QIMR Berghofer
Medical Research Institute

THE FUTURE OF HEALTH

STUDENT PROJECTS 2018/19

2018/19 STUDENT PROJECTS

CONTENTS

Director's Welcome

QIMR Berghofer is one of Australia's largest and most successful medical research institutes. The Institute's diverse research program extends from tropical diseases to cancers to Indigenous health, mental health, and infectious diseases.
As a QIMR Berghofer student, you would be part of an active scientific community that is investigating the genetic and environmental causes of some of the world's deadliest diseases as well as developing new diagnostics, better treatments and prevention strategies. Our research leads directly to treatments. As an example, currently there are 22 clinical trials ongoing based on discoveries at the institute. You could be part of the team that discovers and develops the next translated treatment.

You will be an integral part of the QIMR Berghofer community where a friendly atmosphere of interdisciplinary collaboration & breakthrough research is achieved. Throughout your candidature you will be supported, mentored, and have access to assistance. Past students have found that their experience here is both intellectually stimulating but they also develop friendships for life.

You will find that there are many interesting projects available in this book and we hope that QIMR Berghofer will be where you will develop your research potential. I also invite you to our Institute Student Open Days to tour the state of art facilities, talk to current staff and students about available opportunities.

Professor Frank Gannon

Director and CEO

QIMR Berghofer Medical Research Institute


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V4
V3B
V3A

QIMR Berghofer Student Committee

Hello from the QIMR Berghofer Student Committee!

Being at QIMR Berghofer means that our student experience is fun, engaging and supportive. Our Student Committee consists of our Student Society, Higher Degree Committee (HDC) Representatives and Seminar Convenors. We organise social and fundraising events throughout the year, our biennial student retreat and our annual student Christmas party. We also represent our cohort on the QIMR Berghofer HDC and organise the yearly student symposium. An Early Career Research Seminar Series each week is hosted to effectively communicate our research with our peers (and to share beer and pizza with beforehand, of course!). QIMR Berghofer is a hub for world-class research and we are a close community, with a great support staff, a large student body and an esteemed group of medical scientists.

Why study at QIMR Berghofer?

Studying at QIMR Berghofer provides students with a unique opportunity to have access to diverse clinical and cutting edge research. Our proximity to RBWH and the Herston Campus makes us ideal for clinical research collaborations.
In addition to your research training, QIMR Berghofer is committed to your overall professional development. This includes expanding your skills in critical scientific writing, statistics, leadership, communication skills and understanding and protecting your intellectual property. Your broader skill base, due to studying at QIMR Berghofer, 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 (population studies, statistics to public health and tropical medicine to immunology and cancer).
- Opportunities for international collaboration and travel.
- Competitive Honours and PhD top-up scholarships.
- Travel support available for attending international conferences, 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.
- Weekly seminar series presented by QIMR Berghofer researchers, national and international speakers.
- An active student society, student symposium and student retreat for networking and training purposes.

The QIMR Berghofer student body is a diverse group of Australian and international students involved in a wide range of research endeavours. Make a real difference to directly relevant health issues for Australians and the rest of the world.

QIMR Berghofer Medical Research Institute was established in 1945.

QIMR Berghofer is a world leading translational research institute focused on cancer, infectious diseases, mental health and a range of chronic disorders.

QIMR Berghofer is home to more than 800 scientists (of which approximately 170 are students) in over 60 separate research groups.

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

QIMR Berghofer Services

Histology Facility

The QIMR Berghofer Histology Facility is a fully equipped service and research laboratory. The facility caters to the needs of scientists and postgraduate students from QIMR Berghofer as well as external and international institutions. The QIMR Berghofer Histology Facility is a fully equipped service and research laboratory. The facility caters to the needs of scientists and postgraduate students from QIMR Berghofer as well as external and international institutions.

The unit provides technical services and also trains and consults on matters relating to routine paraffin and cryo histology, special stains, immunohistochemistry (Tyramide Signal Amplification), antibody optimisation, FISH and CISH labelling, tissue preparation and sectioning for transmission electron microscopy and high-resolution digitisation of histology slides (e.g. Vectra Imaging System).

Sample Processing

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

Flow Cytometry and Microscopy

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

DNA Sequencing

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

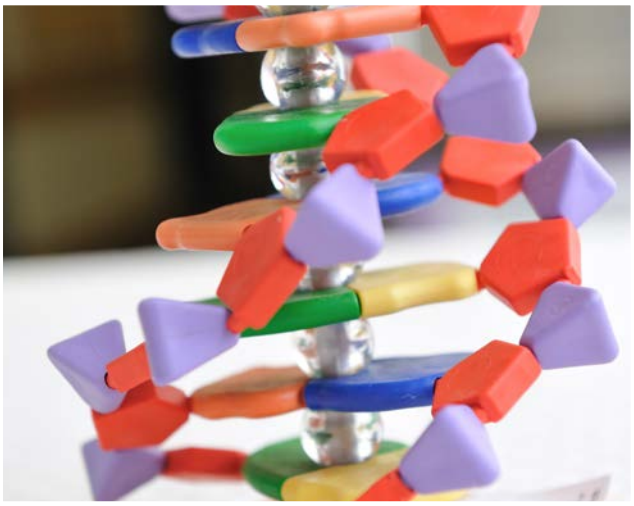
Analytical Services

QIMR Berghofer Analytical Services contain fully equipped service and research laboratories, enabling delivery of high quality and reproducible data. Analytical Services caters to the needs of scientists and postgraduate students from QIMR Berghofer as well as external and international institutions.The facility provides technical services and also trains

and consults on cell line authentication, culture media services unit, glassware and waste disposal.

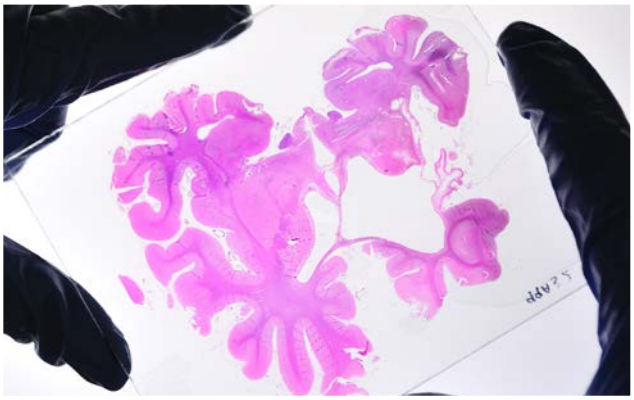
Proteomics

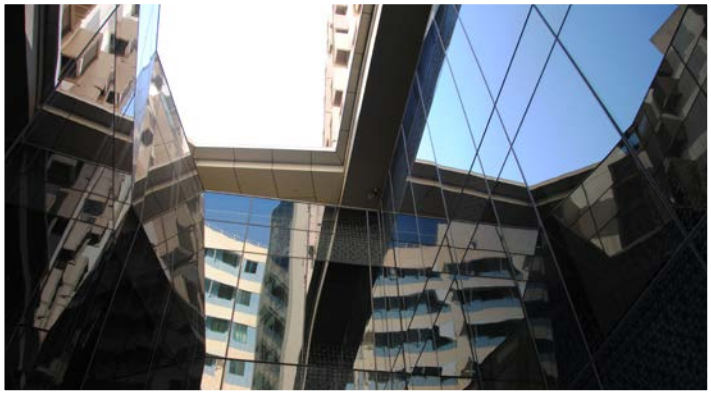
The QIMR Berghofer Proteomics Facility is an expert centre for state-of-the-art proteomics analysis. The experienced team of scientists develop and implement innovative mass spectrometric and bioinformatic methods, for qualitative and quantitative characterisation of proteins, in simple or complex mixtures. The facility team can provide comprehensive standard and specialised proteomic workflows.



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 disk to store and tens of thousands of CPU hours to analyse.





QIMR Berghofer Facilities

QIMR Berghofer Statistics Unit

The QIMR Berghofer Statistics Unit is comprised of 10 statisticians, who provide statistical consultancy and research collaboration services to medical and clinical researchers. Services range from laboratory research through 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 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; and PK/PD modelling.

Q-Pharm

Q-Pharm is a state-of-the-art early-phase clinical trials company. We provide a broad range of high-quality services to commercial and academic clients around the world. Since 2002, Q-Pharm has safely and successfully conducted more than 400 early-phase trials, vaccine and challenge studies in more than 15 000 volunteers. Q-Pharm's team is highly qualified and our leaders have a wealth of experience in clinical development. This experience enables Q-Pharm to understand the needs of a diverse range of clients and deliver clinical services to meet and exceed client expectations. Clinical trials conducted at Q-Pharm have been accepted by regulators throughout the world, including Australia, Europe and North America.

Q-Gen Cell Therapeutics

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

Q-Gen Cell Therapeutics has expertise in and 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 through to clinical interpretative reports, can be provided to pharmaceutical and biotechnology companies, researchers, clinical research organisations and pathology service providers.

Medical research opportunities at QIMR Berghofer

Options for students to be part of QIMR Berghofer are:

A

Research higher degree student at QIMR Berghofer Medical Research Institute (PhD, MPhil, Masters Coursework or Honours)

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

B

Vacation research programs

Through University of Queensland, QUT and Griffith University, we offer vacation research experience. These are small projects carried out over a 4-10 week period during the University summer (November-February) or winter (UQ only) 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 are unpaid placements are 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/students/university-students

Projects webpage: http://www.qimrberghofer.edu.au/student_projects

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

Guide for student admission

1. Check you are eligible for the degree you are interested in undertaking; this is specific to the university you are enrolling through.

2. Check the QIMR Berghofer website and identify a student project or Research group that matches your research interests.

3. Contact the QIMR Berghofer scientist via email providing the following information:

   a) Whether you want to undertake MPhil or PhD study
   b) Discuss your research interests and any previous research experience,
   c) Provide your academic CV

4. Arrange to meet in person or have a Skype 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 via email to you.

7. International students must also have an appropriate visa from the Department of Immigration and citizenship**.

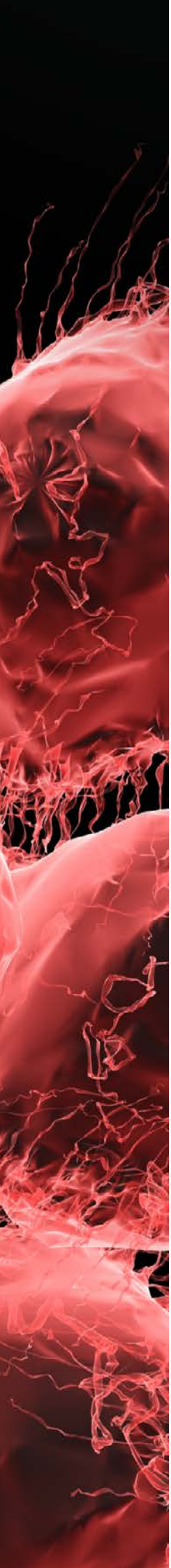
8. Provide evidence of full admission/enrolment to an Australian university and scholarship (if you are joining the PhD program). Congratulations, you are ready to begin your candidature.

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

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

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

Cancer



Cancer is one of the major causes of illness and death in Australia and the developed world. More than 120,000 Australians are diagnosed with cancer (excluding non-melanoma skin cancer) annually, and cancer accounts for about 30% of deaths in Australia, making it the second most common cause of death, after cardiovascular diseases.

Cancer is a disease caused by abnormal cell growth and spread (metastasis) to other parts of the body. Some cancers are common within a family and this risk is inherited, while the majority of cancers are caused by environmental factors or the accumulation of genetic changes in normal cells. Many forms of cancer can be treated successfully if detected early. New generation molecularly targeted therapies and immunotherapies are extending life for a large proportion of individuals with certain late-stage cancers and are providing cures in some cases.

The Cancer Program at QIMR Berghofer offers a wide variety of research opportunities for higher degree students, ranging from public health and epidemiology, to genetics, epigenetics, genomics, immunology, cell biology, molecular biology and bioinformatics

Gynaecological Cancers

Group Leader:
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This group 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 gynaecological cancer.

Much of this work is conducted within two national population-based case control studies: the Australian Ovarian Cancer Study (AOCS) and the Australian National Endometrial Cancer Study (ANECS).

The group is also running projects focused on renal and thyroid cancers.

Ovarian cancer – lifestyle, survival and quality of life

The projects would be suitable for Masters/PhD students but some experience in statistics and data analysis is essential and a background in epidemiology and/or an interest in cancer are highly desirable.

Background: More than 1300 women are diagnosed with invasive ovarian cancer in Australia every year and five year survival is only ~40%. Most women diagnosed with ovarian cancer face a poor prognosis and almost uniformly ask what they can do to improve their chances of survival.

Women with clinically and pathologically similar ovarian cancers can have very different outcomes suggesting other factors are important in determining survival. There is evidence that lifestyle factors influence recurrence and survival in breast and colon cancer but there is currently no direct evidence as to whether the same is true for ovarian cancer.

The Ovarian Cancer Prognosis and Lifestyle (OPAL) study aims to fill this knowledge gap by following a national cohort of women newly diagnosed with ovarian cancer. It aims to identify whether potentially modifiable lifestyle choices including physical activity, diet and medication use are associated with recurrence and survival.

Aims: To identify whether potentially modifiable aspects of lifestyle (e.g. diet, physical activity, smoking, alcohol consumption, use of dietary supplements, common medications and complementary medicines) are independently associated with patient outcomes including wellbeing, quality of life, progression-free and overall survival.

Cancer & Population Studies

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Severity of weight gain among heart transplant recipients

- Suitable for Honours, Masters, or MPhil students.

Supervisors:
Prof Adèle Green and Dr Kyoko Miura

Heart transplantation is a life-saving measure for end-stage heart failure patients. It is also a massive investment by the community through the health care system and personally by donors' families. However, the growing problem of weight gain after transplantation is eroding the life-saving potential of this procedure because post-transplant overweight and obesity exacerbate underlying cardiovascular disease, diabetes, risk of organ rejection and ultimately reduce survival. In addition, the subgroup of patients on the wait-list for transplant

who need a ventricular assist device appear especially susceptible to rapid and excessive weight gain after device implantation but Australian data are lacking . In this retrospective cohort study, we aim to describe the extent of changes in body-weight after transplantation, and document cardiovascular biomarkers (e.g. blood pressure, blood lipids) among adult heart transplant recipients. We also plan to specifically study the patients with pre-transplant ventricular assist devices, the configuration of the ventricular assist device and duration on the ventricular assist device and weight gain.

Interested students should have a Health or Medical Science background. The project involved extraction of weight data from medical records and then supervised data analysis, so knowledge of statistics and experience with data analysis are both essential.

Molecular Cancer Epidemiology Group

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

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

- Can be adapted in scope for Hons 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.

Repurposing existing drugs to treat endometrial cancer

- Honours or PhD

Supervisors:
Dr Dylan Glubb and Dr Tracy O'Mara

Background: There is promising evidence that genetic studies of cancer will advance the development of new therapies. For example, clinically approved drugs are more likely to target proteins that have been linked to disease traits through genome-wide association studies (GWAS) than proteins with no such links. Indeed, several drugs already used to treat endometrial cancer are known to target proteins that have been linked to genetic variation associated with endometrial cancer risk. To expedite the development of new cancer therapies, we plan to use existing drugs to target proteins that relate to the genetic risk of endometrial and, potentially, other cancers.

