratory studies the epidemiology and genetics of breast, ovarian, and endometrial cancer. Our research is focused on identifying molecular signatures of normal and tumour tissue that can point to the genetic and environmental causes of these cancers, and identify new targets for drug therapy. The laboratory covers a range of projects with the themes of clinical genetics, cancer epidemiology, molecular pathology, genome-wide analyses and drug development.

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

Co-supervisor: Dr Aimee Davidson

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This project can be adapted in scope for Honours or PhD.

BACKGROUND

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

AIM

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

APPROACH

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

OUTCOME

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

Evaluation of pharmacogenomics variants from genome sequencing data

Honours and/or flexible for clinical students.

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

Expanding genetic diagnoses into non-coding regions of the genome

Co-supervisor: Dr Rehan Villani

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This project is suitable for Honours, Masters, MPhil, MD.

BACKGROUND

A molecular diagnosis informs many aspects of treatment for a patient with an inherited condition, however current techniques provide a diagnosis in only around 25% of cases. Non-coding regions of the genome remain underrepresented in clinical cases and variants in these regions are therefore a potential source of diagnoses for undiagnosed patients. Non-coding variants remain elusive as there is insufficient evidence to predict their impact and/or disease-causality. In order to improve diagnosis in these regions, we are working to determine which of the current research tools provide sufficient evidence to predict disease-causality in a clinical setting. We are testing methods to determine how to apply bioinformatic tools with best predictive power; to provide evidence based clinical recommendations for clinical diagnostics inclusive of non-coding regions. This work will increase diagnostic yield for patients undergoing genetic testing.

AIM/S

To improve diagnostic yield for patients with inherited disease by evidencing new methods for applying computational and experimental evidence in variant curation across expanded areas of the genome.

METHOD

We use a range of computational methods and statistics, but can support across levels of skill and experience. Using clinical and public data, we investigate research tools to determine if they can be applied in clinical genomic diagnostics and evaluate their predictive power and impact to determine clinical recommendations. We will access a variety of publicly available data and software, with analysis techniques including those used in health quality assessment and diagnostic evaluation.

PROJECT POTENTIAL

The projects that we offer are very applied and translate well for clinical understanding of genomics and genetic variant curation. We also support building bioinformatic, coding skills, statistics along with research translation and implementation projects aligned with this area. This project has real world translational potential as it will provide results enabling improved clinical diagnostic practice, to improve health care for patients.

Statistical Genetics Group

Group Leader: Professor Stuart MacGregor

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https://www.qimrberghofer.edu.au/our-research/population-health/statistical-genetics/

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 variation in various cancers. Cancers studied include melanoma, ovarian cancer and oesophageal cancer. This work will lead to better understanding of why particular individuals are affected by cancer or why they respond poorly to cancer treatment. Another major interest is ophthalmological genetics, with ongoing work to identify the specific genes involved in both eye disease and in underlying quantitative risk factors.

Eye disease genetics

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

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. We have developed genetics-based risk prediction tools for glaucoma, and are now exploring how to implement these to prevent blindness.

AIM/S

To apply risk prediction tools for glaucoma based on genetic data. To translate these genetic findings into improved screening for the disease. To integrate genetics-based prediction approaches with methods harnessing artificial intelligence. The project may also consider gene-mapping and prediction analysis for other eye diseases such as myopia, age-related macular degeneration and dry eye.

PROJECT POTENTIAL

The QIMR Berghofer Genetics of Glaucoma Study is one of the largest studies of its kind internationally, with large scale genetic data recently collected on thousands of Australians. This will be supplemented with very large-scale genetic data sets (genome wide association studies, exome/genome sequencing, proteomics) which are available in the lab. 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.

Bridging gaps on the genetics of age-related disorder among under-represented populations

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This project is suitable for PhD students only. Some experience in biostatistics and data analysis is essential, and a background in statistics, engineering, health sciences, epidemiology, health economics, computer science and/or public health is recommended. Crucially, candidates must demonstrate adequate interpersonal skills, critical thinking and cultural competence to effectively engage with stakeholders from diverse backgrounds. Special attention will be given to ensuring the respectful engagement of under-represented populations and safeguarding their rights throughout the research process.

INTRODUCTION

Genomics research stands as a pivotal domain providing insights into the genetic foundations of human diseases, paving the way for personalized treatments. However, it is increasingly evident that this research has not been conducted equitably across diverse populations. The historical Eurocentric bias in genomics has resulted in a notable lack of representation for non-European populations in significant genetic discoveries. Such disparity holds profound implications for health equity and precision medicine, underscoring the necessity to address hurdles in genomics research among diverse populations.

AIM

This project meticulously examines opportunities and challenges in human genetic research on age-related disorders across diverse ancestries. It involves identifying factors affecting statistical genetics techniques, evaluating feasibility of genetic screening programs, and addressing disparities in research capacity.

OBJECTIVES AND SCOPE

The PhD candidate will analyse multi-ancestry genetic data on various age-related human diseases, contributing to diversity in genomic research. They'll have the opportunity to work on genomic data from large established biobanks and co-design pilot genetic studies focused on under-represented populations. The project is flexible, allowing candidates to focus on specific/multiple disease endpoints or ethnicities; or focus on specific research question of interest.

METHODOLOGY AND APPROACH

The candidate will employ a multifaceted approach, examining technical and non-technical aspects influencing genetic research adoption across regions. Utilizing various research methodologies and technologies, including AI, they'll explore factors such as perception, culture, policy, and community engagement to enable genomic medicine in different healthcare landscape. The candidate will also work closely with relevant stakeholders will validate research assumptions and derive equitable solutions

INNOVATION AND IMPACT

This project offers an innovative opportunity to address the need for equitable representation in genomic research. Through co-designing pilot studies and leveraging emerging technologies, the candidate will advance genomic knowledge, promote health equity, and guide capacity-building efforts in diverse communities.

Genetics of skin cancer

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Co-supervisor: Associate Professor Matthew Law

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The project is suited to a PhD student with experience in genetic epidemiology, epidemiology, biostatistics or bioinformatics. Experience in the analysis and manipulation of large datasets and a good knowledge of computing is desirable. Experience in cancer genetics 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

Skin cancers, including melanoma and keratinocyte cancers (KCs), are the most common cancers in Australia leading to significant morbidity, mortality and health costs. Each year over 15,300 Australians are diagnosed with melanoma, the deadliest skin cancer with over 1,400 Australians succumbing to advanced or metastatic disease every year. Early diagnosis and appropriate treatment are crucial in improving survival outcomes. Over the last decade, new drug therapies known as immunotherapy have drastically improved treatment outcomes in patients with metastatic melanoma. Despite this success, there is significant variability in response to treatment amongst patients, with 59% patients experiencing life threatening immune-related adverse events or toxicities, while a third acquire complete remission. The biology underlying why some people do or do not develop immunotherapy-related adverse events, or why others do or do not acquire remission, is poorly understand.

Due to immunosuppression, transplant patients have up to 100-fold risk of developing KC compared to the general population, with the majority (57%) of recipients developing multiple KCs. Unlike in the general population, for transplant patients KC is very aggressive, and highly metastatic. It is also a major cause of death in transplant patients accounting for 15% of cancer deaths, a 51-fold

increase compared to mortality in the general population. There is an increasing need to effectively manage these cancers in transplant patients

AIMS

- Explore the genetic predisposition to poor immunotherapy efficacy in patients with metastatic melanoma.
- Assess genetic-based prediction of immunotherapy efficacy in metastatic-melanoma patients.
- Explore putative causal factors for immunotherapy response in patients with metastatic melanoma.
- Explore clinical translation of genetic risk prediction of skin cancers in transplant patients.