Aim: To test existing drugs that target the products of genes related to cancer risk for their effects in cancer cell models

Approach: We will use CRISPR/Cas9 to knockout druggable genes in cancer cell lines and then treat knockout and wild-type cells with compounds that target the products of the druggable genes. This approach will enable us to determine whether anti-cancer cellular responses are mediated through the druggable gene and also whether the druggable gene has effects on cellular phenotypes that are related to tumourigenesis.

Outcome: Identification of existing drugs that have anti-cancer effects in cancer cell models would provide the foundation for follow-up studies that assess the effects of these drugs on tumours in animal models.

Identifying the regulatory targets of common endometrial cancer risk variants

- Honours or PhD

Supervisors:
Dr Dylan Glubb and Dr Tracy O'Mara

Background: We and our Endometrial Cancer Association Consortium (ECAC) collaborators have identified common genetic variation at 20 genomic regions that associate 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, at two regions we have used DNA looping analyses to identify genes that interact with risk variants and, in follow-up experiments, shown that risk variants regulate gene activity. These experiments constitute an essential step for the translation of genetic findings into advances in our knowledge of endometrial cancer biology.

Aim: To identify the gene regulatory targets of endometrial cancer risk variants using DNA looping analyses and other experimental techniques.

Approach: DNA looping analyses can be identified using approaches such as HiChIP that can identify genomic regions that interact with the promoters of all active genes, while other techniques (e.g. 3C) can be used to analyse interactions with specific genes. We will use both approaches to identify genes that are targeted by endometrial cancer risk variants. We will also perform follow-up experiments using reporter gene assays to determine if risk variants affect gene activity.

Outcome: The identification of the gene targets of risk variants will not only identify pathways that are involved in endometrial cancer development but also provide potential targets for the repurposing of existing drugs or the development of novel therapies.

Functional Cancer Genomics & Functional Genetics Group

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The Functional Cancer Genomics Laboratory focuses on understanding the regulation of cancer genes and how defects in regulatory elements controlling their expression contribute to cancer risk and development. The laboratory also works closely

with the Functional Genetics Laboratory to understand the mechanism by which DNA sequence variants lead to an increased cancer risk.

Group Leader (2):
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The Functional Genetics Laboratory investigates how genetic variation can contribute to disease. The laboratory works closely with the Functional Cancer Genomics laboratory to understand the mechanism by which DNA sequence variants confer and increased risk to breast and ovarian cancer. The major focus in the laboratory is how DNA variants affect regulatory processes such as long-range transcriptional regulation and lncRNA biology. Another major interest in the laboratory is identifying DNA variants that can affect the regulation of the breast cancer susceptibility gene, BRCA1.

Ultimately, understanding the mechanism by which DNA variants contribute to disease will provide new routes to novel treatments and preventive measures for women's cancer.

Post-GWAS functional characterisation of breast cancer susceptibility loci

- PhD project, may also be considered for an Honours project

Background: More than 170 different breast cancer risk loci have now been discovered via genome wide association studies (GWAS) but until recently it has not been possible to identify the causal variants that are directly responsible for the altered risk. Importantly, the majority of variants lie within non-coding regions of the genome such as introns and intergenic regions, therefore regulatory elements, rather than protein-coding transcripts, are likely responsible for the associated risk. These regulatory elements act as long-range enhancers or repressors of genes outside these regions through long-range interactions mediated by the formation of chromatin loops. This project will involve analysing regulatory elements containing candidate causative variants and identifying the target genes and the relevant changes in their regulation that confer an increased risk of breast cancer.

Aims:

1. Identify/confirm the target genes of the putative regulatory elements using chromosome conformation-based techniques.

2. Evaluate the likely functional DNA variants at breast cancer susceptibility loci using a combination of in vitro studies.

Approaches: We will initially use an in silico approach to assess whether the top variants from GWAS fine-mapping data fall in regulatory elements. The analysis will integrate multiple complementary genome-wide data sets, including ChIP-seq for histone modifications and DNA binding proteins. We will then employ multiple experimental approaches to identify target genes that physically interact with the regulatory elements identified in our breast cancer risk loci. These include chromosome conformation capture (3C)-based techniques, eQTL analyses and reporter assays. To functionally evaluate the risk-associated DNA variants, we will use a combination of in vitro assays including chromatin immunoprecipitation (ChIP) assays, allele-specific 3C, gene silencing using RNAi or gene overexpression using retroviral expression systems. We will also generate isogenic cell lines for the best candidate DNA variants using CRISPR/Cas9 technology. These specialised lines will be used to measure target gene expression and activity, identify allele-specific chromatin interactions and assess transcription factor binding.

Exploring the function of breast cancer-associated variants in long non-coding RNAs

- PhD project, may also be considered for an Honours project

Background: Genetic factors are important contributors to breast cancer risk. Mutations in known breast and cancer susceptibility genes such as BRCA1 and BRCA2, account for approximately one quarter of total familial breast cancer genetic risk. The remainder is likely conferred by a

combination of multiple low-penetrance variants. More than 170 different breast cancer risk loci have now been discovered via Genome Wide Association Studies (GWAS) but until recently it has not been possible to identify the causal variants that are directly responsible for the altered risk. Importantly, the majority of disease associated variants at these loci lie within intergenic regions and within introns of protein coding genes, raising the possibility that undiscovered RNA transcripts such as long non-coding RNAs (lncRNAs), may be responsible for the associated risk at a subset breast cancer risk loci. This project aims to characterise breast cancer associated SNPs that fall in regions encoding lncRNAs, to explain the associated risk at breast cancer risk loci.

Aims:

1. Identify lncRNAs at breast cancer risk loci.

2. Examine the function of the identified lncRNAs in breast cancer.

3. Evaluate the likely functional variants within lncRNAs at breast cancer risk loci.

Approaches: We will identify lncRNAs at breast cancer risk loci using a combination of in silico approaches and RNA-CaptureSeq technology. We expect that the prioritised lncRNAs will have cancer-related biological functions and will therefore examine the effects of these lncRNAs on processes disrupted in cancer such as cell proliferation, response to DNA damage, apoptosis, migration, invasion and tumour formation. The assays we will perform will involve overexpression and knockdown of the lncRNAs in normal breast and breast cancer cell lines. We will also assess the function of lncRNAs in breast tumour formation using an explant assays in mice. The ability of breast cancer associated SNPs to modulate lncRNA function will also be examined using a combination of in vitro assays.

Cancer Genetics Group

Group Leader:
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The Cancer Genetics Laboratory investigates why some people get cancer, and how these cancers, particularly those of the breast, ovary and stomach, develop from a normal cell. The laboratory also looks at why these cancers are often found together in the same families and share many similar characteristics.

We are looking for other genes that might predispose to breast or ovarian cancer, using families from the Australasian consortium of familial breast cancer, kConFab, to identify high-penetrance genes, and case-control studies to identify low-penetrance genes. In addition, the laboratory is studying an inherited form of gastric cancer which we have recently described.

The laboratory also has an interest in genes involved in response to chemotherapy in ovarian cancer patients, and have done a genome-wide association study in cases from the Australian Ovarian Cancer Study, with validation in additional cases from the Ovarian Association Consortium.

Germline variation underlying individual differences in risk of, and outcome from, breast and ovarian cancer

- Suitable for PhD students only

Background: As members of the Breast Cancer Association Consortium (BCAC), the Consortium for Investigators of Modifiers of BRCA1/2 (CIMBA), and the Ovarian Cancer Association Consortium (OCAC), we have been very successful recently in finding loci associated with cancer risk using genome-wide association studies (GWAS). In total, we have identified more than 200 'tagging' single nucleotide polymorphisms (SNPs) associated with risk of breast and ovarian cancer, but so far very few associated with outcome. However, a major bottleneck in understanding the mechanism underlying these GWAS 'hits' has been moving from the tagging SNPs, to identifying the candidate causal SNPs, and their method of action.

Through our international collaborations, we have access to extensive genotyping data from tens of

thousands of cancer cases and controls which allow us to perform 'fine mapping' to identify the putative causal SNPs at the loci we have found through GWAS. These data put us in a leading position worldwide to move from identifying GWAS 'hits' to determining the functional variants and their mechanisms of action. Almost all of these SNPs are in intergenic or non-coding regions of the genome. The challenge is now to identify the target genes on which these SNPs act, and the mechanisms by which they alter risk or prognosis. Once we have narrowed down the list of putative causal variants through statistical analyses, we then use a combination of bioinformatic analysis (particularly of data from ENCODE and FANTOM5), chromatin conformation capture (3C), expression quantitative trait loci (eQTL) analysis and luciferase assays to identify the target gene nearby. We also plan to use genome editing to make isogenic cell lines that differ only by the genotype at these SNPs to further explore their function.

A major aim of post-GWAS studies is to translate evidence of genetic association into molecular mechanisms which ultimately lead to more effective clinical interventions. A recent study suggests that drugs which target genes that are implicated by GWAS are twice as likely to be effective treatments for the studied trait. For this reason, we are particularly focusing on breast cancer susceptibility loci where we predict that the target gene/protein is one for which an approved drug (for another disease) is already available. In collaboration with Dr Fares Al Ejeh, at QIMR Berghofer, we are starting to evaluate the effects of some of these drugs in animal models. In addition, we hypothesize that a subset of breast cancer susceptibility SNPs act in cells of the immune system to influence cancer risk by regulating genes important in immunosurveillance, and we are starting to explore this possibility in collaboration with immunologists at QIMR Berghofer.

Cancer Drug Mechanisms

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The Cancer Drug Mechanisms Group combines expertise in cancer biology with drug studies.

Our cancer biology work currently focuses on understanding the development and progression of cancers of the skin and oral cavity. Specifically, we are investigating the molecular mechanisms involved in the progression and metastasis of melanoma, head and neck cancer, as well as cutaneous squamous cell carcinoma. These molecular mechanisms also impact on drug resistance of cancers. The identification and understanding of aberrantly regulated pathways in these cancers is crucial prior to the design or identification of suitable agents to treat the diseases.

What causes treatment resistance in melanoma?

- Honours or PhD

Supervisor:
Assoc Prof Glen Boyle and
Dr Jacinta Simmons

B**ackground:** Currently there are no treatments capable of curing metastatic melanoma and resistance to most treatment options occurs within six months. The complete absence of key transcription factors in a small subpopulation of tumour cells may contribute towards resistance to therapy. This project will investigate the importance of these two transcription factors for response to therapy.

Aim: To determine if dual loss of MITF and BRN2 is responsible for recurrent, therapy resistant, metastatic melanoma.

Approach: This project will require the generation of melanoma cell lines with the inducible removal of both MITF and BRN2. Two and three dimensional growth assays will be utilised to measure drug sensitivities. The project will also determine

the downstream targets that lead to therapy resistance with the ultimate goal of designing new treatments to help patients beat melanoma.

Can we prevent melanoma metastasis?

- Honours or PhD

Supervisor:
Assoc Prof Glen Boyle and
Dr Jacinta Simmons

Background: The incidence of malignant melanoma has increased dramatically over the past three decades, faster than any other solid malignancy. It is now the third most commonly diagnosed cancer in Australia. It is estimated that 14,320 Australians will be diagnosed with melanoma in 2018, and over 1,905 will die, mainly from metastatic disease.

Heterogeneous tumours, including melanoma, contain different sub-populations of cells. It is now emerging that these sub-populations can influence the invasive behaviour of other cells or populations within the tumour, although the mechanisms behind the interactions are largely undefined. This project will address the important concept that heterogeneity within the tumour is important in the invasion and dissemination of melanoma due to intercellular communication and co-operation. The project will aim to understand the specific interactions between the heterogeneous sub-populations, and to identify and develop inhibitors of these interactions as potential future therapeutics to prevent or treat metastatic melanoma.

Aim: To determine the role of heterogeneity and co-operativity in the local invasion and metastasis of melanoma.

Approach: This study will produce fluorescently tagged cell lines with controlled deletion of key factors to investigate growth and invasion of metastatic melanoma. Two- and three-dimensional cell culture assays will enable us to identify the functions of individual cell populations and how they interact. The project will use a combination of fixed and live-cell microscopy to monitor growth with newly developed assays. The project will also look at ways to stop communication between the cell populations. The overall aim is to use therapy to help prevent or to treat patients with metastatic melanoma for a longer and better life.

Epigenetics and Disease

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Determining the therapeutic efficacy of epigenetic drugs in ovarian cancer

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

Hypothesis:

1. Deregulation of epigenetic modifiers is responsible for cancer progression and metastasis,

2. Inhibiting the activity of epigenetic modifiers will allow re-expression of genes that may improve outcome of cancer patients.

Aim: The overall goal of this study is to develop a novel therapy targeting epigenetic modifiers and validate the epigenetically-suppressed gene signature that predicts outcome in aggressive cancer patient samples to

generate a signature-based diagnostic tool that can identify cancer patients at high risk of recurrence and metastasis

Approaches:

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

Combining epigenetic drugs with immunotherapy in melanoma

Whereas advances in immune and targeted therapies have made tremendous progress recently they are effective only in distinct subsets of patients or result in the emergence of drug resistance. Also, prohibitive cost of immunotherapy can be overcome by therapy that uses relatively inexpensive small molecules. Patients suffer considerable side effects and these may be alleviated by changed drug doses when used in combination with other drugs. Thus investigation of alternative approaches is essential. Recent studies have shed light on the importance of epigenetic regulation in cancer biology including overexpression of histone methyltransferases in cancers and combining inhibitors of epigenetic modifiers may either enhance the efficacy of immunotherapy or treat those patients that have become resistant to therapy.

Hypothesis: We hypothesise that combining epigenetic modifier inhibitors with immunotherapy will be more effective compared to using one drug alone.

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

Approaches:

- Cellular models and treatments
- Characterisation of the epigenetic modifier change by RNA-seq
- In vivo mouse model of melanoma
- Protein complex purification and proteomics
- Characterisation of putative target genes by ChIP-seq

Signal Transduction Group

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

Several genes involved in the DNA damage response pathways are known to contribute to breast cancers. This group seeks to identify other known or new genes in these pathways which might have similar involvement in cancer susceptibility by preventing the generation of mutations in our DNA. This area is of critical importance to cancer research as the

pathway controlling the DNA damage response are involved in tumour suppression and are believed to be mutated at the early stage in the evolution of cancer.

Please contact Professor Kum Kum Khanna with an attached CV by email and indicate which project you are interested in.

To understand oncogenic role of Promyelocytic Leukemia gene in triple negative breast cancer

- Honours or PhD

Supervisors: Prof Kum Kum Khanna and Dr Andrea Rabellino

Background: This project aims to investigate the role of the Promyelocytic Leukemia gene (PML) in triple negative breast cancer (TNBC). PML is very well known for its tumour-suppressive functions, however, in TNBC, PML is over-expressed and acts as an oncogene, and the reasons of this unusual behaviour are still largely unknown. We will investigate the mechanisms that lead to PML over-expression in a large cohort of breast cancer samples. The data obtained by these analyses will provide clinical correlation of underlying biology. Using several TNBC cellular models, we will test wether PML over-expression occurs in a transcriptional dependent-manner or it occurs at proteins levels through the alteration of its ubiquitin/degradation pathway. PML forms distinct structures into the nucleus known as PML Nuclear Bodies (PML-NBs). Despite the pivotal roles of PML-NBs in cell physiology, their composition has been elusive and PML-NBs have not yet been characterised. Through a new methodology (RIME) that combines chromatin/protein-complexes purification and mass spectrometry analysis, we will purify and characterise the PML-NBs of TNBC for the first time. These studies, will share light on the composition of the PML-NBs in TNBC, elucidating their role in TNBC and opening new opportunity to discovery new potential targets for TNBC therapy. Finally, we want to propose to use arsenic trioxide (ATO) for TNBC treatment. ATO binds directly to PML, and it is the drug of choice for the treatment of Acute Promyelocytic Leukemia (APL), caused by the fused oncoprotein PML-RARA, and induces the complete regression of the disease. We propose to study in vitro and in vivo the effect of ATO in TNBC. We reason that, since PML is over-expressed only in TNBC, ATO treatment will show a selective effect only in TNBC. We will initially test the effect of ATO on a large panel of breast cancer cell lines and we will then further characterise ATO treatment in a series of xenografts experiments. These experiments will determine the efficacy of ATO treatment in vitro and in vivo in TNBC. Future studies will be directed to propose ATO for treatment of TNBC patients.

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

- Honours or PhD

Supervisors:
Prof Kum Kum Khanna
Dr Murugan Kalimutho
Dr Devathri Nanayakkara

Background: Precursor metastatic cells, referred to as 'cancer stem cells' (CSCs), play a pivotal role in metastasis and relapse in breast cancer (BC) patients. Thus, effective management of breast cancer will require new therapeutic strategies that eliminate CSCs. Nonetheless; drugs that specifically target CSCs are extremely under-developed. We have made a novel finding that expression of a new kinase is linked to breast cancer stemness as well as radioresistance. To date, this kinase has not been studied in breast cancer. Moreover the signalling pathways regulated by kinase or its upstream regulators are unknown at present – not to mention in a context of radiobiology and chemotherapy. It clearly warrants further investigation.

The study will establish the clinicopathological importance of identified kinase with other breast CSC markers in primary human BCs with clinical outcome data, providing clinical correlate to underlying biology and paving the way for companion diagnostic. We will study the effect of combined kinase depletion followed by IR treatment or chemotherapy on tumour recurrence in in vivo murine xenograft models in order to generate basic and preclinical data to support the development of kinase inhibitors that target cancer stem cells in women with BC. These studies will determine the role of resistant CSCs in tumour regrowth (recurrence) and

how the specific eradication of these cells provides means for successful and curative approaches. It is anticipated that our mechanistic study on this kinase in in vitro cell line models and/or in vivo xenograft models will shed light on a new signalling axis that is critical to regulating breast cancer stemness and improving current clinical radiotherapy and chemotherapy for BC patients. The long-term aim of our research is to develop more effective therapies for advanced breast cancer. The identification of therapeutically exploitable kinase that is an important mediator of CSCs function after chemo- and radiotherapy will improve the success of standard and widely used DNA damage-based chemotherapy. If the proposed mechanistic studies demonstrate a causal role for this kinase and its regulated pathways in causing disease recurrence/relapse, a unique opportunity will exist to develop a new therapy in a group of patients with poor outcome. By inhibiting this kinase it will be possible to substantially reduce CSC levels thereby diminishing cancer recurrence.

Repurposing a FDA-approved drug to treat p53-mut cancers

- Honours or PhD

Supervisors: Prof Kum Kum Khanna and Dr Prahlad Raninga

TP53 is the most frequently mutated gene, with over half of all human tumours harbouring mutation of this gene. Unlike the majority of tumour suppressor genes that are inactivated as a result of truncating mutations, the majority of TP53 mutations are missense resulting in accumulation of mutant protein and gain-of-function activity. The mutational status of p53 predicts poor outcomes, resistance to chemotherapies, and shorter overall survival in multiple types of cancer, including breast cancer (BC)), which is the focus of this project. Over several decades considerable effort has been applied to develop drugs to target mutant p53 (mut-p53), with none in routine clinical use. In this proposal we aim to repurpose a FDA approved drug to target mut-p53 tumours. We propose to develop clinically relevant combinatorial approaches that will yield novel therapeutic strategies to treat cancers with p53 mutations.

We have compelling data that an FDA-approved drug (designated as molecule-1) used for another disease indication, can be repurposed for therapeutic targeting of mut-p53 cancers. Our data convincingly demonstrate that treatment of mut-p53 expressing cells with molecule-1 can reactivate the wild-type transcriptional activity of mut-p53. In this project, we will optimise the anti-tumour effect of this molecule in our clinically relevant mut-p53 patient derived xenograft (PDX) models in combination with conventional chemotherapies. Additionally, we will identify other FDA-approved compounds that synergise with this molecule to further improve its efficacy in mut-p53 cancers. We will also establish the mechanism of mut-p53 reactivation by this molecule through p53 structural analysis, providing valuable insights into the actions of this drug on mut-p53, thus identifying further potential opportunities for therapeutic targeting of mut-p53 in tumour cells.

Understanding the pathophysiological role of Novel repair proteins

- Honours or PhD

Supervisors:
Prof Kum Kum Khanna
Dr Amanda Bain

Background: Cells have developed a vast array of repair and signalling proteins in order to prevent the loss of valuable genetic information that results from DNA damage. Our work centres on elucidating the roles of two newly identified single-stranded DNA binding proteins designated as SSB1 and SSB2 that plays a crucial role in the repair of DNA damage. We have generated conditional knockout mouse models for these genes and we have published phenotypic characterization of SSB1 in a recent paper in Plos Genet. 2013;9(2):e1003298. The SSB1 knockout mice die at birth from respiratory failure due to severe rib cage malformation and impaired alveolar development, coupled with additional skeletal defects, indicating that Ssb1 is necessary for proper development of the embryonic skeleton. Furthermore, conditional deletion of Ssb1 in adult mice led to increased cancer susceptibility with broad tumour spectrum, impaired male fertility with testicular degeneration, and increased radiosensitivity and IR–induced chromosome breaks, indicating SSb1 is essential for spermatogenesis, and genome stability in vivo. Interestingly, we observed profound upregulation of Ssb2 protein levels in bone marrow and spleen from conditional Ssb1-/- mice, indicating a potential functional

compensation between these two proteins. To further investigate this aspect, we generated double inducible knockout mouse model of Ssb1 and Ssb2 (DKO) and we will use Ssb1-/-, Ssb2-/- and DKO mouse models to comprehensively characterize their roles in embryogenesis, spermatogenesis, and genome stability in vivo. The studies using knockout mouse models will help us understand unique and overlapping roles of these proteins in the various organs of a living organism.

Characterisation of a novel regulator of cell division.

- Honours or PhD

Supervisors:
Prof Kum Kum Khanna
Dr Murugan Kalimutho

Aberrant cell growth and division is a hallmark of cancer. A number of checkpoints exist to regulate the passage of cells through cell division cycle to ensure that cells copies their DNA and divide it equally amongst two daughter cells. One of the major interests in our lab is to define these checkpoints at a molecular level in order to understand how cancer cells bypass them. We have identified a novel regulator of mitosis (NRM). Cells depleted of NRM arrest in prometaphase due to an activated spindle checkpoint. These cells are unable to progress through the cell cycle due to a loss of mitotic spindle stability. Recent mass spectrometry results have indicated potential pathways of regulation and possible mechanisms. The project will involve characterisation of the spindle stability defect and the role of NRM in mitosis. The techniques learned will include transfection of mammalian cells, analysis of protein expression, protein localization, protein-protein interaction, knock-down of protein expression using siRNA technology, high-resolution live cell imaging to monitor cell division.

Deciphering the molecular mechanisms of metastasis suppression by RARRES3

- Honours or PhD

Supervisors:
Prof Kum Kum Khanna
Dr Murugan Kalimutho

In breast cancer metastasis, the dynamic continuum involving pro- and anti-inflammatory regulators can become compromised. Over 600 genes have been implicated in metastasis to bone, lung or brain but how these genes might contribute to perturbation of immune function is poorly understood. To gain insight into these processes, through network analysis we identified the metastasis suppressor RARRES3, also categorised as class II tumour suppressor gene that regulates immunoproteasome (IP), a specialized proteasome induced under inflammatory conditions (see our recent article Anderson et al. Sci Rep. 2017; 7: 39873). In this article, we showed that knockdown of RARRES3 in a panel of breast cancer cell lines increases overall transcript and protein levels of the IP subunits through IRF1. In this project we will investigate the role of RARRES3 in controlling pro- and anti-inflammatory regulators during metastasis. We will use established resources in our laboratory to study the process of pro- and anti-inflammatory signalling during breast cancer metastasis. We will use various cell lines and molecular techniques including xenograft models to underpin the role of RARRES3 in immune regulation and metastasis suppression.

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

- Honours or PhD

Supervisors:
Prof Kum Kum Khanna
Dr Murugan Kalimutho
Dr Devathri Nanayakkara

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

will unravel novel therapeutic targets and opportunities.

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

Tumour Microenvironment

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The tumour microenvironment is a complex system of many cell types, including cancer cells, fibroblasts, endothelial cells, leukocytes and antigen-presenting cells. The microenvironment is integral in determining the functionality, physiology and spread (metastasis) of cancer. Therefore, it represents a viable target for cancer therapy and preventative strategies.

The Tumour Microenvironment Laboratory focuses on how specific processes between cancer cells and surrounding non-tumour stromal cells influence carcinogenesis and its metastasis to distant organs. In particular, our work aims to understand how low oxygen (hypoxic) environments and other stress conditions, changes the physiology between tumour cells and stromal cell lineages. Additionally, we aim to understand the role of hypoxia to generate receptive secondary metastatic sites (pre-metastatic niches).

The group combines in vitro experimental studies with animal models, as well as using clinical samples to determine the significance of targeting the tumour microenvironment to improve patient outcomes.

The identity, role and function of immune cells at sites of metastasis in breast cancer

- Suitable for Honours, PhD or clinical students

Immune cells are key mediators of anti-tumour and pro-tumour functions at both the primary and metastatic sites of breast cancer. While the role of monocyte derived cells at the primary site of breast cancer is slowly being understood, there is very little known about the role and composition of immune cells at metastatic sites. We have generated a unique breast cancer model, utilising fluorescently marked immune and tumours cells, to assess the immune cell infiltrate at metastatic sites in breast cancer. We found that immune cell infiltration into metastatic sites is directed and orchestrated by the primary tumours, and results in a permissive environment at secondary sites for metastatic outgrowth.

In this project, bone marrow chimeras and orthotopic breast cancer mouse models will be used to determine the composition and function of the immune cell infiltrate at the metastatic site. Using FACS and immunohistology, the immune cell lineages will be investigated in great detail. Isolated immune cells, which are induced by tumours to populate the metastatic site, will be assessed for their cytokine production. Furthermore, the frequency of metastasis will be assessed in experiments where the immune cell lineages which populate the metastatic site have been ablated. These experiments will provide an insight into the metastatic progression of breast cancer and will be the first of their kind. Ultimately the goal is to understand the identity, role and function of immune cells at the metastatic site and explore the potential to use this information to reduce metastatic tumour burden in breast cancer patients. Students will have access to unique reagents

and mice, and will acquire skills in mouse tumour model experimentation, immune cell isolation, multi-colour flow cytometry, IHC, and other basic cellular immunology techniques.

How do exosomes mediate pro-metastatic changes in lung and breast cancer?

- Suitable for Honours, PhD or clinical students

Exosomes are small microvesicles secreted by cells and contain various proteins, mRNA and miRNA. Exosomes are emerging as a key cell-to-cell communication method, which importantly can be used for long-distance transfer of messages from one tissue to another. Our current work identified that breast and lung cancer cells secrete exosomes with unique protein and RNA content. Hypoxia is not only capable of increasing exosome secretion, but also changes the protein and RNA composition.

In this project, exosomes from breast and lung cancer cells will be isolated and analysed for morphology, composition and abundance using state-of-the-art equipment. Exosomes derived from genetically modified cell lines will be identifiable by fluorescence. Exosomes secreted by cancer cells will be traced in animals to determine the tissues the exosomes are accumulating. Tissues and cell lineages will be tested for their ability to take up exosomes, and the functional modifications in the behaviour of the recipient cells will be assessed. Key interests of the laboratory are cells of the innate and adaptive immune response, and myeloid-derived suppressor cells. The impact of cancer cell-derived exosomes on anti-cancer immune responses will be tested in vitro, by activation, tumour killing and ELISA-based methods, and complemented by flow cytometry.

Medical Genomics

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

The approaches taken include:

- classification of samples into significant subtypes
- identification of driver mutations
- identification of mutational processes that underlie tumour development

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

A single cell approach to cancer genomics

- Suitable for PhD only

Cancer is a major burden to the health system causing 1 in 8 deaths worldwide. Our group uses bioinformatic approaches to analyse large sequence datasets generated from tumour tissues. The data has helped to redefine the genomic and transcriptomic landscape of cancers and has focused on characterizing the mutation profiles of cancer cells in a tumour mass. However, tumours are complex and made up of cells with different properties which include cancer cells as well as immune cells within the tumour micro-environment. Recently single cell sequencing has allowed us to study individual cells within a tumour to an unprecedented resolution. This project will analyse single cell sequence data from cancers to determine the extent of the differences within individual cancer and immune cells. This will provide insights into the tumour micro-environment and how to improve treatment in the future. The project will suit a student with experience in bioinformatics and the student will work closely with postdoctoral researchers in the lab.

Bioinformatic tools for the analysis of next generation sequence data

- Suitable for PhD only

Supervisors:
Dr Nic Waddell
Mr John Pearson

Next generation sequencing is an approach which is often applied to sequencing the DNA or RNA from patient derived samples. We use and develop bioinformatic approaches to analyse large datasets to characterise a variety of cancers. The overall aim of this project is to develop, test and implement a variety of tools for the analysis and/or visualization of next generation sequence data. This is a computational project and will suit a student with experience in computer programming. The student will work closely with postdoctoral researchers and computer programmers in the lab.

Clinical Genomics

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Deciphering patterns of intra-tumour heterogeneity in cancer

- Suitable for PhD only

Cancer is driven by germline and somatic DNA changes. Cancers can be comprised of sub populations of cells that can have distinct genetic, epigenetic and phenotypic characteristics. These sub populations are referred to as sub-clones and the genomic differences between them intra-tumour heterogeneity. The overall aim of this project is to detect the signals of intra-tumour heterogeneity from whole genome and single cell RNA sequencing to identify new therapeutic opportunities in cancer.

This is a computational based project. It will involve identifying patterns of intra-tumour heterogeneity and the generation of methodology for identifying sub-clonal indels and structural variants from whole genome sequencing. Analysis of single cell RNAseq data to assess heterogeneity for individual cells. Then the integration of these datasets with patient clinical data to identify the sub-clonal characteristics of tumours that influence patient outcome. The project will suit a student with experience in computer programming.