METHODS

For Part 1 the candidate will use statistical genetics approaches (e.g. Genome-wide association study techniques), multi-omics data (DNA, gene expression, metabolomics), and clinical data to uncover the genetic risk for developing severe adverse events, and poor treatment response/efficacy (disease progression/remission). They will use this genetic data with clinical information to generate genetic risk prediction models for adverse events, and treatment response. They will also use other approaches such as Mendelian randomisation to investigative putative causal factors (e.g. gut microbiome, diet, etc) for treatment response.

In Part 2 the candidate will use large genetic data (from >1 million people) to develop genetic risk prediction models for KC to help identify transplant patients at the highest risk of developing multiple/invasive skin cancers. They will also explore the efficacy of using genetic risk prediction models to triage transplant patients for personalized early chemoprevention, improved screening, and modulation of immunosuppressive medication.

PROJECT POTENTIAL

We have large-scale genetic data sets available in the lab for skin cancer risk, treatment, and treatment outcomes. We also have access to other national and international biobanks, as well as deeply phenotyped data sets for transplant patients. The candidate will use a range of statistical genetic approaches to interrogate these data and to determine the genes and pathways underlying melanoma treatment response and use these in prediction models. They will also use these data sets to develop and apply genetic prediction models for skin cancer in transplant patients. The project may also consider similar gene-mapping and prediction analysis for other complex traits such as other cancers e.g. colorectal carcinoma, and glaucoma in non-European ancestries.

Global Health & Tropical Medicine Group

Program Director (Population Health) & Group Leader: Professor Darren Gray

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https://www.qimrberghofer.edu.au/our-research/population-health/global-health-tropical-medicine/

Our research investigates the transmission and control of tropical infectious diseases and diseases of poverty, including some of the most prevalent and important infections that cause much suffering and economic loss worldwide. We aim to develop new public health interventions against these diseases that will lead to their sustainable control and eventual elimination.

Cardiovascular Disease Prevention Group

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https://www.qimrberghofer.edu.au/our-research/population-health/cardiovascular-disease-prevention/

The Cardiovascular Disease Prevention Group focuses on generating epidemiological evidence to guide policy and practice decisions to improve the prevention of cardiovascular and related chronic diseases. A particular focus is on using big data and modelling to enhance disease risk prediction to guide treatment decisions in primary care and generating evidence to address gaps in implementation of preventive interventions.

Mosquito Genomics Group

Team Head: Associate Professor Gordana Rasic

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Better control of mosquito-borne diseases through mosquito genomics.

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 and other "omics" data from a single mosquito cell to a system of mosquito populations.

We use genomics to understand how mosquitoes move, mate and survive in different environments so that we can find optimal control strategies (spatial population genomics, simulation modelling), and to identify new targets for genetic control (molecular biology).

We collaborate with the leading scientists in Australia, USA, Asia-Pacific and Europe to address the current challenges and predict future obstacles in protecting the communities in Queensland, Australia and around the globe from the mosquito-borne diseases.

Cancer & Chronic Disease Group

Group Leader: Associate Professor Patricia Valery

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https://www.qimrberghofer.edu.au/our-research/population-health/cancer-and-chronic-disease/

The Cancer and Chronic Disease Research Group covers four main broad research areas including:

- The management of chronic liver disease (e.g. cirrhosis, non-alcoholic fatty liver disease (NAFLD), chronic hepatitis C) and hepatocellular carcinoma (the most common type of liver cancer).
- Quality of life, supportive care needs and health literacy of patients with cirrhosis and liver cancer aimed at designing suitable interventions that may delay the natural progression of disease to cirrhosis complications and liver cancer.
- Epidemiology of chronic liver disease (e.g. cirrhosis, NAFLD, chronic hepatitis C, and liver cancer.
- Investigating the reasons for poorer health outcomes for Aboriginal and Torres Strait Islander people diagnosed with cirrhosis and liver cancer compared to other Australians.

Health Economics Group

Group Leader: Associate Professor Louisa Collins

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Health economics is concerned with issues of efficiency, effectiveness, value, health behaviours and the functioning of healthcare systems. We need a health system which provides the best services not because those who can shout the loudest insist on them but because they are high-value, fair, equitable, transparent and evidence-based. Australia has no shortage of

pressing public health problems and we need to get spending right on healthcare if we are to meet future population needs.

Our Health Economics team is led by Associate Professor Louisa Collins. Our research is focused on economic evaluations and decision-modelling of healthcare interventions that span a range of health conditions and populations but has a key theme around cancer control strategies, from prevention through to survivorship care.

Economic evaluations in health care assess the costs and patient benefits of new services and technologies to determine their value for money. This usually involves both short-term 'within-trial' analyses and long-term decision-analytic modelling. Ultimately, this work assists in the translation of interventional research into clinical practice so that effective services also demonstrate good economic value. The team also undertakes work that highlights areas of inefficiency where healthcare resources are misused or could be more efficiently delivered. Finally, we recognise that initiatives which promote the prevention of disease is paramount to preserving a sustainable health system, and view economics around this work as a priority.

Infection and Inflammation Program

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

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

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

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

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

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

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

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

Immunology and Infection Laboratory

Program Director (Infection & Inflammation) and Distinguished Scientist: Professor Christian Engwerda

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www.qimrberghofer.edu.au/our-research/infection-and-inflammation/immunology-and-infection/

The Immunology and Infection laboratory studies malaria and leishmaniasis, two important parasitic diseases that affect millions of people around the world every year. Our research focuses on CD4+ T cells because of their central role in controlling anti-parasitic immunity. We use our discoveries to improve immune responses following vaccination or drug treatment with the aim of generating long-lasting immunity in communities to reduce the numbers of infections, and ultimately eliminate these diseases. Our findings relate to inflammation, and as such, our work also has important implications for developing treatments for infections, cancer and autoimmune diseases that impact thousands of Australians.

Characterising CD4+ T cell responses during parasitic infections

This project is suitable for PhD or Honours students.

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

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

AIMS

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

Genomics and Machine Learning Laboratory

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https://www.qimrberghofer.edu.au/our-research/infection-and-inflammation/genomics-and-machine-learning-lab-2/

The Genomics and Machine Learning Lab (GML) studies cancer and infected tissues in patient samples and mouse models. They generate novel data from spatial and single cell technologies and develop new computational and statical methods to find clinically important patterns from this complex data. They pioneered the merging of two big data fields, sequencing, and imaging, to advance understanding of pathological processes one cell at a time and across all cells within a diseased tissue. By mapping cell types, their spatial organisation and cell-cell interactions in tissues, GML focuses on discovering new patterns and cellular regulation mechanisms that are hidden from traditional research approaches. Examples of outcomes include cell and gene markers for predicting cancer progression risks, stratifying disease subtypes, discovering new drug targets to modulate the immune systems, and adding new capabilities for prioritising drugs most effective to each patient.

Gut Health Group

Honorary Group Leader: Associate Professor Graham Radford-Smith

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https://www.qimrberghofer.edu.au/our-research/infection-and-inflammation/gut-health/

Crohn's disease (CD) and ulcerative colitis (UC) are the major forms of inflammatory bowel disease (IBD) in developed nations such as Australia. It is common for a patient's symptoms to first appear while they are in their 30s, although these diseases can affect children and older adults. IBD is a chronic illness and the symptoms, including diarrhoea, rectal bleeding, and abdominal pain, have a significant impact on quality of life.