Antigen Presentation and Immunoregulation

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Globally, haematological malignancies represent the fifth most commonly occurring cancers and the second leading cause of cancer death. Hematopoietic stem cell transplantation (SCT) is the most effective curative therapy, and the therapy of choice for the majority of these cancers of bone marrow origin. The curative property of SCT lies in the graft-versus-leukemia effect which is required for ablation of residual cancer burden. This process is absolutely dependent on donor T cells contained within the graft, however these T cells are also the primary mediators of graft versus host disease (GVHD), a life threatening complication which significantly limits the success of SCT therapy. GVHD occurs in both acute (aGVHD) and chronic forms (cGVHD), which together contribute to the significant mortality and morbidity associated with SCT. Research undertaken in the Antigen Presentation and Immunoregulation Lab is primarily focused on using preclinical murine models

to dissect the immune mechanisms underpinning GVHD. Driven by the increasing prevalence and severity of cGVHD in clinical SCT patients, and the paucity of useful therapies for this disease, our research in the past 5 years has centred on determining the mechanistic mediators of the fibrotic manifestations of cGVHD. The overarching goal is to identify and translate novel effective therapies, as such our studies aim to identify targetable cellular and molecular mediators of cGVHD pathology, to confirm efficacy of targeted inhibition/promotion of these pathways in preclinical models of cGVHD and test these pathways in preclinical models of liver fibrosis to establish their broader application. Finally, targeted inhibition/promotion of these pathways will be tested in clinical SCT patients using established national and international clinical collaborations.

We have the following exciting projects that utilise novel reagents, animal models and a unique clinical sample bank, that are suitable for HDC students and have tailored projects for students entering the MD-PhD program. These projects will give students an understanding of cellular and molecular immunology with a focus on clinical translation.

The role of autophagy dependent regulatory T cells in the control of chronic graft versus host disease

In contrast to aGVHD, where increased understanding of its pathophysiology has led to improved immunomodulatory chemotherapy and cellular therapeutics, the pathophysiology of cGVHD remains poorly defined. The majority of SCT recipients (70%) now develop cGVHD which represents the major cause of late non-relapse death following SCT. Unfortunately, there is currently no satisfactory therapy for the treatment of cGVHD, which represents an increasing clinical burden. FoxP3+ regulatory T cells (Treg) are crucial for the establishment and maintenance of tolerance after SCT. We have identified the disruption of Treg homeostasis as a critical lesion contributing to cGVHD. (1) However factors which contribute to Treg deficiency and the mechanism by which their absence results in pathology are poorly understood. Recently however, we demonstrated autophagy, as a crucial survival pathway for Treg with a memory like phenotype, and demonstrated the requirement for Treg intrinsic autophagy for efficient Treg reconstitution required for the control of GVHD after SCT.(2)

Importantly, we identified the bone marrow as a niche for autophagy-dependent Treg exhibiting activated/memory like phenotype. Notably, we observed enrichment in the BM of the highly suppressive dependent TIGIT+ Treg population which is marked by the unique capacity to preferentially suppress Th1/Th17 T effector responses while sparing Th2. As outlined in our recent review on BM Treg,(3) although a poorly studied population, the BM Treg appear phenotypically and functionally unique compared to Treg in the periphery. Importantly, we have strong published (2, 3) and unpublished data implicating the functional contribution of BM Treg in the control of cGVHD.

Treg restorative therapies including low dose IL-2 administration and Treg adoptive transfer are currently in use or being trialled in the clinic. While promising results are observed in aGVHD only 50% of cGVHD patients respond. In our preclinical studies the adoptive transfer of Treg attenuated cGVHD pathology, but the effects were only partial. Moreover, in preliminary data we have found IL-2/IL-2R complex administration preferentially expanded peripheral Treg with minimal effects on the BM Treg compartment. These data suggest the BM Treg exhibit cytokine requirements distinct from those in the periphery. Consistent with this, TIGIT+ Treg which are enriched in the BM, express low levels of the IL-2 receptor CD25 compared with splenic Treg, and BM Treg exhibit higher expression of IL-7R, suggesting the BM Treg, like tissue residing memory Treg rely on IL-7 and not IL-2 for their survival. These data suggest that alternative cytokine therapy may preferentially improve BM Treg reconstitution and cGVHD control.

We have recently reported that the defect in Treg homeostasis in cGVHD is downstream of defective antigen presentation within MHC (major histocompatibility

complex) class II by antigen presenting cells (APC) particularly by CD11c+ dendritic cells (DC) that is induced by aGVHD.(1) The role of plasmacytoid (pDC) and conventional Dendritic cells (cDC) in Treg maintenance in periphery is well established. Our study and others illustrated the tolerogenic properties of pDC to control aGVHD and to improve antigen specific Treg after SCT. However, we have also reported impaired pDC reconstitution during GVHD.(4) Notably, the DC compartment in the BM is highly enriched in pDC however, their contribution to BM Treg homeostasis at steady state or after SCT remains to be elucidated.

Taken together these studies demonstrate the BM as a niche for highly suppressive Treg required for the control of cGVHD. We hypothesize that after SCT, the BM niche is disrupted, resulting in diminished BM Treg numbers and this represents a primary lesion which directly contributes to cGVHD pathology. Thus we aim to define the factors required for the enrichment and survival of BM Treg to instruct the development of new Treg restorative therapies that promote BM Treg engraftment after SCT.

Specific Aims:

Aim 1- Identify a unique molecular signature for BM Treg

Aim 2- Determine the cytokine requirement for BM Treg

Aim 3- Determine the contribution of DC in Treg maintenance in the BM

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The role of IL-17 signalling in monocytes and macrophages in promoting cGVHD

We have identified CSF-1 and Th17/Tc17 derived IL-17 as key cytokines that promote sequestration and differentiaton of fibrogenic tissue macrophages, and the critical role of Ly6Clo monocyte derived macrophages, in driving cGVHD pathology. Although each represents a targetable entity, IL-17,CSF-1, TGFβ and macrophages themselves all play important roles in homeostatic processes including mucosal immunity and microbiome diversity (IL-17), tissue remodelling (CSF-1, TGFβ) and tolerance (TGFβ). Thus, the ablation of any one of these modalities will likely have associated deleterious consequences. We therefore propose to elucidate how IL-17 signalling in monocytes/ macrophages promotes fibrogenic macrophage differentiation after SCT to identify new targetable fibrogenic pathways and molecules evoked in these cells after SCT. This will allow the development of alternative therapeutic strategies to preferentially attenuate fibrogenic responses whilst sparing protective homeostatic pathways.

Hypotheses:

1. IL-17 promotes pathogenic profibrotic donor macrophage differentiation after SCT.

2. Pathogenic macrophages utilise differentiation programs that will serve as tractable therapeutic targets for the treatment of cGVHD.

These studies will utilize our established preclinical models of skin and lung GVHD to elucidate the direct and relative

contribution of IL-17 to the migration, activation, and/or differentiation of profibrogenic monocytes/macrophages within target organs.

The effects of Ibrutinib on monocyte/ macrophage differentiation after SCT

Our studies have identified the involvement of Bruton's tyrosine kinase (BTK) and IL-2 inducible T cell kinase (ITK) in both skin and lung GVHD, and demonstrated that treatment with Ibrutinib, an FDA-approved irreversible inhibitor of BTK and ITK, delayed progression, improved survival, and ameliorated clinical and pathological manifestations of cGVHD (1). Although BTK inhibition has been shown to attenuate macrophage activation and inflammatory gene expression, the effects of Ibrutinib on monocyte and macrophage activation and differentiation during cGVHD has not been examined. This project will utilize our unique preclinical models of macrophage dependent skin and lung cGVHD to address this. These studies are aimed at increasing our understanding of the mechanisms by which Ibrutinib attenuates cGVHD and have the potential to identify new myeloid targets for the development of much needed novel and efficacious anti-fibrotic therapeutics.

(1) Dubovsky JA, et al. J Clin Invest. 2014;124(11):4867.

Immunology in Cancer and Infection

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The Immunology in Cancer and Infection Laboratory focuses on advancing understanding of the basic principles underlying an immune response to cancer (and metastases) and infection, as well as further understanding these processes at the molecular level, with particular emphasis on the role of the innate immune system. In particular, NK cells, innate lymphoid cells, dendritic cells and neutrophils.

In particular, work is being undertaken that deletes various genes in NK cells in the context of tumour initiation and metastases. ILC in tumour development is also being tracked and quantitifed. Therapeutically, various antibodies and cytokines are being used in combination on mice to stimulate strong innate and lasting adaptive immunity to cancer.

The laboratory has developed approaches to block two new pathways, including lymphocyte CD96/TIGIT and adenosine metabolism. Findings are being used to develop more effective biological and cellular therapies for human cancer, in particular, melanoma, breast and prostate cancer, lung cancer, head and neck cancer, and haematological cancers, such as multiple myeloma.

NK cells and type 1 innate lymphoid cells (ILC1s) in cancer

Avoiding destruction by immune cells is a hallmark of cancer, yet how tumours ultimately evade NK cell control remains incompletely defined. We have a project based upon the previously unrecognized TGF-β-dependent differentiation of conventional NK (cNK) cells in settings of lymphopenia and tumours. Strikingly, a higher proportion of cNK cells and their capacity for relatively high IFN-γ/TNF-α production favored host protection from tumour initiation and growth, whereas tumour-localized NK cells that had differentiated appeared exhausted and corresponded with tumour growth. These data highlight the unexpected plasticity of cNK cells under

pathophysiological conditions and reveal a novel mechanism by which tumours escape innate immune responses. We now wish to understand the role of innate-like cells in tumours and we wish to identify in preclinical models using various new fusion proteins the cancer therapeutic potential of specifically inhibiting NK cell differentiation and TGF-β signaling in cNK cells.

The project will concern research work in a team in the areas of cellular and molecular immunology, cancer cell biology, and angiogenesis in both mouse and human tumours. Theoretical training in immunology is highly desirable. Technical skills in animal experimentation, flow cytometry and/or cellular immunology are preferable.

Co-targeting RANKL-RANK and immune checkpoints in cancer

- Suitable for PhD/MD students

Supervisors:
Prof Mark Smyth,
Dr Michele Teng and
Asso Prof Brett Hughes

Receptor activator of NF-κB ligand (RANKL) and its receptor RANK, are members of the tumour necrosis factor and receptor superfamilies, respectively. Antibodies targeting RANKL have recently been evaluated in combination with anti-CTLA4 or anti-PD1/PD-L1 in mouse models of cancer. Blockade of RANKL improves anti-metastatic activity of antibodies targeting PD1/PD-L1 and/or anti-CTLA-4 and further reduces subcutaneous growth in mouse models of melanoma, prostate, lung and colon cancer. Early-during-treatment assessment reveals an increased the proportion of tumour-infiltrating CD4+ and CD8+ T cells that can produce both IFN-γ and TNF. These data set the scene for clinical evaluation of denosumab (anti-human RANKL) use in patients receiving contemporary immune checkpoint blockade. Recently we have established a novel trial of **P**re-**o**perative evaluation of anti-**P**D1 checkpoint inhibition (Nivolumab) with **R**ANKL blockade (Denosumab) in patients with operable stage IB-IIIA **N**SCLC (POPCORN). We now wish to use mouse models and samples from the trial to determine the function of RANK signalling in shaping the tumour microenvironment, to determine the optimal combination and sequence of these agents in treating established cancers, including NSCLC. The trainee will learn and use mouse models of cancer, flow cytometry, cellular immunology, multiplex immunohistochemistry, nanostring and RNA sequencing technologies.

Understanding the interplay between inflammation and tumour progression in blood cancers

- Suitable for Honours/ Masters students

Supervisor:
Dr Kyohei Nakamura

Multiple myeloma is a type of blood cancer that grows in the bone marrow (BM). Myeloma progression is tightly associated with destruction of the normal BM architecture and remodelling. We hypothesize that sterile inflammation triggered by tissue-injury and cellular damage has a prominent impact on myeloma immunopathology. Indeed, we have recently showed that a certain type of inflammatory component and its downstream pro-inflammatory cytokine critically drives myeloma progression by generating an immunosuppressive BM niche (Nakamura et al. Cancer Cell 2018).

Now we wish 1) to obtain an in-depth understanding of the vicious cycle of inflammation and immunosuppression in the BM milieu, and 2) to design the optimal anti-myeloma therapy by targeting several candidate inflammatory signalling pathways in preclinical mouse myeloma models. In recent clinical trials, immunotherapies have shown promising results in patients with multiple myeloma. This project will provide important translational implications for next generation of anti-myeloma therapies.

In the proposed project, the student will learn following research techniques: 1) in vivo murine models (various drug treatments, bioluminescence imaging), 2) in vitro cell culture (T cell stimulation assays, macrophage activation assays, 3) flow cytometry analysis, and 4) immunoblot analysis.

Cancer Immunoregulation and Immunotherapy

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The Teng Cancer Immunoregulation and Immunotherapy Laboratory investigates how tumour-induced immunosuppression controls the three phases of cancer immunoediting. In particular, my laboratory has a strong interest in investigating the immunosuppressive role of regulatory T cells (Tregs), T cell anergy/exhaustion (mediated by checkpoint receptors), the cytokine IL-23 and its associated cytokine family and immunosuppressive metabolites (adenosine) in the local tumour microenvironment using experimental and de novo mouse models of cancer.

A major focus of the laboratory currently lies in determining the optimal scheduling of immunotherapy to maximise its anti-tumour efficacy. Recently, our group provided the first demonstration in pre-clinical tumour models that neoadjuvant compared to adjuvant immunotherapies were more efficacious in the eradicating of metastases in the context of cancer surgery. This study now raises many key questions about the mechanism of long-lasting immunity created by neoadjuvant immunotherapy, the role of the primary tumour, the possible discovery of new biomarkers in the tumour and blood, and the potentially shortened treatment schedule that may deliver cheaper and safer alternatives for cancer patients. Ongoing work in the laboratory now aims to understand the key mechanism and pathways that are activated and/or required by neoadjuvant immunotherapy which may allow for their selective targeting and thus further improve the efficacy of immunotherapies. In parallel, our study has now spurred many of our clinical colleagues to undertake new clinical trials to compare the efficacy of neoadjuvant compare to adjuvant immunotherapies.

Currently, the next frontier in cancer immunotherapy lies in combination approaches and this can potentially benefit a greater proportion of patients with cancer. Although new combination immunotherapies induce better efficacy, they can potentially induce severe immune-related adverse events (irAE) in humans and can lead to discontinuation of treatment and can result in fatalities if not promptly treated. Clinicians are currently faced with the dilemma of what combination immunotherapies to test in different cancers. The laboratory has also recently developed a preclinical mouse model that allows the therapeutic index (antitumour efficacy vs immune-related adverse events (irAEs)) of antibodies targeting various immunomodulatory receptors to be simultaneously assessed for the first time. Filling a need, this mouse model may be used to preclinically assess the therapeutic window of novel immunotherapy combinations in different tumour types to aid clinicians and pharmaceutical companies weigh up their risk/cost–benefit profile. Furthermore, our model offers an opportunity to dissect whether the molecular pathways governing the development of antitumour immunity and irAEs are related or distinct to allow more specific targeting.

Dissecting the immunological mechanisms underlying the efficacy of neoadjuvant cancer immunotherapy

- This project is suitable for a highly motivated PhD student.

Supervisor: Dr Michele Teng

Cancer immunotherapy, which harnesses and enhances tumour-specific T cell responses, has become the new fourth pillar of cancer treatment (to surgery, radiotherapy and chemotherapy). Antibodies targeting the T cell immune

checkpoint receptor PD1 or its ligand PDL1 alone or in combination with CTLA4, have demonstrated efficacy in more than 20 different cancer types, particularly where the tumour microenvironment (TME) contains T cells and PDL1. Anti-PD1/PDL1 are FDA-approved to treat many advanced cancers including metastatic melanoma and lung cancer due to their ability to promote long-term regression and potential cures2. New trials are testing the efficacy of α-PD1 or α-CTLA4 in earlier stages of cancer, particularly in an adjuvant setting following surgery to prevent recurrence of distant metastases. However, the scheduling and efficacy of immunotherapy combined with cancer surgery has not been systematically examined. Using pre-clinical mouse models of spontaneously metastatic cancers, our group recently demonstrated for the first time, that neoadjuvant immunotherapy and surgery is superior to surgery followed by adjuvant immunotherapy for eradicating metastatic disease and promoting long-term survival. This pre-clinical data was used by our clinical collaborators to initiate new comparative trials of neoadjuvant and adjuvant immunotherapy in melanoma with preliminary results validating our findings. However, the overall survival data from this and other neoadjuvant immunotherapy trials are several years away and the immunological mechanisms underlying neoadjuvant-treatment's efficacy are not well understood. This project aims to understand the key mechanisms and/or pathways activated by neoadjuvant immunotherapy may allow for their selective targeting and further improve the efficacy of immunotherapies in general.

The project will concern research work in an international team of highly motivated scientists in the areas of cellular and molecular immunology, cancer biology, in experimental mouse models and human patient materials. Theoretical training in immunology is highly desirable. Technical skills in animal experimentation, bioinformatics, flow cytometry and/or cellular immunology are preferable.

Targeting immunosuppressive adenosine in cancer.

- This project is suitable for a highly motivated PhD student.

Supervisor:

Dr Michele Teng

Prof Mark Smyth

Antibody-based therapies that target CTLA4 or PD1/PDL1 alone or in combination have demonstrated clinical efficacy in advanced cancers. Nevertheless a considerable proportion of patients remain unresponsive to these therapies (known as innate resistance) and amongst those who respond, a significant proportion develop acquired resistance and relapse. This suggests that multiple non-redundant immunosuppressive mechanisms co-exist within the tumour microenvironment (TME) and their rational co-targeting can increase the efficacy of host anti-tumour immunity. It is now recognized that the metabolic pathways activated or repressed in the TME create a barrier to anti-tumour immunity to favor tumour growth and progression. A major immunosuppressive mechanism is the adenosinergic pathway, which now represents an attractive new therapeutic target for cancer therapy. Activation of this pathway occurs within hypoxic tumours, where extracellular adenosine exerts local suppression through tumour-intrinsic and host-mediated mechanisms. We have previously demonstrated in preclinical tumour models that adenosine receptor antagonists and antibodies induce favourable anti-tumour immune responses with some definition of the mechanism of action. Within a tumour niche, adenosinergic molecules are expressed by tumour cells, stromal cells and immune cells although their critical point of action is not yet fully understood. We now wish to understand to understand the kinetics of tumour, stroma or immune cell expression of adenosinergic molecules before and after treatment with existing and new immunotherapies and how this relates to response.

The project will concern research work in an international team of highly motivated scientists in the areas of cellular and molecular immunology, cancer biology in both mouse and human tumours. Theoretical training in immunology is highly desirable. Technical skills in animal experimentation, flow cytometry and/or cellular immunology are preferable.

Oncology and Cellular Immunology Group

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The role of Neutrophils in cancer immunotherapy and metastatic progression.

Neutrophils are the most abundant immune cells in humans and are thought to promote tumour progression and therapy resistance. However, the underlying cellular and molecular mechanisms are incompletely understood. We have recently, identified a novel target to inhibit neutrophil migration into tumours and the tumour draining lymph node, thus improving cancer immunotherapy. We have unravelled phenotypic plasticity of neutrophils as a key regulator of immune suppression. This project aims to elucidate where neutrophils interact with and how they suppress T cells using mouse reporter strains and intra-vital imaging techniques as well as RNA-sequencing and multi-parameter flow cytometry. Moreover we want to identify signalling cues that modulate the phenotypic plasticity of neutrophils.

The project will concern research work in an international team of highly motivated scientists in the areas of cellular and molecular immunology, cancer cell biology, and microscopy in both experimental mouse models and human patient material. Theoretical training in immunology is highly desirable. A substantial interest in microscopy and imaging techniques is required. Technical skills in animal experimentation, flow cytometry and/or cellular immunology are preferable.

The role of neutrophils in melanoma metastasis

- Some components of this project are suitable for Honours students, flexible for clinical students and entire project is suitable for PhD students.

Research Area: Neutrophil biology, NK cells, Melanoma, Metastasis

Malignant melanoma is a very aggressive disease with a high mortality. Melanoma cells can disseminate and from distant metastasis in vital organs even if the primary tumour is very small. Melanoma cells are extremely metastatic, because the can acquire properties of neuronal stem cells, which migrate throughout the body during development. In other words, melanoma cells are highly plastic and able to adapt their phenotype to environmental changes. Neutrophils can foster the acquisition of migratory properties. However, the underlying mechanisms remain elusive. On the other hand natural killer (NK) cells detect and destroy disseminated cells. In this project we aim to understand the intercellular communication of neutrophils, NK cells and melanoma cells in the metastatic niche. For this we will use state of the art primary and transplantable tumour models as well as genetically engineered mouse models. Furthermore, you will learn multi-colour flow cytometry, histology and intravital imaging. Finally, we aim to translate our findings into the human system by assessing human melanoma samples.

Phenotypic plasticity of neutrophils in cancer and infection

- Some components of this project are suitable for Honours students, flexible for clinical students and entire project is suitable for PhD students.

Research Area: Neutrophil biology, Neutrophil development, TGF-beta signalling;

Phenotypic plasticity means that cells are able to quickly respond to environmental changes by losing and gaining properties. Myeloid immune cells including dendritic cells, macrophages, monocytes and granulocytes are known to be highly plastic. This concept is best described in macrophages. Macrophages can acquire a so called M1

(anti-tumour) or M2 (pro-tumour) phenotype in the context of cancer. We believe that neutrophils are as plastic as macrophages. However, signalling pathways modulating the phenotype of neutrophils are unknown. We have generated genetically modified mice in which signalling components of the TGF-beta pathway are deleted specifically in neutrophils. Using these mice and disease models for cancer and infectious diseases we will study neutrophil plasticity. In this project you will learn how to plan and conduct animal experiments, multi-colour flow cytometry, RNA-sequencing and various cell culture assays.

ILC1s orchestrate the tumour microenvironment

- Some components of this project are suitable for Honours students, flexible for clinical students and entire project is suitable for PhD students.

Research Area: NK cells, Innate lymphoid cells, Angiogenesis, Metastasis;

Phenotypic plasticity means that cells are able to quickly respond to environmental changes by losing and gaining properties. Myeloid immune cells including dendritic cells, macrophages, monocytes and granulocytes are known to be highly plastic. This concept is best described in macrophages. Macrophages can acquire a so called M1 (anti-tumour) or M2 (pro-tumour) phenotype in the context of cancer. We believe that neutrophils are as plastic as macrophages. However, signalling pathways modulating the phenotype of neutrophils are unknown. We have generated genetically modified mice in which signalling components of the TGF-beta pathway are deleted specifically in neutrophils. Using these mice and disease models for cancer and infectious diseases we will study neutrophil plasticity. In this project you will learn how to plan and conduct animal experiments, multi-colour flow cytometry, RNA-sequencing and various cell culture assays.

Conjoint Gastroenterology

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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.

Colorectal Cancer – from Genetics to Chemoprevention

Supervisor:
A/Prof Vicki Whitehall

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

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

Genetic changes underlying colorectal cancer initiation and progression

Supervisor:
A/Prof Vicki Whitehall

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

Potential Honours and PhD projects will examine candidate genes for a role in the development of colorectal cancer, selected from bioinformatic analysis of genome-wide data including expression arrays, DNA methylation array profiling and next generation genomic sequencing. Candidate genes will be examined in a clinically and molecularly well-defined series of colorectal polyps and cancers. Functional studies will be conducted in colorectal cancer cell lines and in xenograft models. Projects are also available to examine strategies for pharmacoprevention using our BRAF mutant murine model

Cancer Precision Medicine Group

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

Delineating mechanisms of acquired resistance to kinase inhibitors

- Suitable for PhD Students

Background: Drug resistance has limited the efficacy of almost all targeted therapeutic agents used to treat cancers. Although some of the most successful anti-cancer drugs to emerge in the last 2 decades are kinase inhibitors, they are invariably associated with relapse due to development of resistance during the course of treatment. In this project, we will derive and characterize drug resistant clones to delineate mechanisms of acquired resistance to kinase inhibitors. This research work has the potential to reveal clinically relevant drug resistance mechanisms for some of the widely used anti-cancer agents. These resistance mechanisms could be targeted to achieve durable responses to cancer therapy.

Aim: Delineating mechanisms of acquired resistance to kinase inhibitors

Hypothesis: Unbiased investigation of drug resistant cancer cells by employing genomic, transcriptomic and proteomic methods can reveal clinically relevant mechanisms of acquired drug resistance to small molecule kinase inhibitors used in cancer treatment

Approaches

- Generate drug resistant derivatives of cancer cell lines by subjecting them to selection pressure under targeted kinase inhibitors that are in clinical use
- Genomic, transcriptomic, proteomic and phosphoproteomic characterization of drug resistant clones
- Determine molecular basis of acquired resistance by integrating multi-omics data
- Determine novel therapeutic intervention

strategies to target acquired drug resistance

Micropeptides produced by cancer cells and their role in tumourigenesis

- Suitable for PhD Students

Background: For several years, it is known that human genome has ~20,000 protein coding genes. Transcriptome sequencing studies in the past decade have revealed that a large portion of human genome is transcribed. However, most of it is thought to be non-coding. Recent studies have revealed that some of the annotated non-coding RNAs harbor small open reading frames that code for micropeptides/small peptides. We have previously discovered several small ORFs in annotated non-coding RNAs and UTR regions of mRNAs (Nature. 2014 509(7502):575-81). Various studies in the last five years have demonstrated that micropeptides regulate several functions including development, muscle performance and DNA repair. Ribosome profiling studies (Ribo-Seq) have also revealed the possibility of many small open reading frames that could potentially code for micropeptides. It appears that several micropeptides encoded by human genome are yet to be discovered. Until then, various cellular functions regulated by these micropeptides and their role in various human diseases remains out of bounds for systematic investigation.

Aim: Identification of micropeptides produced by cancer cells

Hypothesis: Cancer cells produce micropeptides that are involved in regulating tumourigenesis

Approaches:

- Cell culture
- Isolation of micropeptides from cancer cell lines
- Identification and characterization of micropeptides by mass spectrometry
- Characterization of role of micropeptides in tumourigenesis

Oncogenomics Group

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The research focus of the Oncogenomics Laboratory is understanding genetic susceptibility to melanoma and characterizing the genomic dysregulation underlying melanoma development and progression. There are three main avenues of investigation: melanoma susceptibility in the general population; melanoma predisposition in rare high case-dense families; somatic mutations, chromosomal structural changes and gene expression perturbations that drive each of the various histological subtypes of melanoma.

Identification and functional characterisation of melanoma susceptibility loci

- PhD project

Project description

Genetic variation is an extremely important factor contributing to melanoma risk. High penetrance mutations in one of 8 known melanoma susceptibility genes collectively account for about 50% of predisposition in high density melanoma families. The cause in the remainder is unknown but could be due to very rare single-gene mutations in as yet unidentified familial melanoma genes, or may be due to inheritance of a combination of low to medium penetrance variants. To date, genome-wide association studies (GWAS) have identified >40 low to medium penetrance cutaneous (skin) melanoma risk loci.

Aims

1. Identify candidate new high penetrance melanoma susceptibility loci through exome or genome sequencing of multiple affected members of ‘melanoma’ families.

2. Conduct in vitro assays to functionally assess the cellular mechanism by which these candidate genes may confer melanoma risk.

3. Determine the contribution of low to medium penetrance risk alleles to familial clustering of cutaneous melanoma.

Approaches: Whole genome or exome sequencing will be conducted on DNA from multiple melanoma cases in high-density 'melanoma' families. Candidate novel familial melanoma genes will be determined by identifying those for which rare variants segregate with melanoma. In silico predictions of likely pathogenicity will be used to prioritize genes and variants. A range of in vitro assays such as growth, cell cycle control, apoptosis, migration and invasion, will be used to functionally characterize potential new melanoma predisposition genes. Single-nucleotide polymorphism arrays will be used to genotype family members to determine relative polygenic risk scores and how this collection of more common risk alleles contributes to the familial clustering of melanoma.

Flicking the switch: Determining if a novel microRNA controls drug-resistance in late-stage melanoma

- Honours project

Supervisor: Dr Ken Dutton-Regester

Project description

Treatment for late-stage melanoma is challenging due to the frequent occurrence of resistance with current therapies. One mechanism of drug-resistance that has been identified and which largely remains misunderstood, is the switching of cell-states (defined as the relative genes expressed in a cell at any given point in time). In order to determine how melanomas can switch from a drug-sensitive to a drug-resistant cell state, we have analyzed large scale multi-omic datasets performed on a series of melanoma cell lines. Intriguingly, we have identified a novel microRNA that is specific to drug-resistant melanomas. This project will determine if this microRNA is responsible for controlling cell-states, and if so, explore whether we can use this information to improve therapies by delaying or overcoming drug-resistance.

Aims

1. Confirm if the relationship of the novel microRNA is associated with the drug-resistant cell state in independent melanoma datasets

2. To see if manipulating the activity of this microRNA, either through deletion or over-expression, can cause a shift in cell-states in melanoma cell lines

3. Determine the functional mechanism of how this microRNA controls cell-states through bioinformatic and experimental approaches

Approaches

This project will involve basic bioinformatic analysis of existing multi-omic datasets (including microRNA arrays, expression arrays and RNA-Seq data) and predictive microRNA binding databases. Experimental approaches will include cell-culture techniques and general molecular biology assays; proliferation, invasion and other functional related assays; protein detection methods including multi-fluorescence semi-quantitative Western Blot or Flow cytometry approaches; microRNA manipulation approaches and pharmacological inhibition through small molecule inhibitors, and RT-PCR. Depending on the timeline of progress, there may also be the possibility to perform microRNA pull-down ChIP-like methods to determine binding regions within the genome.

Assessing the impact of common genetic aberrations in uveal melanoma on cellular signalling and therapeutic responses

- PhD project, may also be considered for an Honours project

Supervisor: Dr Kelly Brooks

Project description

Uveal melanoma is the most common ocular cancer. Metastatic spread occurs in approximately 50% of cases, despite intervention at the primary disease stage. There are currently no effective treatments available for metastatic disease. The common genetic alterations that occur in uveal melanoma are different from those in cutaneous melanoma and targeted therapies developed for cutaneous melanoma are ineffective in uveal melanoma. A better understanding of the functional consequence of common uveal melanoma genetic alterations is required in order to identify potential therapeutic targets for its' treatment. Monosomy of chromosome 3 is a common

genetic alteration that is strongly associated with poor prognosis, however, the underlying mechanism of this and how chromosome 3 monosomy may influence therapeutic responses is poorly understood.