The origin of IBD is not well understood, but the most favoured theory is that a genetically at-risk individual encounters a single or series of environmental triggers that lead to disease. Discovery of the first susceptibility gene for CD (called NOD2) and its proposed role in the body, support this hypothesis. The Gut Health Group is currently investigating several other genes for links to IBD.

Both CD and UC are characterised by a series of relapses and remissions. There is limited understanding of the clinical, environmental and genetic factors that may influence how severe the disease is or how often it recurs. The Gut Health Group is analysing a broad range of factors in a large cohort of IBD patients.

A pilot RCT of patients with mild-moderate ulcerative colitis starting basic treatment with 5ASA to either a 12-week low food additive diet or standard care

Co-supervisor: Dr Gareth Walker

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This project is suitable for PhD students.

BACKGROUND

Inflammatory Bowel Disease (IBD) is a chronic immune-mediated disorder which consists of two main forms; Crohn's disease (CD) and ulcerative colitis (UC). It is a global disease, with an accelerating incidence in newly industrialised countries whose societies have become more westernised. Commonly, mesalazine drugs are positioned as first line treatment for patients with mild-moderate UC, however, only approximately 40%–70% achieve symptomatic response. Specialised dieticians are key members of an integrated approach to modern IBD management, delivering dietary therapies that can reduce symptoms and inflammation. An ultra-processed dietary pattern (UPD) has been shown to correlate with higher circulating inflammatory cytokines and markers of oxidative stress. Characteristic of an UPD is the regular consumption of food additives such as artificial sweeteners, emulsifiers and carrageenan gum. In previous work our team have developed a low food additive diet (LFAD) and demonstrated a reduction in food additives was correlated with significant improvements in faecal calprotectin, disease activity scores and quality of life after 8 weeks in adults with mild to moderate IBD. A growing body of evidence from in vitro and animal models suggests that food additive exposure damages the mucous layer of the gut wall and perturbs the microbial ecosystem.9 However, whether these findings translate to individuals with IBD is unknown.

STUDY ORIGINALITY/INNOVATION

Mild to moderate active ulcerative colitis (UC), commonly treated with mesalazine, only has symptomatic response rates of between 40%–70% and symptomatic remission rates of 15%–20%.7,8 This pilot study's novelty is in the combination of multi-omic rigorous basic science exploring the biology and predictors of treatment response, alongside a closely phenotyped newly diagnosed ulcerative colitis cohort with an easily translatable clinical question.

AIMS

The primary aim of this pilot study is to determine whether a low food additive diet can improve symptomatic response as compared with a standard diet in patients with mild-moderate ulcerative colitis taking oral mesalazine treatment. Secondary aims include: validation of a purposely developed food additive assessment tool through targeted metabolomic analysis of urine, stool and blood samples.

Molecular Parasitology Laboratory

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The Molecular Parasitology Laboratory was founded by the late Professor McManus, and is now headed by Professor Malcolm Jones. The laboratory leads the world in parasitic worm research with the goal of global control of neglected tropical helminthiases. The group translates laboratory findings into effective disease interventions paving the way for improved health outcomes. Along with a multidisciplinary collaborative team, the laboratory pioneers research on the development/application of schistosomiasis vaccines, in diagnostics, genomics and in tropical/international health, contributing a cohesive and remarkable body of 650 publications in an extensive career. Many are transformational, shaping policy/practice leading to improved treatment/control of worm infections with wide-scale application for informing government agencies, including Australian, globally on intervention options in other parasite-endemic communities.

Development of CRISPR based technology in schistosome bloodflukes

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Can be adapted to suit Honours, Masters, and PhD level 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 (clustered regularly interspaced short palindromic repeat)-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-mediated gene editing (including Cas9, CRISPR inhibitory/activation) 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-Cas13 based system, we will develop fast, accurate and portable diagnostic tools for the diagnosis of schistosomiasis and other neglected tropical diseases in the future.

Epidemiology of Schistosomiasis in the Philippines

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BACKGROUND

Asian schistosomiasis is caused by the blood fluke Schistosoma japonicum. Infection with this helminth can cause long-term chronic health problems due to eggs becoming lodged in body tissues, particularly the liver leading to hepatosplenomegaly and liver fibrosis.

In children infection is linked with growth and cognitive stunting. The life cycle of this helminth is complex, comprising the definitive mammalian host as well as an intermediate molluscan host. Transmission occurs when eggs are excreted in the faeces of infected definitive hosts. The eggs hatch on contact with water into miracidia, which then penetrate the molluscan host undergoing asexual reproduction. Cercariae, the infective stage, emerges from the snail and directly penetrates the skin of an infective host. S. japonicum occurs in China, the Philippines, and Indonesia, and is zoonotic with 46 different mammalian hosts potentially acting as reservoir hosts of infection.

Previous work has identified water buffalo in both China and the Philippines, where they are referred to as carabao, as the major reservoir hosts contributing to human infections in endemic areas. Control efforts to target these hosts have included animal chemotherapy with praziquantel, vaccines, and removal of animals and replacement with tractors, the latter of which has only occurred in China. However, to date animal chemotherapy and vaccines have not been included in any national control programs, and animal replacement does not occur in the Philippines. There have also been very limited studies examining other potential hosts in the Philippines, which may also contribute to transmission, with the most recent occurring in 50 villages of Samar province. However, that study used insensitive techniques, as proven by previous projects in our lab, which identified the native carabao as major reservoir hosts.

Animal vaccination and chemotherapy is part of ongoing projects. Here, we would like to explore other interventions such as education of animal owners and livestock management to prevent animal infections and thereby decreasing environmental contamination with parasite eggs. This step would be developed in partnership with local farmers.

AIMS

In this project, we aim to examine in more detail using highly sensitive diagnostics animal definitive hosts in an endemic area of the Philippines, and develop novel interventions for preventing animals contributing to transmission.

1. To examine animal hosts (cattle, carabao, dogs, pigs, goats, rodents) in Leyte, a schistosomiasis endemic region of the Philippines, utilizing sensitive molecular (qPCR, dPCR) and coprological (FEA-SD) diagnostics.
2. To conduct surveys and questionnaires of animal owners about how the animals are kept, how they receive or interact with water, and other animal management information.
3. To develop novel animal management practices in consultation with local animal owners to animals from contributing to transmission and thus reducing human infections.
4. To investigate and develop a model for economic loss from animals due to infection with schistosomiasis.

Inflammation Biology Group

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The Inflammation Biology Group has developed, refined and characterised a number of 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 cause by arthritogenic alphaviruses such as chikungunya virus and Ross River virus. We have also developed 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.

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Mosquito Control Laboratory

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There are no effective vaccines against malaria or most arboviruses. There are no chemotherapeutants for the treatment of arbovirus infection. Mosquito surveillance, management and manipulation remain the mainstays of most mosquito-borne disease control programs. The Mosquito Control Laboratory (MCL) manages state-of-the art pathogen and insect containment facilities with the capacity to undertake studies on all aspects of vector biology and disease transmission. We work on innovations in mosquito surveillance and control that might help interrupt parasite and pathogen transmission.

We are unique in the Southern Hemisphere with regard to our size, capacity and expertise. This makes us a key partner in a national, regional and international network. Our presence significantly enhances Australia's ability to investigate emerging vector-borne disease threats in the region. A major remit of the refurbished (2013), MCL is to exploit this unique facility through building strong collaborative links with parasitology, virology and vector biology laboratories throughout the world.