Aims

1. To develop cell lines models representing different uveal melanoma genetic states associated with chromosome 3 monosomy

2.Determine the biological consequences of chromosome 3 monosomy-associated alterations on cellular signalling and tumourgenicity

3. Determine if chromosome 3 monosomy-associated changes impact therapeutic response to treatments currently being trailed or novel therapeutic targeting strategies identified through modelling and functional work.

Approaches: This project will involve genetic engineering of cell lines through plasmid, siRNA and CRISPR/Cas9 based approaches. An array of molecular biology techniques including FACS analysis, proliferation/migration assays, qRT-PCR, western blotting and reverse-phase protein arrays will be used to characterise the functional consequences of these alterations. Drug screening in generated models and existing cell lines will also form part of this project. Basic bioinformatic analysis and immunohistochemical analysis of patient samples will also be utilised to confirm/translate results in the patient setting. Depending on the timeline of progress, there is also the possibility of testing cell line models in mice xenograft models to assess consequences on tumourigencity, metastasis and therapeutic response.

Cancer & Chronic Disease

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Group supervisor:
Prof Elizabeth Powell

The Cancer and Chronic Disease Research Group is currently working on projects that ultimately aim to improve the management of chronic liver disease (e.g. cirrhosis, non-alcoholic liver disease (NAFLD)) and hepatocellular carcinoma (the most common type of liver cancer).

Cirrhosis Care (CirCare): quality of care study

(comparing treatment received against evidence-based guidelines for cirrhosis)

- PhD project, may also be considered for a MPhil or Honours project

Supervisors: A/Prof Patricia Valery (QIMRB) and Prof Elizabeth Powell (hepatologist, University of Queensland, Princess Alexandra Hospital)

Australian data on the patterns of care of cirrhosis, the level of adherence to clinical guidelines, and patient outcomes for cirrhosis are limited. We are currently collecting data for a large cross-sectional study of people diagnosed with cirrhosis (over 300 patients have been recruited and interviewed to date). Through medical chart review the study will: (i) describe and compare treatment received against evidence-based guidelines; and (ii) examine the associations between: (a) clinical, socio-demographic, and hospital factors and adherence to clinical guidelines; and (b) adherence to clinical guidelines and patient outcomes (readmissions, death).

Relevant data collected through patient interviews will be available. The student will be involved in data collection (medical chart review) and data analysis. Interested students must have a clinical background (medicine or nursing). With this project, the student will gain experience in public health research, epidemiology, and statistics, particularly in the field of chronic liver disease.

Cirrhosis Care (CirCare): patient factors study

(understanding patient factors that impact on health outcomes for patients with cirrhosis)

- PhD project, may also be considered for a MPhil or Honours project

Supervisors:
A/Prof Patricia Valery (QIMRB)
Prof Elizabeth Powell (hepatologist, University of Queensland, Princess Alexandra Hospital)

Effective chronic disease management can be optimised if patients have the knowledge and skills to contribute to their health management. Self-management has been shown to be important for other chronic diseases, and improvements through education interventions have been reported. The study will be the first to comprehensively assess health literacy and support needs among patients with cirrhosis. We have the potential to identify new areas where suitable interventions may delay the natural progression of disease.

We are currently collecting data for a large cross-sectional study of people diagnosed with cirrhosis (over 300 patients have been recruited and interviewed to date). Through patient interviews the study will: (i) assess patients' (a) knowledge about cirrhosis and self-care tasks; (b) adherence to medications and self-care tasks; (c) source of health information and health education preferences; (d) prevalence of unmet supportive care needs; and (e) use of hospital, community and allied health services; and (ii) Assess the impact of clinical and socio-demographic factors on health literacy (knowledge about cirrhosis/self-care tasks), adherence to medications and self-care tasks, preferences in health education, unmet supportive care needs, and use of hospital, community and allied health services.

The student will be involved in data collection (patient interviews) and data analysis. Interested students should have a clinical background (preferably medicine or nursing but allied health professionals would be considered).

With this project, the student will gain experience in public health research, epidemiology, and statistics, particularly in the field of chronic liver disease.

General practitioners' referrals of patients with non-alcoholic fatty liver disease: are they knowledgeable?

- Master or Honours project

Supervisors: A/Prof Patricia Valery (QIMRB) and Prof Elizabeth Powell (hepatologist, University of Queensland, Princess Alexandra Hospital)

Non-alcoholic fatty liver disease (NAFLD) affects over 5.5 million Australians and this figure is rising as a direct consequence of the increasing prevalence of obesity and obesity-related complications. While most patients are asymptomatic and many don't progress to non-alcoholic steatohepatitis or cirrhosis, the most important predictor of mortality in NAFLD is the extent of liver fibrosis.

NAFLD is the most common chronic liver disorder seen in primary care. However, many general practitioners (GPs) don't know how to assess the extent of liver fibrosis in NAFLD patients and when to refer patients for liver specialist assessment.

Through passive follow up of GP referrals to hepatology clinic (medical chart review) we will estimate numbers and rate of patients referred to the hepatology clinic with a final diagnosis of NAFLD; the proportion of referral letters that appropriately consider NAFLD as a potential diagnosis ("knowledgeable referrals"); and the proportion of NAFLD patients referred for assessment that have advanced fibrosis/cirrhosis.

The student will be involved in data collection (medical chart review) and data analysis. Interested students should have a clinical background (preferably medicine or nursing but allied health professionals would be considered).

With this project, the student will gain experience in public health research, epidemiology, and statistics, particularly in the field of chronic liver disease

Translational Brain Cancer Research Group

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Our laboratory studies the most common and aggressive form of both adult brain cancer, Glioblastoma (GBM) and paediatric brain cancer Medulloblastoma. The focus of our research is on understanding the molecular mechanisms which are responsible for the initiation and recurrence of brain cancers and to develop and test new and effective

therapies to treat these aggressive diseases.

Understanding the molecular mechanisms which drive brain cancer recurrence and defining novel therapies to target these aggressive tumour cell populations

Glioblastoma (GBM) is the most common and aggressive adult primary brain cancer. Median survival is <15 months and only about 10% of patients survive two years without disease recurrence. Therefore, there is a critical need to search for new and innovative approaches to patient management and treatment. It is well understood that GBM cells are adaptive to chemotherapy and radiation treatment which is the cause for tumour recurrence and subsequent death. The mechanisms that lead to this recurrence are poorly understood.

As part of the QIMR-Berghofer Brain Cancer Tissue Bank, we have collected a series of patient specimens which include primary tumours that have not undergone treatment and matching post-treatment recurrent tumours. This is a valuable and rare resource. We are utilising these pair-matched specimens and cell cultures to elucidate how malignant brain tumours develop resistance. By understanding the molecular functions that cause treatment resistance, we will be able to design therapies to prevent recurrence and improve patient outcomes.

Aim: The aim of this project will be to understand how these aggressive tumours reform following therapy by undertaking an in-depth analysis of pre- and post-treatment paired GBM specimens. We believe that to significantly improve outcomes for patients with GBM we first need to understand in detail how tumour cells can survive standard therapies and recur. Once differences between multiple primary and recurrent GBM specimens have been identified, the project will aim to validate candidate therapeutic targets in preclinical animal models. Outcomes from this project will include the definition of novel molecular mechanism's associated with recurrence and potentially define novel therapies suitable for testing in clinical trial. Ultimately these therapies could prolong the life of sufferers of these incurable diseases.

Drug Discovery Group

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Identification and validation of the molecular targets of EBC-46, a novel anti-cancer drug.

Supervisor: Dr Jason Cullen

Background: Previous work performed by the Drug Discovery Group, together with QBiotics Ltd. (an Australian based biotech company situated in North Queensland), has led to the identification of a novel protein kinase C (PKC)-activating agent, EBC-46, from a rain forest tree. Intratumoural injection of EBC-46 gives long term ablation, approaching cure, of cutaneous tumours in dogs, cats and horses. We have also shown at QIMR Berghofer that intratumoural injection of EBC-46 ablates subcutaneous tumour xenografts of human cell lines in nude mice, with few recurrences. Commercial development of the compound is underway, with a Phase I trial in humans. Localised hemorrhagic necrosis appears to be the overt mechanism of efficacy in vivo but the molecular subtleties behind this and the potential to exploit them for enhancing efficacy are still being explored. A number of analogues of EBC-46 have been isolated from the same plant, and many more have been generated by semisynthesis. These include candidates in development for indications other than cancer.

Although EBC-46 is a bone fide PKC activating agent we have a selection of in vitro data which suggests that the anti-tumour efficacy of this drug may also involve PKC-independent pathways. To this extent, we are interested in identifying further molecular targets of EBC-46. The following aims are a guide

to the work that could be done in this area, although this may be subject to change.

Aims:

1. Identification of potential EBC-46 targets.

   a. Development of a suitable protocol to isolate EBC-46 interacting proteins from cells in culture. Various EBC-46 analogues, modified for use in click chemistry/ Halotag based assays, will be used to pull down EBC-46 interacting proteins for subsequent mass spectroscopy (MS) based identification.

   b. Identification of interacting proteins using MS based peptide mass fingerprinting. Subsequent pulldowns will be processed via SDS-PAGE/on column digests and identification performed using MS/MS based peptide sequencing and database searches.

   c. Confirmation of MS derived hits. Drug conjugated resin will be used in pull down experiments with cell lysates and potential targets identified via MS will be confirmed via immunoblotting.

2. Determine physiological significance of identified targets using siRNA/CRISPR knockdown/knockout methodology.

1 or 2 targets identified in Aim 1 will be ablated using either siRNA/CRISPR based technology, to understand their role in EBC-46 mediated anti-tumour efficacy.

Translational Cancer Immunotherapy Group

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The Translational Cancer Immunotherapy Laboratory studies the interaction between the immune response and tumour control, with a particular emphasis on translating our ever-expanding basic science knowledge into clinically applicable therapeutic platforms. It has particular interest and expertise in bone marrow transplantation and cell and gene therapy, and is currently one of only a few centres in Australia that are conducting investigator-driven clinical trials using gene-modified T cells. In addition to developing new approaches to target cancer cells, the laboratory is also developing a method to expand donor-derived regulatory T cells to treat graft-versus-host disease, which is a common and life-threatening immune-driven complication of bone marrow transplantation. Using state-of-the-art technology, including gene-marking and single cell transcriptomics, immune reconstitution following bone marrow transplantation can be understood. Basic science research is focussed on the impact of cytomegalovirus reactivation on graft-versus-leukaemia effect. Cytomegalovirus is a common virus that is typically acquired during childhood; it has a marked influence on the immune landscape and, interestingly, has been associated with improved graft-versus-leukaemia effect following bone marrow transplantation. Our laboratory has developed a murine model of cytomegalovirus reactivation to investigate the mechanistic underpinnings of this observation, which may lead to new ways to enhance anti-leukaemic immunity.

The immune system can be effective in eliminating cancer cells and providing constant surveillance against cancer relapse. One of the earliest and most established form of cancer immunotherapy is bone marrow transplantation in which donor-derived immunity can be effective in treating otherwise incurable high-risk blood cancers. In the past decade, a number of new immunotherapeutic approaches have emerged but, whilst promising, significant challenges remain.

Individualised killers – the peripheral maturation of natural killer (NK) cells

- Suitable for Honours and PhD students.

Natural killer (NK) cells mediate important anti-pathogen and anti-tumour effects. Their

effectiveness in mounting these protective immune function is shaped by past infections. Cytomegalovirus (CMV), which infects 60- 80% of healthy individuals, has a particularly striking effect on NK cell maturation. We recently completed single-cell RNA-sequencing (scRNA-seq) of NK cells from patients undergoing CMV reactivation following bone marrow transplantation. The current project will use this unique set of single-cell data to investigate the changes in metabolism and acquisition of effector function during virus-driven NK cell maturation, and how these interact with the different combinations of activating and inhibitory receptors expressed by individual NK cell. This project is important because virus-driven NK cell maturation has an impact on NK cell anti-tumour efficacy and the findings can point to ways to make NK cells more effective 'killers' for cancer immunotherapy.

Human gene-marking study – regulatory T cells to treat graft-versus-host disease (GVHD) after bone marrow transplantation

- Suitable for Honours and PhD students. Clinician researcher can also have a role in this project.

Bone marrow transplantation (BMT) can cure high risk leukaemia because the donor immune system is very effective at eradicating residual leukaemia cells. However, the donor-derived immune system can also cause tissue damage in the recipient, known as graft-versus-host disease (GVHD). Regulatory T cells (Tregs) can modulate the immune response and early phase clinical studies suggest that Tregs obtained from the bone marrow donor and infused into the recipient can help ameliorate GVHD. However, progress in the field is hampered by a lack of understanding of the fate of these Tregs after infusion because they cannot be distinguished from Tregs that are already pre-existing in the patients. Gene-marking involves the insertion of a unique DNA sequence that is integrated into the cell's genome and passed on to all the cell's progenies, thus enabling the infused cells and their progenies to be distinguished from endogenous non-gene-marked cells. In this world-first clinical study, we will use a form of gene-marking that enables the infused Tregs and all their progenies to be easily tracked by flow cytometry long term. This study will provide unprecedented insight into the fate of transferred Tregs in the clinical setting and whether their persistence, expansion and function can be improved with the co-administration of other drugs, such as interleukin-2. Because the infused Tregs can be readily distinguished from pre-existing Tregs, we will also be able to find out whether particular drugs have different effects on infused versus endogenous Tregs. This study is important because GVHD is a major cause of death after BMT. Furthermore, the use of Tregs is also being explored in other medical conditions including solid organ transplantation and type 1 diabetes.

Show me the way – CARs redirecting T cells for cancer immunotherapy

- Suitable for Honours and PhD students.

Chimeric Antigen Receptors (CARs) are genetically engineered molecules that can redirect T cells to recognise particular antigens, such as those expressed by cancer cells. T cells that are transduced by CAR targeting CD19 have been effective in treating B cell cancers, e.g. B-cell acute lymphoblastic leukaemia and B-cell lymphoma, where conventional treatments have failed. This exciting technology is one of the major breakthroughs in cancer therapy this decade but many challenges remain. These include cancer relapse due to loss of CAR T cells, antigen escape (loss of CD19) or other as yet undefined mechanisms; life-threatening neurological adverse events and cytokine release syndrome; and lack of significant success to date with CAR T cells targeting other cancers. This project involves engineering CAR T cells for use in cancer immunotherapy.

Infectious diseases

Scientists at QIMR Berghofer aim to develop drugs, vaccines and prevention and education strategies against diseases caused by parasites, bacteria and viruses.

Research involves understanding the genetics of the parasite, investigating immune responses to the invading pathogen, and developing new treatments and diagnostics to combine with our knowledge about the disease.

Infectious diseases we research

- Epstein-Barr virus (EBV)
- Glandular fever
- HIV and AIDS
- Hydatid disease
- Intestinal worms
- Leishmaniasis
- Malaria
- Mosquito-borne viruses
- Rheumatic fever and rheumatic heart disease
- Scabies
- Schistosomiasis (blood flukes)
- Streptococcal-related infections
  (toxic shock syndrome, necrotising fasciitis, scarlet fever, impetigo, strep throat)

Scabies Group

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General overview: Work in this laboratory concentrates on the control of diseases caused by the scabies mites, *Sarcoptes scabiei* which burrow under the skin to cause the condition commonly known as scabies.