The MCL has permission to hold a number of exotic mosquito species in addition to native Australian mosquitoes. These include insecticide-resistant and susceptible Aedes aegypti strains, Aedes albopictus and Anopheles stephensi. The MCL has local access to real-world mosquito-virus transmission systems through a number of native mosquito vectors and their associated alphaviruses (including Ross River and Barmah Forest). We have field work in progress in Asia, Europe and the Americas.

Mosquito-borne disease transmission in a changing world

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BACKGROUND

In recent decades, arthropod-borne viruses (arboviruses) have emerged or re-emerged as human and animal pathogens with important implications for public health. These include dengue, Zika and chikungunya viruses, which circulate between humans and the urban mosquitoes, Aedes aegypti and Aedes albopictus, as well as zoonoses with complex transmission pathways that involving multiple vectors and vertebrate hosts. These include Japanese encephalitis virus (JEV), Murray Valley encephalitis virus (MVEV) and Ross River virus (RRV).

We are particularly interested in incriminating transmission pathways, and the factors that drive human spill-over for JEV, MVEV and RRV. The former is vaccine preventable, but in Australia we do not know where and when to target vaccination campaigns because the disease is highly unpredictable in its spatial and temporal prevalence. MVEV is endemic to Australia and Papua New Guinea, but in this case there are no vaccines or therapeutants for a disease whose appearance is also impossible to predict across regions or years. Both MVEV and JEV are deadly and untreatable in a small proportion of human cases. RRV is Australia's commonest mosquito-borne disease (ca 5000 cases per annum) causing debilitating arthritogenic symptoms. It has caused explosive epidemics in the Pacific countries and territories, involving > 100,000 human cases. Recent sero-surveys suggest that it may now be endemic across the Pacific and that transmission is becoming more common in urban Australia.

Globally, anthropogenic and ecological changes, particularly those related to climate and extreme weather events, may increase vector and host prevalence, expose new reservoirs to infection or induce arboviruses to adapt to new maintenance cycles. These factors may favour the emergence and spread of human zoonotic infectious diseases. Detailed studies on JEV, MVEV, RRV, and their vectors and its hosts are required to 1) track the diversity and evolution of viruses across habitats, 2) understand their key transmission dynamics, and 3) determine the risks of human spill-over.

OBJECTIVES

- Demonstrate how new surveillance technologies (mosquito trapping, and molecular xeno-monitoring) can incriminate vectors and vertebrate reservoirs of disease.
- Identify key pathways of arbovirus transmission and human spill-over in urban and rural environments in Australia.
- Apply these new insights to prioritise future research and to target interventions (i.e. health communication, insecticidal control, and vaccines).

SUB-OBJECTIVES

- Gain a fine-scale understanding of how specific virus variants emerge, spread and dominate particular habitats.
- Support the longitudinal collection and identification of mosquitoes (including blood-fed individuals) and vertebrates around areas associated with virus transmission.
- Employ a range of diagnostic tools (serology of mosquito blood meals, metabarcoding and virus sequencing of trap collections) to identify transmission pathways.
- Application of modelling techniques (SIR or matrix models) to explore the impacts of different vectors and hosts on transmission.

PROJECT POTENTIAL

- This work will draw on recent developments in arbovirus surveillance, molecular xeno-diagnostics, and risk mapping to define key transmission pathways (virus variants, habitat, vectors and reservoirs) for mosquito-borne zoonoses.
- The resulting "toolbox" of methods, and their interpretation, will have relevance for risk prediction and control campaigns.
- The project is pertinent, not only for Australia, but for the emergence of zoonotic arboviruses in the Pacific.

Scabies Group

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The Scabies research group is focused on understanding the molecular interactions of scabies mite molecules with host defence systems in the skin. Scabies is one of the most common infectious skin disorders worldwide, particularly among children and in tropical regions. In Aboriginal and Torres Strait Islander communities of remote northern Australia scabies prevalence is high and extreme rates of scabies-associated streptococcal and staphylococcal infections. The group, which has been working on scabies for more than 15 years, aims to develop new options for reducing scabies incidence and improving disease outcomes.

Scabies mites are host-specific, 'obligatory' parasites without environmental reservoirs. Chemotherapy is the only way to combat scabies and its transmission in humans. There is no vaccine and the broad-spectrum anti-parasitic drugs available fail to control the disease. Emerging mite resistance against leading drugs is of growing concern. Another problem is diagnosis. There are numerous skin conditions with similar symptoms but no reliable, simple methods to detect scabies. This makes efficient therapy, management and surveillance at individual, household and community levels very difficult.

Novel drugs and diagnostic tools to treat scabies are urgently needed. A central challenge is to comprehend mite biology and scabies pathogenesis, which are poorly understood, resulting in a lack of knowledge of specific drug targets in the parasite.

Disease mechanisms, novel therapeutics and molecular diagnostics for scabies

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Prospective students (Honours/Masters or PhD) will learn a wide range of molecular biology techniques, protein technology, including protein expression and purification techniques, microscopy, animal work and more.

Scabies and associated co-infections cause substantial illness and a major health burden in Indigenous communities of Northern Australia. In particular scabies-caused childhood pyoderma (bacterial skin infection) can cause severe complications in later life. Scabies-associated Streptococcus infections for example, significantly contribute to an immune complication of streptococcal infection that can leads to heart and kidney disease (rheumatic heart disease and post-streptococcal glomerulonephritis).

Diagnosis of scabies relies mostly on epidemiological and clinical algorithms rather than pathogen detection. Incorrect diagnosis can result in rapid community transmission and pathology exacerbation. New scabicides are urgently needed, as current drugs often fail because they do not kill parasite eggs and/or have short half-lives. Drug resistance is emerging.

RESEARCH PROJECTS:

1. Recognising the health risk of scabies-associated pathogens, we have commenced dissecting the link between scabies and bacterial infections at a molecular level and we lead the international scabies microbiome program to define the impact of scabies on the healthy skin flora and examine the synergy between mites and bacteria.
2. Drug resistance is an emerging problem in controlling the mites (causing scabies) and the bacteria (causing secondary infections). Our current research program combines cutting-edge basic research and unique pre-clinical studies, to compare the efficacy of several new candidate drugs that kill all stages of the scabies parasite including eggs to develop new candidate drugs.
3. Early and accurate diagnosis of scabies is critically important, as it can help prevent transmission and/or stop scabies outbreaks, it can improve the effectiveness of treatment and clinical management and avoid long-term disease complications in patients. Inappropriate treatment of undiagnosed scabies can cause further serious disease and contribute to emerging parasite resistance. For these reasons, we are developing the first Scabies Rapid Antigen Test (RAT) System for Point-of-Care.
4. Understanding the molecular mechanisms underpinning this disease is crucial to the development of diagnostics, treatments and cures. Therefore, we are also studying key aspects of mite biology and scabies pathogenesis. These more basic research projects are for example aimed at understanding the skin immune modulation by the parasitic mites or the severe itching, which is the main debilitating symptom of scabies infection. We have generated comprehensive integrated multi-omics databases from which we hope to identify and analyse molecular mechanisms unique to scabies. We have a powerful in vivo model and supporting technologies for pre-clinical work. We collaborate nationally and internationally with researchers and clinicians with a wide range of expertise.

Our program was developed in consultation with consumers and in response to concern over persistent high rates of scabies in remote A&TSI communities across Australia.