Skin infestations with the mite Sarcoptes scabiei are becoming increasingly prevalent and have been recognised as a primary risk factor for secondary bacterial skin infections in tropical settings worldwide, including Northern Australia's Aboriginal and Torres Strait Islander population. As resistance to current drugs is emerging there is a critical need for new therapies.

The Bacterial Pathogenesis and Scabies Laboratory at QIMR Berghofer investigate how parasitic scabies mites cause disease and how they promote serious downstream infections. Another focus point is the development of new treatments.

Laboratory work on scabies has previously been hampered because scabies mites cannot be cultured in vitro and are difficult to collect from patients. We have established an EST database and are working towards sequencing the entire scabies mite genome and transcriptome, to accelerate the use of molecular tools in the identification and study of mite virulence factors, pathways of host-parasite interactions and further candidate therapeutic targets. As a first set of candidate targets we have investigated several classes of mite essential intestinal proteases. In identifying mite complement inhibitors that promote the survival of mite associated *S. pyogenes* and *S. aureus* we are beginning to understand the molecular mechanisms that underpin the link between scabies and bacterial pathogens. We have commenced microbiome studies to elucidate the impact of scabies on the healthy skin microbiota and to identify the pathogenic and symbiotic bacteria carried by scabies mites.

The techniques you will be exposed to when working with us include molecular biology, protein expression and purification, basics of enzymology and complement research, bacteriological work (*Streptococcus, Staphylococcus*), immunohistology and more.

If you are interested in potential projects with our group please seek further details from Dr Katja Fischer. The particular aims of your project will be discussed at the time of application.

Targeting the egg – novel strategies towards ovicidal scabies therapeutics.

- Suitable for PhD students only

Most drugs currently in use have limited ovicidal activity, a major reason for treatment failures. Ivermectin and Permethrin are neuro-inhibitors targeting molecules involved in parasite mobility, but they have no effect on the immobile egg stage with its protective shell. Eggs are laid into the stratum corneum and are separated by desquamation from the serum-containing lower epidermal layers, out of reach of host defence mechanisms and systemically administered drugs. This scenario underlines the importance of topical treatments that specifically target mite eggs.

The focus of this PhD project is to identify egg-specific drug targets, understand their biological roles, identify inhibitors and test them in vitro and in our porcine in vivo model.

Expected outcome: Fundamental knowledge about scabies mite embryogenesis and drug(s) that prevent egg hatching, to be developed as topical agent.

Analyses of the impact of scabies on the healthy human skin microbiota

Given the association between scabies and severe microbial disease, there is a need to understand how anti-scabies treatment impacts on pathogens associated with the mite. Our

work showed that current scabies treatments may not restore healthy microbiota in porcine skin. This is important because broad-spectrum antibiotics are only used to treat advanced scabies, but early scabies lesions often show signs of bacterial infection. In collaboration with the Menzies School of Health Research in Darwin, we will study scabies lesions for their microbial content compared to contralateral uninfected sites during the course of treatment of patients involved in the moxidectin Phase II dose-finding study. This study, commencing in mid-2018, is a perfect opportunity to monitor the longitudinal impact of drug exposure on mite infestation and skin microbiota.

Molecular Parasitology

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

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

Establishment of a CRISPR-Case9-mediated gene knock-down system in Schistosoma japonicum targeting the acetylcholinesterase gene

- Suitable for PhD students only

Schistosomiasis is a serious global problem and the second most devastating parasitic disease following malaria. Currently, there is no effective vaccine available and treatment is entirely dependent on praziquantel chemotherapy, raising a significant threat to public health. 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/vaccine candidates.

In this project we aim to establish a CRISPR (clustered regularly interspaced short palindromic repeat)-Case9-mediated gene knock-down system in Schistosoma japonicum. The CRISPR/Cas9 system allows cell genomes to be edited at targeted locations using the *Streptococcus pyogenes* Cas9 nuclease (SpCas9) under the guide of a single-guide RNA (sgRNA). Cas9-gRNAs targeting on gene-acetylcholinesterase (AChE) will be delivered into the schistosomule larval stage of S. japonicum by electroporation to induce gene mutation in a model locus. To test CRISPR/Cas9-mediated gene knock-down in S. japonicum schistosomula, we will target SjAChE and assess the degree of AChE loss using AChE activity assays. SjAChE knocked-down schistosomula will then be used to infect mice. At six-weeks post-challenge infection the mice will be perfused, and adult worms will be counted and used for further phenotypic studies. The establishment of a CRISPR-Cas9 system in schistosomes will significantly improve the ability to manipulate the schistosome genome; and will help in the identification of new drug/vaccine targets and the unravelling of drug resistance mechanisms.

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

- Suitable for PhD students only

The Neglected Tropical Diseases (NTDs) are a group of parasitic/bacterial diseases that cause substantial morbidity for more than one billion people globally.

Affecting the world's poorest people, NTDs cause severe disability, hinder growth, productivity and cognitive development, and often end in death; children are disproportionately affected. Asia is a NTD hot spot claiming some of the highest infection rates in the world, second only to that of sub-Saharan Africa. Approximately one-third of the world's parasitic worm infestations occur in this region. Our laboratory focuses on understanding the biology and epidemiology of NTDs caused by parasitic worm infections due to the Schistosoma bloodflukes (*schistosomiasis*), the Echinococcus (hydatid) tapeworms (*echinococcosis*) and soil transmitted helminthiases – diseases of the world's poorest people that result both in major suffering and economic loss.

Our laboratory has research projects suitable for PhD study in:

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

This research is supported by project and program grant funding from the National Health and Medical Research Council of Australia, UBS Optimus Foundation of Switzerland, The Australian Infectious Disease Centre and the Chinese Government.

Lung Bacteria Group

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The laboratory studies bacterial pathogens common in cystic fibrosis and related suppuratives lung diseases. Research focuses on mechanisms of cross-infection, determinants of virulence, persistence and antimicrobial resistance linking genomics with the phenome and clinical outcomes. Our group is currently focusing on mechanisms of infection acquisition form the environment and other clinical sources. We aim to provide improved diagnostics for earlier and more accurate infection detection and improved understanding of optimal treatment of chronic infection to improve patient outcomes.

The emerging problem of non-tuberculous mycobacteria infection: understanding aetiology, geospatial epidemiology and developing interventions.

- PhD project (microbiology background)

Non-tuberculous mycobacteria (NTM) infection is an increasingly common infection in people with cystic fibrosis (CF), can be very difficult to treat and can have an adverse impact on an individual's ability to have a successful lung transplant. This project will represent the largest study of NTM infection in CF and aims to significantly advance our knowledge about the prevalence of NTM, what risk factors (including treatments, health status, other airway-based infection and local environments) are important to its acquisition.

This research project is a multicentre study and the largest internationally, building on existing collaborations and includes centres with patients living in widely different climates and environments. The NTM in Aus Consortium is equipped with leading experts in the fields of lung infection in CF, NTM infection and environmental epidemiology and has strong links with both the Australian CF Data Registry.

The research aims are to:

1. Determine the prevalence, and the host and geographic characteristics associated with NTM infection in people with CF in Australia.

2. Quantify correlations between lower airway microbiota composition and identified risk factors, as a basis for development of a biomarker for NTM acquisition risk.

3. To identify whole genome mutation and airway microbiota signatures associated with virulence, treatment response, and transmissibility.

Funded by NHMRC project grant 2016-2020.

Elucidating antibiotic resistance mechanisms in chronic Pseudomonas aeruginosa infection

- Honours project or is flexible for a clinical student

This project will provide an exciting opportunity for an enthusiastic honours student to join the Lung Bacteria group at QIMR Berghofer Medical Research Institute. The student will work in the research area of Pseudomonas aeruginosa lung infection in cystic fibrosis (CF). In particular, the student will investigate antibiotic resistance mechanisms in P. aeruginosa, which causes the majority of mortality and morbidity in CF.

In vitro susceptibility testing is used routinely to determine if a bacterial strain is susceptible or resistant to an antibiotic; however, there is a lack of correlation between predicted in vitro susceptibility and clinical outcomes in the setting of chronic P. aeruginosa infection. Therefore, there is an urgent need to improve understanding of the underlying antibiotic resistance mechanisms in multi-drug resistant P. aeruginosa strains so that we can identify markers for better evidence-based decisions on antibiotic selection. Using whole genome sequencing we recently found that chromosomal mutations constitute the major mechanism of acquired antibiotic resistance in P. aeruginosa from the CF lungs.

In the proposed project the student will learn how to perform site-directed mutagenesis to determine the impact of mutational events on antibiotic resistance in P. aeruginosa. These comprise >50 mutations, including: a nucleotide substitution in the ampC-ampR intergenic region (-10 promoter of ampC) that could cause hyper-production of the AmpC cephalosporinase; a specific mutation in oprD (outer membrane porin) that could cause prevent uptake of carbapenems; missense or frameshift mutations within efflux pump regulators (including mexT, mexS, mexZ) that could affect susceptibility to antibiotics from different classes.

Immunology and Infection

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The Immunology and Infection Laboratory studies host immunity during infection. Our research aim is to identify immune responses that control infection and distinguish them from those that cause disease. The diseases we study are malaria and leishmaniasis, two important parasitic diseases responsible for much morbidity and mortality each year. We use experimental disease models, as well as samples from patients and human volunteers deliberately infected with parasites for our research. The long term goal of our research is to develop better vaccines and therapies to prevent and treat infectious diseases.

Identifying metabolic pathways used by regulatory T cells during infection.

Major changes in immune cell metabolism occur after activation and/or infection. These changes have a

significant impact on the functions of cells and may be used to identify cell populations at distinct stages of development and/or differentiation, as well as reveal a recent history of antigen exposure. Importantly, there is an increasing number of ways to target T cell metabolism for therapy. Our preliminary results identified metabolic changes in CD4+ T cells from malaria and leishmaniasis patients. In this project, we will identify metabolic pathways employed by various CD4+ T cell subsets during disease. In addition, we will investigate how cell metabolism influences the function of these immune cells.

Discovering novel immunoregulatory molecules that can be manipulated for clinical advantage.

Diseases caused by intracellular protozoan parasites that cause malaria and leishmaniasis require the generation of CD4+ T (Th1) cells that produce pro-inflammatory cytokines. These molecules stimulate dendritic cells (DCs) and macrophages to expand CD4+ T cell responses and activate phagocytes to kill captured or resident pathogens. However, the inflammatory cytokines produced by Th1 cells also damage tissues, and as such, need to be tightly regulated. A downside of this regulation is that it can allow parasites to persist and cause disease. We identified unique gene signatures associated with regulatory CD4+ T cell subsets and will test if molecules associated with these signatures can be manipulated to improve responses to drug treatment and/or vaccines.

Molecular Immunology

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This group has focuses on three areas of research:

1. Identification of host molecular pathways or immunological signals that contribute to protection against malaria
2. Investigating the pathogenesis of malaria; and
3. Development of treatments for malaria.

Identification of novel therapeutic treatment for cancer

The Molecular Immunology laboratory is interested in cancer immunology and in identifying new therapeutic molecules or markers which can be harnessed to control tumour progression. The laboratory has been characterizing new targets and exploring novel combination therapies with complimentary anti-tumor mechanisms.

The project offered aims to identify molecules that maybe over expressed or under expressed during cancer. Carry out in vivo and in vitro studies to identify the effect of blocking or stimulating the identified molecules using antibodies or transgenic mice. Isolation of tumour infiltrating lymphocytes (TILs) will be carried out to further understand tumour immunology.

This project will give an honours student experience in a variety of laboratory skills and animal work, immunological assays including ELISAs, flow cytometry and advanced imaging techniques.

Translational and Human Immunology

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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 which can be implemented in clinical settings. Our 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.

Development of off-the-shelf cell therapies for solid tumours

Adoptive cellular therapy has shown great potential for the treatment of some forms of leukaemia and virus-associated diseases. These approaches are now moving towards the development of "off-the-shelf therapies" generated from healthy individuals to provide more rapid and cost-effective intervention. However, it remains to be determined if these off-the-shelf approaches will be applicable for the development of therapies for solid tumours. This project will investigate the development of novel "off-the-shelf" therapies targeting common cancer antigens expressed in solid tumours.

Modelling immune dysfunction during primary EBV-infection

Infection with Epstein Barr Virus (EBV) increases the risk of developing a number of diseases, including Multiple Sclerosis. This risk is further exacerbated in individuals who develop infectious mononucleosis (IM) during primary exposure to EBV. We recently demonstrated previously unappreciated immune defects during infectious mononucleosis, including an almost complete loss of circulating dendritic cells (DCs) in the blood of individuals with IM. Using a humanised mouse model of EBV infection, this project will focus on delineating the viral immune mediators that regulate the loss of DCs during primary infection

Tumour Immunology

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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.

Cellular immunotherapy for virus-associated human cancers

Current approaches for the treatment of human cancers typically employ broad acting radiotherapeutic and chemotherapeutic approaches, which have led to high success rates but can be associated with unwanted side-effects. Cytotoxic T cell (CTL)-based immunotherapy offers an alternative approach that is designed to specifically target protein antigens expressed in malignant cells and is thus likely to limit any adverse side-effects. Defining tumour-specific antigens is therefore critical for the successful application of CTL based therapy. Herpesvirus-associated malignancies offer an attractive target for CTL-based immunotherapy due to presence of virally encoded antigens in the malignant cells. Recent success in treating Epstein-Barr virus (EBV)-associated post-transplant lymphoproliferative disorder (PTLD) using CTL-based immunotherapy has led to interest in the development of CTL-based immunotherapy to treat other virus-associated malignancies in which antigen expression patterns are well defined but limited to a restricted number of proteins. Our immunotherapy program is aimed at developing new platform technologies to rapidly expand human T cells and also develop new systems immunology tools to identify novel biomarkers which may be helpful in identifying patients who are more amenable to

immunotherapy. In addition, we are also aiming to exploit this knowledge to develop novel therapeutic vaccines for virus-associated cancers.

Malaria Immunology

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Malaria is a life-threatening infectious disease caused by *Plasmodium* – a single-celled parasite that invades our bodies and hijacks oxygen-carrying red blood cells. Once inside these cells, Plasmodium feeds on haemoglobin molecules and replicates itself many times over. The parasites then burst out – only to invade more red blood cells.

This cyclical process can produce billions of parasites in an infected person and these numbers must be brought under control to prevent or cure severe malaria symptoms. Our lab staff focus on understanding how *Plasmodium* parasites and the body's immune system interact with each other. Our approach is highly collaborative – we combine our expertise in experimental models of malaria with researchers around the globe who are world-leaders in the areas of experimental immunology, mathematical modelling, single-cell genomics, computational biology and parasite genetics. Through this network, we explore host/parasite interactions in vivo by combining high-throughput technologies, systems biology approaches and state-of-the-art quantitative methods.

Most importantly, we provide an intellectually creative, vigorous and enjoyable training environment for the next generation of biomedical researchers. We welcome interest from prospective Honours, Masters, and PhD students.

Using high-throughput gene editing techniques to examine CD4+ T cell responses in vivo during experimental malaria.