Translational and Human Immunology Group

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The major focus of the Translational and Human Immunology group is to delineate the mechanisms that regulate human immune responses in health and disease. Knowledge gained from these studies forms the basis for developing novel immune interventional and diagnostic strategies that can implemented in clinical settings. The group is also interested in understanding the transcriptional and epigenetic regulation of human immune responses during persistent viral infections and human cancers, and in developing strategies to manipulate this regulation to improve outcomes following immune intervention.

- Developing novel T cell immunotherapies to treat viral diseases, emerging pathogens and cancer.
- Understanding the attributes of T cell immunotherapy that improve therapeutic outcome.
- Exploring T cell dysfunction in immunocompromised patients and its impact on infectious complications.
- Characterising T cell immunity to SARS-CoV-2 and the impact of immune senescence.

Tumour Immunology Laboratory

Distinguished Scientist: Professor Rajiv Khanna

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

Structural biology

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This project is 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), which allows us to observe atomic-level detail of proteins and molecules of viruses and the immune system. This furthers our understanding of how viruses develop cancer-related sequelae and allow us to effectively design and tailor vaccines and treatments against these diseases.

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

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

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

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This project is suitable for Master or PhD Students.

BACKGROUND

The control of viral infections and cancers is reliant on a well-functioning and organized immune system. Natural killer (NK) and cytotoxic T cells are the primary immune cells responsible for killing virus-infected and tumour cells. However, uncontrolled virus replication and cancer growth result in dysfunction of these immune cells and lead to disease progression.

AIMS

This project aims to discover new targets that can activate or enhance dysfunctional immune cells and boost their ability to fight against diseases. The study will use genetically modified mouse strains, specifically gene knockout, to investigate the role of specific molecules in regulating immune cell functions and their impact on viral and tumour control. The molecules that demonstrate potential will undergo further examination in human immune cells to translate these findings into human disease settings.

METHODS

1. Preclinical mouse models for viral infection and cancer- animal handling, adoptive cell immunotherapy or drug treatments.
2. Engineering immunotherapeutic drugs- Developing CAR (chimeric antigen receptor) T or NK cell products from human blood samples and assessing their antitumour efficacy in vivo using mouse models and in vitro utilizing immunological techniques such as flow cytometry, immune cell activation or killing assays.
3. Gene editing/overexpression technology: Knocking out (CRISPR/Cas9-based) or overexpressing (lentivirus-based) genes in human immune cells to assess their antiviral and antitumour potential for therapeutic purposes.
4. Other techniques: Bacterial work including plasmid transformation, amplification and purification, and mammalian cell transfection with plasmids for lentivirus generation. qPCR, RNA-seq and western blot will also be utilized to identify the impact of manipulated molecules on different immune pathways.

PROJECT POTENTIAL

Identification of novel targetable molecules could lead to the development of therapeutic drugs for cancer and viral infection treatment.

Adoptive T-cell therapy for HPV associated cancers

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This project is suitable for PhD, Masters or Honours students.

BACKGROUND

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 vitro 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.

PROJECT POTENTIAL

The characterisation of HPV16 specific transgenic TCR T cells through examining their effectiveness and therapeutic applicability contributes to the development of an advanced cellular therapy.

Cellular immunotherapy – engineering "custom built" cells to treat cancer

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

BACKGROUND

Current standard approaches for the treatment of human cancers typically employ broad acting radiotherapeutic and chemotherapeutic approaches. There has been growing interest in approaches using immunotherapy with adoptive cell transfer (ACT): using patient's immune cells to treat their cancer. A specific type of ACT uses chimeric antigen receptors (CARs). These are genetically engineered molecules, which are custom built to specifically target protein antigens expressed on malignant cells. There are three FDA-approved CAR T cell-based therapies targeting CD19 on certain B-cell malignancies. CAR19 treatment, of children with relapsed or refractory acute lymphoblastic leukaemia (ALL), and of adults with advanced lymphomas, has demonstrated remarkable success and complete remission in some patients. Although approved therapies are limited to blood cancers, a growing number of CAR T-cell therapies are being developed and tested in clinical studies in multiple solid tumours. There are promising clinical data targeting tumour-associated antigens in melanoma, lung, liver, breast, and brain cancers.

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

AIM

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

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.

Hepatic Fibrosis Group

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The Hepatic Fibrosis Laboratory investigates the cellular and molecular mechanisms of scar tissue formation in the liver. This leads to fibrosis and cirrhosis in adult liver diseases such as haemochromatosis and in children in diseases such as cystic fibrosis and biliary atresia. If left untreated chronic liver disease can lead to liver cancer.

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 and that can be manipulated to control liver scarring or fibrosis. This project is designed to generate novel, chemically modified microRNAs that can be used as anti-fibrotic therapeutics to treat hepatic fibrosis and thus control the development of cirrhosis and liver cancer in patients with chronic liver disease.

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

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 Group

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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 interested in iron nutrition and iron deficiency, diseases of iron loading (haemochromatosis, thalassaemia), perinatal iron metabolism, and the use of nanotechnology to modulate body iron levels. The laboratory integrates genetic and molecular studies with biochemical and physiological approaches. We have a particular interest in understanding how the liver-derived hormone hepcidin regulates body iron homeostasis. The ultimate goal of our work is to improve the diagnosis and treatment of a range of conditions where iron metabolism is perturbed.

Molecular Nutrition Group

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Associate Professor David Frazer is passionate about improving the health of people with iron-related conditions such as iron deficiency and the iron loading disorder hereditary haemochromatosis, both of which affect a surprisingly high number of Australians. In fact, iron-related disorders represent some of the most common conditions affecting humans worldwide. In the Molecular Nutrition Laboratory, we are working hard to understand the molecular basis of these disorders and to use this knowledge to develop better treatments for affected individuals.

Iron homeostasis during pregnancy and the effect of iron supplements

This project is suitable for PhD students.

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 effect of such supplements has not been well studied, and while the benefits of supplementation on maternal iron stores and haemoglobin levels are well accepted, any benefit to pregnancy outcomes and fetal development is less evident, with many studies showing 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.

AIMS

To investigate how iron homeostasis is regulated during pregnancy and to determine the effect of various forms of iron supplementation, with particular emphasis on the placenta and fetus.

APPROACHES

Most of the studies to be carried out will use the mouse as a model, but some of the work will utilize human placental samples. Initial studies will use time mated mice to examine the factors involved in placental iron transfer and to assess the response of the placenta and fetus to oral iron supplements. The effect on the offspring after birth will also be investigated. Subsequent studies will examine the potential benefits of novel iron supplements.

PROJECT POTENTIAL

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.

Iron homeostasis in developing red blood cells

This project is suitable for PhD students.

BACKGROUND

Most of the iron in the body is contained within red blood cells in the form of haemoglobin and is important for the transport of oxygen around the body. During development, red blood cells must have a highly efficient iron uptake pathway to obtain sufficient iron for haemoglobin synthesis. While many proteins involved in this pathway have been identified, recent data from our laboratory has shown that our understanding of this process is incomplete, particularly in utero. Many red blood cell disorders also detrimentally affect systemic iron homeostasis, although, again, the molecular pathways are incompletely understood.

AIMS

There can be a range of aims associated with this project, broadly split into the following:

1. Determining the molecules involved in red blood cell iron uptake in adulthood and during development.
2. Investigating how red blood cell development affects whole body iron homeostasis.

APPROACHES

Most of the studies to be carried out will use the mouse as a model, including several knockout strains, to determine the involvement of various proteins in red blood cell iron uptake. In vitro studies will also be carried out on primary haematopoietic stem cells differentiated in tissue culture.

PROJECT POTENTIAL

Many red blood cell disorders are associated with pathological changes in iron homeostasis. A greater understanding of how developing red blood cells handle iron, and the associated effects on systemic iron levels, could lead to the development of more effective treatments for these conditions.

The regulation of body iron homeostasis

This project is suitable for PhD students.

BACKGROUND

Human conditions with disrupted iron homeostasis are very common and most involve 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 the anaemia of inflammation and the iron loading conditions hereditary haemochromatosis and ß-thalassaemia.

AIMS

To investigate the pathways regulating hepcidin production and to develop ways to manipulate these pathways to treat disorders of iron homeostasis.

APPROACHES

A range of techniques and models will be used to examine the regulation of hepatic hepcidin expression. Various mouse models will be used to determine the involvement of proteins of interest in hepcidin production, including the use of adenovirus and siRNA to alter production. Studies will also be carried out in cultured cells to determine how the proteins regulating hepcidin production interact. Identified pathways can then be targeted in mouse models of human disease to determine whether their manipulation can alter disease progression.

PROJECT POTENTIAL

Inherited iron loading disorders, such as hereditary haemochromatosis and ß-thalassaemia, represent some of the most prevalent genetic disorders known and the anaemia of inflammation is the most frequent anaemia in hospitalised and chronically ill patients. The development of new treatments for these conditions would have a major impact on the quality of life for those afflicted with these disorders.

Mucosal Immunology Group

Team Head: Associate Professor Severine Navarro

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https://www.qimrberghofer.edu.au/our-research/infection-and-inflammation/mucosal-immunology/

The Mucosal Immunology group seeks to develop innovative treatments for inflammation and chronic illnesses, like allergies, asthma and inflammatory bowel diseases, with a particular focus on children. We work in collaboration with other academics, clinicians, paediatricians, dietitians, chemists, and computational biologists to translate our efforts to the clinic and bring our findings to the public. We are interested in the mechanisms of immune dysregulation, the role of the microbiome and its interaction with the different immune compartments to understand disease onset.

Respiratory Immunology Group

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

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

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

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

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.

Clinical Malaria Group

Group Leader: Associate Professor Bridget Barber

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The focus of the Clinical Malaria Group is the evaluation of the safety and efficacy of candidate antimalarials, using the induced blood stage malaria (IBSM) model in healthy human volunteers. Developed by the previous group lead Professor James McCarthy, the model has been used to evaluate 10 investigational medicinal products. Models have been established for an artemisinin-sensitive and an artemisinin-resistant P. falciparum strain, and other Plasmodium species including P. vivax and P. malariae. The model has also enabled the conduct of studies to evaluate transmission-blocking interventions, and has enabled the conduct of exploratory studies to evaluate immunological and pathophysiological response to infection.

Immunopathology Laboratory

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https://www.qimrberghofer.edu.au/our-research/infection-and-inflammation/immunopathology/

The Immunopathology Laboratory is focused on understanding the cellular and molecular mechanisms that drive immune-mediated pathologies. Our recent focus is on adaptive immune polarisation following allogeneic stem cell transplantation and its influence on graft versus host disease (GVHD). Donor stem cell transplantation is an important curative therapy in the treatment of blood cancers, however its application is limited by serious complications such as GVHD that have a significant impact on patient mortality and quality of life.

Early inflammatory responses during preparative transplant conditioning initiate a cascade of adaptive immune responses that manifest as acute and/or chronic tissue damage in >50% of transplant recipients. GVHD treatment options are relatively limited and focused on immunosuppression and steroidal therapy, which are problematic due to opportunistic infection and refractory disease, therefore new therapies are urgently needed.

HIV & Molecular Virology Group

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The HIV and Molecular Virology Laboratory analyses human immunodeficiency virus (HIV) replication. This includes the process by which HIV is able to convert its genetic material composed of RNA into a form compatible with human DNA. Our focus is the discovery of key viral or cellular molecules required for HIV to grow, and then to target their action so that HIV growth can be effectively blocked. The lab is also interested and dengue and SARS-CoV-2 virus replication. Our dengue and SARS virus research includes development of novel inhibitors called defective interfering particles.

Cardiac Bioengineering Laboratory

Senior Group Leader: Professor James Hudson

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https://www.qimrberghofer.edu.au/our-research/infection-and-inflammation/cardiac-bioengineering/

The Cardiac Bioengineering Laboratory aims to develop state-of-the art bioengineering approaches for human myocardium. The team uses our screening platforms in house, in collaboration with research partners, and together in industry partnerships for a variety of different discovery science and therapeutics development applications. These include understanding the mechanisms of cardiac maturation, interactions between different cell populations in the heart, the role of metabolism in maturation and regeneration and development of new therapeutics for patients to prevent heart failure.

Gene Regulation & Translational Medicine Laboratory

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Though all genes exist within every cell in the human body, only a defined gene expression program is executed at any time via reprogramming of the epigenome in response to environmental cues. These dynamic events are elegantly orchestrated by writer and eraser enzymes; generating a 'histone code' within the epigenetic landscape of genes. The therapeutic implications of targeting novel domains of epigenetic enzymes are beginning to be appreciated in immuno-oncology.

The laboratory's focus on immune-oncology is on metastatic cancers and potential implications for viral therapy and the immune response in the aged population. We are also addressing the potential implications for the utility of epi-therapy in combination with immunotherapy and chemotherapy for a variety of metastatic cancers. My team is in the process of developing sensitive liquid biopsies using our newly identified novel biomarkers for patient responsiveness to immunotherapy in the context of the tumour microenvironment. We are also in the process of developing clinical based epigenetic platforms for drug screening and biomarker discovery in collaboration with global technology partnerships.

Lung Inflammation & Infection Group

Group Leader (Honorary): Associate Professor David Reid

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https://www.qimrberghofer.edu.au/our-research/infection-and-inflammation/lung-inflammation-and-infection/

A major focus of the Lung Inflammation and Infection program is to investigate the interaction between bacterial pathogens and the host innate immune response within the lung. Chronic respiratory diseases characterised by infection are prevalent in Australia and globally. The group are studying the role of iron and other biologically active metal ions in promoting bacterial infection in the lungs of patients with the genetic disease cystic fibrosis (CF) and other suppurative lung diseases. To do this the group is studying bacterial and host immune system interactions in vivo using a number of biochemical, molecular and cell imaging methods and also modelling these interactions using mouse models. They are developing molecules to interfere with bacterial iron acquisition with the goal of developing these as antibiotic adjuncts.

Mental Health and Neuroscience Program

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

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

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

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

Neurological conditions such as Parkinson's disease, multiple sclerosis (MS), moto 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

Distinguished Scientist: Professor Sarah Medland

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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.

Please note this is a dry lab analysis focused project.

The role of genomics in understanding psychiatric and neurological disease

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

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

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

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

Please note this is a dry lab analysis focused project.

Health and wellbeing in people with bipolar disorder

This project is suitable for PhD students only.

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

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

Please note this is a dry lab analysis focused project.

Exploring the genetic basis of depression

Co-supervisor: Dr Brittany Mitchell

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

BACKGROUND

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

AIMS

The overall aims of this project is to i) better understand how genes play a role in depression risk as well as depression features such as age of onset, recurrence etc; ii) assess whether depression treatment response traits are heritable and iii) identify genetic variants influencing these traits.

METHODS

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

Statistical genetic analyses of psychotic and mood disorders

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

BACKGROUND

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

AIMS

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

METHODS

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

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

Co-supervisor: Associate Professor Penelope Lind

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

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

I have previously recruited a cohort of Australian adults who completed an online questionnaire in order to:

1. Identify risk factors associated with these behaviours.
2. Investigate the emotional and educational or occupational impacts of these behaviours.
3. 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.

Genetic and environmental influences on brain structure and function

Co-supervisor: Dr Lachlan Strike

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The project is suitable for an Honours student.

BACKGROUND

Genetic and environmental factors influence the structure and function of the human brain. Disentangling and quantifying these sources of variation (genetic and environmental) may be crucial to understanding the brain's genetic architecture and how it relates to typical and atypical brain function.

AIM

To provide a normative reference of healthy brain structure for future studies of neurological and psychiatric disorders by establishing a robust map of genetic and environmental influences on the brain.

METHOD

This project uses brain structure and function measures collected in genetically informative datasets. Statistical approaches such as twin modelling and polygenic risk scores will be applied to neuroimaging measures to elucidate genetic and environmental influences on brain structure and function.

PROJECT POTENTIAL

To identify the factors contributing to differences in brain structure and function between individuals and highlight brain regions especially vulnerable to genetic and environmental influences.

Brain Modelling Group

Group Leader: Associate Professor James Roberts

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

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

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

Modelling brain dynamics across the lifespan

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

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

- How ageing brain structure changes our brain activity.
- How non-invasive brain stimulation perturbs brain network activity.
- How disorders such as epilepsy, schizophrenia, or ADHD may emerge from biologically-plausible changes to model parameters.
- Modelling sleep dynamics.
- Developing novel analysis methods for complex spatiotemporal dynamics.
- Model the early development and maturation of brain networks (collaboration with experimental neuroscientists at UQ).

Physiological signal analysis from infancy to adolescence

This project is suitable for PhD, Masters or Honours students.

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

Modelling neural circuit control of effort under stress

This project is suitable for Honours, Masters, or PhD students.

BACKGROUND

The decision to put in effort to attain rewards is essential for success in life, and critical for survival. Yet, we understand very little about the brain processes that promote persistence and enable individuals to 'keep going' instead of 'give up' when increasing amounts of effort are required. This project is a collaboration with experimental neuroscientists at The University of Queensland and the University of Newcastle.

AIM

We aim to investigate how the decision to persist in exerting effort to obtain a reward is encoded in the brain and affected by stress. In particular, we will develop a computational model of the neural circuits involved in decision-making under stress, aiming to identify mechanisms that explain the experimental results of our collaborators.

PROJECT POTENTIAL

This work will generate new knowledge on the neural mechanisms of stress and decision-making—core processes that underpin adaptive behaviours essential for survival. You will become well-versed in both computational neuroscience and the data emerging from animal experiments.

Translational Neurogenomics Group

Senior Group Leader: Professor Eske Derks

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https://www.qimrberghofer.edu.au/our-research/mental-health-and-neuroscience/translational-neurogenomics/

The Translational Neurogenomics Laboratory is headed by Professor Eske Derks. The group currently includes 10 members (two postdocs, two visiting scientists, two PhD students and three undergraduate students). The Translational Neurogenomics Laboratory has identified genetic risk factors for a range of neuropsychiatric conditions, including substance use disorders, schizophrenia, depression, and obsessive compulsive disorder. Researchers in this group use genetic data to address questions, such as: Which genetic variants in the DNA increase the risk of developing a neuropsychiatric disease? What is the genetic overlap across different psychiatric disorders? What are the downstream molecular consequences underlying statistical genetic associations? Which existing drugs may be repurposed for prevention and treatment of neuropsychiatric diseases?

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

Co-supervisor: Dr Jackson Thorp

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This project is suitable for Honours or PhD. 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

Co-supervisor: Dr Jackson Thorp

This project is suitable for PhD or Honours. 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.

Neurogenetics and Dementia Group

Team Head: Associate Professor Michelle Lupton

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The Neurogenetics and Dementia Lab uses genetics to understand disease processes, identify biomarkers and provide access to therapies for dementia.

Dementia is the second leading cause of death for all Australians. Alzheimer's disease is the most common form of dementia, predicted to affect 152M globally by 2050. Common late onset Alzheimer's disease is caused by age-related failure of clearance of toxic proteins (ß-amyloid and tau) from the brain leading to an immune response. Successful treatment or prevention relies on the ability to identify those at high risk or the earliest disease stages.

The Neurogenetics and Dementia Lab run one of the largest cohort studies in the world focused on those at high risk and in the earliest disease stages of Alzheimer's disease, for the identification of affordable, accessible and scalable biomarkers for dementia diagnosis and screening, to be prepared for the best use of newly developed drugs and lifestyle interventions as they become available.

In addition, the Neurogenetics and Dementia Lab carry out large scale genetic studies, including the use of genetic risk prediction and the identification of causal disease processes in Alzheimer's disease and dementia.

Identifying individuals at high risk of Alzheimer's disease

This project is suitable for Honours, Masters, MPhil, MD or PhD students. For those with experience in statistics and an interest in dementia, genetic epidemiology, bioinformatics and machine learning.

BACKGROUND

Dementia affects an estimated 353,800 Australians, with up to 80% being diagnosed with Alzheimer's disease (AD). Newly developed anti-amyloid drugs are set to revolutionise the treatment of AD. These are likely to have the most impact at the earliest disease stages, therefore there is an urgent need for early-stage biomarkers which are affordable, accessible and scalable.

AIM

To generate predictive screening algorithms, opening up opportunities for simple, accurate and effective screening to identify early-stage AD.

METHOD

The student will build on our current work in PISA (the Prospective Study of Aging, Genes, Brain and Behaviour) using datasets including genome-wide genetic SNP chip data, cognitive data, and blood-based biomarkers. Predictive algorithms will be developed using statistical and machine-learning approaches.

PROJECT POTENTIAL

The identification of individuals at the earliest stages of AD will provide the opportunity to allow the selection of individuals for early treatment strategies.

Methylation-based biomarkers for Alzheimer's disease

This project is suitable for Honours, Masters, MPhil, MD or PhD students. For those with experience in coding and statistics, and an interest in dementia, DNA methylation analysis, genetic epidemiology, and bioinformatics.

BACKGROUND

DNA methylation (DNAm) patterns derived from blood samples correlate strongly with chronological age, thereby referred to as the 'epigenetic clock'. Epigenetic clocks are also associated with differences in physical and cognitive fitness. Epigenetic changes in Alzheimer's disease (AD) affected brain regions have been shown to associate with AD pathogenesis, and significant differences in DNAm patterns are identified in the blood between AD cases and controls. Therefore there is great potential for epigenetic patterns to be diagnostic markers for prodromal AD.

AIMS

Test whether the 'epigenetic clock' associated with ageing also associates with genetic risk of AD and prodromal dementia phenotypes. Data from this project will also contribute to a large international consortia carrying out world leading collaborative analysis on the genetics of DNA Methylation.

METHOD

The student will carry out data analysis using an existing genome-wide array-based methylation dataset, including working with specialised software in a Linux environment. Building on current work in PISA (the Prospective Study of Aging, Genes, Brain and Behaviour). Association analysis will be carried out with dementia-related phenotypes such as neuroimaging and cognitive data.

PROJECT POTENTIAL

This study will identify DNA methylation patterns from the entire genome, in the blood which associate with dementia related phenotypes, and future decline in a population at high risk of AD. These could be used as an accessible AD biomarker, allowing the use of early treatment, and enabling monitoring of disease progression.

Using large scale genetic data to understand cholinergic dysfunction in Alzheimer's diseases

This project is suitable for Honours, Masters, MPhil, MD or PhD student. For those with experience in coding and statistics, and an interest in dementia, genetic epidemiology, and bioinformatics.

BACKGROUND

Cholinesterase inhibitors are the primary drugs currently used for the treatment of Alzheimer's disease (AD), but the exact mechanism of action is unclear. Gaining a more accurate and comprehensive understanding of cholinergic dysfunction and its underlying mechanisms at early stages of AD is crucial for facilitating the development of timely and more effective treatment strategies.

AIM

To use large-scale genetic data to understand the causal relationships between the cholinergic pathway and AD.

METHOD

The student will work with available genome-wide SNP chip data from our in house cohorts as well as large scale international datasets (such as UK Biobank). Techniques such as polygenic risk score (PRS) analysis and Mendelian randomisation (MR) will be used to identify genetic correlations and test whether cholinergic degeneration is an early-stage casual disease process in AD.

PROJECT POTENTIAL

This work will facilitate a more comprehensive understanding of the cholinergic system's role in AD.

Cellular and Molecular Neurodegeneration Group

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https://www.qimrberghofer.edu.au/our-research/mental-health-and-neuroscience/cellular-and-molecular-neurodegeneration/

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 for microglia, brain endothelial cells, organoids (mini-brains), and olfactory (nasal) cells.

The lab is utilising these new 2D and 3D human brain cell models to understand brain disease pathways, and the impact of environmental factors such as air pollution, SARS-CoV-2, and bushfire smoke on brain health. We have also established platforms for drug screening to identify potential new therapeutics for treatment of brain diseases.

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 minera, 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 localization. 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 utilize 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 personalized 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.

Drug repurposing to treat childhood dementia

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

BACKGROUND

Childhood dementia is caused by a group of genetic disorders which have effects on infants and children that include dementia (loss of normal brain function). There are no cures, and treatments limited effects. We are collaborating with Prof. Eske Derks and Dr Zac Gerring at QIMR Berghofer to screen currently used drugs to determine if any have therapeutic effects on childhood dementia.

AIM

Drugs and drug targets are identified using computational approaches, and the leading drugs will be tested for effectiveness in pluripotent stem cell derived brain cell models of childhood dementia.

METHOD

Growth of human stem cell-derived brain cell cultures.

PROJECT POTENTIAL

Potential to identify new drugs to treat childhood dementia.

The potential impact of bushfire smoke on brain health

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

Background - In this project, we are using our monocyte and pluripotent stem cell-derived brain cell models to understand how bushfire smoke affects the human brain, particularly its ability to include neuroinflammation. We are also working with Assoc. Prof. Michelle Lupton, and Dr Jodi Thomas at QIMR Berghofer to determine if exposure to bushfire smoke affects the likelihood of being diagnosed with neurodegenerative diseases such as dementia.

AIM

1. Determine the impact of bushfire smoke on human brain cells.
2. Determine if exposure to bushfire smoke increases risk of dementia or other brain diseases.

PROJECT POTENTIAL

Potential to understand the impact of bushfire smoke exposure on human brain health.

Cognitive Fitness Group

Program Director (Mental Health & Neuroscience) and Group Leader: Professor Murat Yucel

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https://www.qimrberghofer.edu.au/our-research/mental-health-and-neuroscience/cognitive-fitness/

The Cognitive Fitness Group uses cognitive neuroscience to create digital tools that measure, monitor and help optimise brain health.

Professor Murat Yücel's work primarily focuses on developing innovative approaches to Digital Medicine. This includes:

1. A gamified measurement tool for assessing cognitive and brain function for use in clinical research, aiming to comprehend the cognitive mechanisms of clinical dysfunction and guide mechanism-targeting interventions to enhance them.
2. An ultra-brief tool for measuring cognitive fitness in clinical conditions, which can be used to build resilience against mental ill-health and improve performance in high-stakes situations, such as those faced by first responders, military professionals, and competitive athletes.

The novel Digital Medicine also includes an interactive virtual reality platform that delivers exposure/response prevention interventions for disorders like obsessive-compulsive disorder (OCD) and gambling disorder.

Professor Murat Yücel is also involved in clinical trials in Lifestyle Medicine, focusing on the neural and cognitive effects of physical exercise and mindfulness meditation. Additionally, he participates in clinical trials of Psychedelic Medicine, examining the cognitive and mental health effects of psilocybin and MDMA.

Child & Youth Mental Health Research Group

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https://www.qimrberghofer.edu.au/our-research/mental-health-and-neuroscience/child-and-youth-mental-health/

The Child and Youth Mental Health Research Group conduct research with a particular focus across four areas.

The first are studies of the causes and consequences of mental ill-health and suicidal behaviour in children and young people. This enables the identification of factors that influence mental health in childhood and adolescence. Modifying these factors can prevent the onset of mental illness and improve the wellbeing of children and adolescents.

The second research area addresses bullying victimisation and perpetration in school-aged children. Bullying victimisation is associated with mental illness and poor academic performance.

The third is psychoneuroimmunology. Our research in this area has demonstrated the interplay between the nervous system and the immune system where we have shown some people have psychosis arising from inflammation in the central nervous system.

The fourth research area focuses on clinical trials and health service research. These studies evaluate the effectiveness of innovative treatments for young people at risk of or living with, mental illness and the outcomes following the implementation of clinical services and lifestyle support for young people living with mental illness.

Computational Neurogenomics Group

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https://www.qimrberghofer.edu.au/our-research/mental-health-and-neuroscience/computational-neurogenomics/

The Computational Neurogenomics Lab at QIMR Berghofer combines genomics, neuroscience, sleep, mental health, data science, and machine learning to unravel the complexities of brain-related traits and diseases. Our aim is to identify the fundamental drivers of individual variation in cognition, behaviour, brain structure, and the risk of neuropsychiatric diseases by examining the natural variations in DNA sequence within populations.

To achieve this goal, we leverage advanced statistical and computational methods, collaborate with researchers from diverse fields, and analyse vast datasets from global scientific consortia and biobanks. Our overarching objective is to gain deeper insights into the underlying causes and mechanisms of human behaviour, neuroanatomy, and brain-related disorders.

Our research portfolio encompasses a wide range of complex health conditions, including but not limited to, Parkinson's disease, Alzheimer's disease and related dementias, chronic pain and migraines, self-harm behaviours, depression, sleep disorders, and other complex traits. We are constantly eager to learn and integrate new methodologies into our research, and our team is always willing to engage in multidisciplinary projects with researchers from other disciplines.

At the Computational Neurogenomics Lab, we are driven by the desire to advance scientific knowledge and improve human health through innovative research. Our diverse and multidisciplinary team is dedicated to pushing the boundaries of science and technology to unlock the secrets of the brain and unravel the mysteries of brain-related disorders.

Genetic Epidemiology Group

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https://www.qimrberghofer.edu.au/our-research/mental-health-and-neuroscience/genetic-epidemiology/

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.

Clinical Brain Networks Group

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https://www.qimrberghofer.edu.au/our-research/mental-health-and-neuroscience/clinical-brain-networks/

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

For further assistance, please contact:

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