We will employ CRISPR/cas9 genome editing techniques with molecular barcoding in *Plasmodium*-specific CD4+ T cells. In combination with single-cell transcriptomics we aim to discover novel genes that control differentiation into distinct effector states.

Using bioinformatics to examine differential gene splicing at single-cell level. (bioinformatics skills essential)

Using existing high-resolution single-cell transcriptomic data in a range of immune cells, we will determine to what extent individual genes are differentially spliced in individual cells during experimental malaria. We will use a range of existing bioinformatics packages, which will require Programming skills in R and/or Python.

Using single-cell transcriptomics and epigenomics to study CD4+ T cell memory in experimental malaria.

Using recently developed *Plasmodium*-specific TCR transgenic CD4+ T cells, we will employ state-of-the-art single-cell techniques such as scRNA-seq and scATAC-seq to explore how T cells develop immunological memory during experimental malaria.

Using single-cell transcriptomics to study T cell responses in the gut during Graft-versus Host Disease

(with Dr. Motoko Koyama, BMT lab at QIMR Berghofer).

In collaboration with Dr. Motoko Koyama, we are interested in how CD4+ T-cells in the gut differentiate into an array of different effector states (Th1/Th17/iTreg) during Graft-versus-host-Disease, a common and severe complication following allogeneic stem

cell transplantation. Using scRNA-seq and TCR transgenic CD4+ T cells we will explore how this process occurs in vivo.

Using Parasite mRNA-sequencing and mathematical modelling to study how Plasmodium responds to the host in vivo. (excellent numeracy skills required)(in collaboration with Prof Miles P. Davenport, UNSW, Sydney)

In collaboration with mathematical modeller, Prof Miles P. Davenport (UNSW, Sydney), we will use experimental models of malaria to examine an exciting new mechanism by which the host appears to control Plasmodium parasite numbers in vivo. We will use parasite RNA-seq and mathematical models developed by Prof Davenport to determine the molecular basis of this new phenomenon.

Human Malaria Immunology

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Malaria is a disease of global importance, with >200 million cases and ~ 500000 deaths annually. Alarmingly, malaria control has stagnated in recent years, highlighting the need for new control strategies including effective vaccines. The Human Malaria Immunology Laboratory aims to understand the development of protective immunity to malaria in order to inform vaccine design for at risk populations. We use human patient samples from populations living in malaria endemic areas, and from human volunteers deliberately infected with malaria parasites for our research. We have a particular focus on understanding the development of protective antibody responses to malaria, and the impact of age on immune development.

Top-up funding is available for competitive PhD students.

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

Induction and maintenance of protective antibodies against malaria

Antibodies that target the blood stages of malaria infection are important in mediating immunity. Specifically, it is the function of antibodies to activate sera complement or to interact with immune cells that mediate protection against malaria. Yet, little is known regarding the induction and maintenance of protective antibodies following malaria.

This project aims to characterise the kinetics of functional antibody induction and wanning following malaria and identify cell types that are involved in antibody maintenance. Findings will inform the development of vaccines that induce long-lived and functional antibody responses.

The impact of human host age on innate immune responses that control parasite replication

The ability to control parasite replication is an important aspect of malaria immunity, with high parasite burdens associated with worsening disease severity. Severe disease is also influenced by host age, with the risk of developing severe disease increased in older individuals. Together, this suggests that age dependent changes to the immune systems ability to control parasite replication are important in disease severity.

This project aims to identify key innate immune responses that control parasite replication in early stages of infection and quantify the impact of host age on these immune responses.

Clinical Tropical Medicine

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The Clinical Tropical Medicine Laboratory investigates how parasites such as the malaria parasite, hookworm, threadworm and scabies cause disease and how they become resistant to drugs used to treat them. The group also identifies new drugs and drug targets, and develops novel diagnostic techniques.

The laboratory's focus is to apply modern techniques in microbiology, molecular biology and immunology to study clinical problems associated with infectious diseases in tropical environments.

A particular interest in this laboratory is the study of drug resistance in a range of parasites, and the development of novel diagnostic techniques.

Development of a Diagnostic PCR for Scabies

Supervisor: Dr. Cielo Pasay

- suitable for Honours student only

Project Description

In recent years, the interest in molecular diagnostic methods for the detection of many pathogens has grown substantially. This escalation in interest has occurred in parallel with data indicating inaccuracy of scabies diagnosis based on currently available methods such as handheld dermatoscopy , burrow ink test and examination of skin samples by standard microscopy. The paucity of mites (5-15) in classical scabies makes it extremely difficult for even an experienced dermatologist to make a definitive diagnosis. Hence, scabies can be easily misdiagnosed as an allergic reaction or eczema. Such a state impedes epidemiologic studies, it complicates control programs, and makes accurate assessment of the effects of intervention difficult (eg for clinical trials of new drugs). The importance of sensitive and accurate diagnostic methods for the detection of scabies cannot be underestimated. Molecular assays using ribosomal and mitochondrial targets have been developed for scabies diagnosis, however, low level infections can be left undiagnosed because these targets are suboptimal. With the recent availability of the scabies genome, we hypothesise that a qPCR assay targeting high copy-number, repetitive sequences can improve the sensitivity and specificity of scabies diagnosis representing a major advance.

Aim:

This project aims to develop a PCR assay for the diagnosis of human scabies.

Materials and Methods

- Mining Next Generation Sequence (NGS) data of scabies mites

We will mine next generation sequencing data and draft genome assemblies of different mite species: Sarcoptes scabiei var canis, Sarcoptes scabiei var hominis and Sarcoptes scabiei var suis for high-copy repeat DNA sequences using Repeat Explorer 2. Promising repeats families will undergo further analysis using the NCBI BLAST tool to exclude possible targets with homology to other targets, especially humans, common skin bacteria or other organisms that may be confused such as lice and eyelash mites (Demodex). The remaining most highly repetitive human and pig mite sequences will be utilised for PCR assay development.

- PCR assay design and optimisation

Candidate primers and probe pairings will be designed using the Primer Quest online tool, utilizing the default parameters for probe-based qPCR and checked for cross-reactivity using Primer-BLAST. Primer/Probe/template optimisation will be undertaken. For optimisation of of new PCR assay, skin crusts will be collected from scabies infected pigs maintained at QASP, UQ, Gatton. Genomic DNA stocks from pig mites will be used to determine sensitivity of the assay. Assay specificity will be tested against human genomic DNA and DNA of common skin pathogens.

- Validation of new PCR assay

For assay validation, skin scrapings will be collected from clinically diagnosed scabies (ordinary and crusted) patients admitted to Royal Darwin Hospital and Darwin Dermatology Clinic. For specificity testing, skin samples will be collected from patients with other skin infections such as tinea and psoriasis, etc. Skin samples from patients without skin infection will also be collected

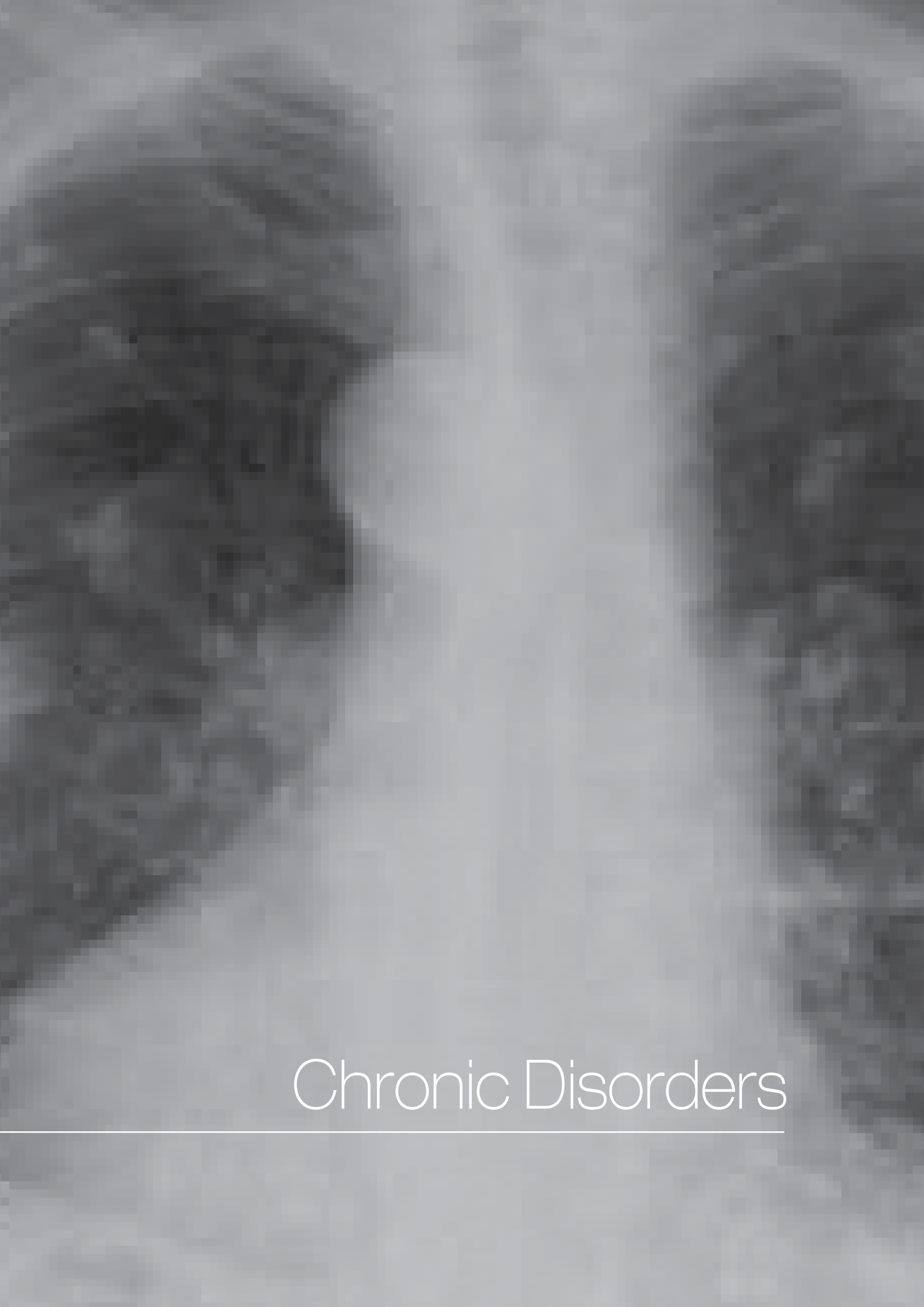
and will be used as negative control.

- Evaluation of new PCR assay

Using pig and human mite DNA, performance of newly developed PCR assay (targeting highly repetitive region of mite genome) will be compared with a Reference PCR Assay targeting a mitochondrial cox 1 gene of the scabies mite.

Expected Outcome

By developing a highly sensitive and specific real time PCR assay using Next Generation Sequencing (NGS) technology to the challenge of repeat DNA discovery, this new diagnostic platform will particularly be useful in areas with decreasing disease prevalence. In a global effort to eradicate neglected tropical diseases such as scabies, the deployment of highly sensitive assays (such as what we propose to develop) is expected to play a critical role in measuring efficacy of control strategies and monitoring disease recrudescence.



Chronic Disorders

The Chronic Disorders Program is one of QIMR Berghofer's four research clusters. Members of the program investigate a wide range of human conditions, but we have particular strengths in respiratory and inflammatory diseases, and disorders of the gastrointestinal tract and liver. These conditions affect a very large number of people both within Australia and globally.

Program scientists approach these problems using diverse strategies ranging from basic molecular studies of disease mechanisms through to human clinical trials.

Conditions we research include:

- Asthma and other allergies
- Biliary Atresia
- Chronic obstructive pulmonary disease
- Cystic fibrosis
- Endometriosis
- Eye disease
- Heart disease
- Hepatic fibrosis
- Infant nutrition and immunity
- Inflammatory bowel disease
- Iron-related conditions

Lung Inflammation and Infection Group

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The lab, headed by A/Prof David Reid, is focused on investigating the interaction between iron metabolism, chronic bacterial pathogens and the host innate immune response within the lungs of cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD) patients. We investigate the role of cystic fibrosis transmembrane conductance regulator (CFTR) in iron metabolism and the induction of chronic lung bacterial infections in lung diseases, using mouse models and primary human airway epithelial cells.

Iron dysregulation in Cystic Fibrosis and COPD

Supervisors:
Dr Ama-Tawiah Essilfie
Dr Pramila Maniam

Background: Cystic fibrosis and COPD are debilitating, life-threatening diseases characterised by airway inflammation, oxidative stress, persistent airway exacerbations and abnormal lung microbiome. CF is the most common lethal genetic disorder in Caucasians, affecting ≥3,500 people in Australia and NZ and more than 70,000 globally. It affects the lungs, gastrointestinal tract, liver and pancreas. CF is caused by mutations in the CFTR gene, encoding a cell membrane chloride channel. Most of the morbidity and mortality relates to airway infection beginning in early infancy and death usually occurs from lung sepsis by the fourth decade. The lung microbiome in CF is complex, but in most patients P. aeruginosa becomes the dominant pathogen and once established in antibiotic resistant biofilms, it is very difficult to eradicate with existing strategies. Strong circumstantial evidence exists that iron regulation in the CF lung is abnormal and that this promotes bacterial infection, especially with biofilm forming P. aeruginosa.

COPD currently affects about 200 million people globally and in most cases is caused by cigarette smoke. COPD is characterised by increased airway inflammation and mucous (bronchitis) and non-reversible destruction and enlargement of the air spaces (emphysema). There are many similarities in the lung phenotype between CF and COPD, and interestingly, increased iron has been shown in the lungs of both CF and COPD patients.

Project aims:

1. Establish in vitro models of cigarette-smoke exposure of healthy and disease epithelial cells

a. Subsequently, incorporate Pseudomonas bacteria in co-culture experiments

2. Characterise lung iron homeostasis in CF and COPD, using in vivo (CFTR knockout mouse) and in vitro models.

3. Investigate if synthetic iron chelators can eradicate Pseudomonas infection, using in vitro and in vivo models.

Student required: This project is suitable for an Honours student only. We are looking for an enthusiastic, hard-working student, who has some basic background in human biology, immunology and microbiology. The student will gain skills in mouse handling, breeding and genotyping of knockout mice; as well as techniques such as RNA extraction, quantitative PCR, western blotting and also skills in cell culture using CF, COPD and healthy cell lines.

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 particularly interested in iron nutrition and iron deficiency, diseases of iron loading (haemochromatosis, thalassaemia and haemolytic anaemias) and the effects of iron on other conditions, notably cystic fibrosis. The laboratory seeks to do this by integrating genetic and molecular studies with biochemical and physiological approaches.

Much of our recent research has been based on understanding mechanisms of cellular iron transport and the way in which these processes are regulated. The group has a particular interest in studying intestinal iron absorption and body iron recycling, and how these processes are altered in disorders of iron metabolism. The role of the liver-derived hormone hepcidin, which regulates body iron transport, has been studied extensively.

The ultimate goal of our work is to improve the diagnosis and treatment of a range of conditions where iron metabolism is perturbed.

Using nanotechnology to deliver iron chelators

- This project can be modified to suit Honours, PhD or Clinical students.

Background: Significant pathology accompanies body iron accumulation in both primary and secondary iron loading disorders, so iron removal is a key therapeutic strategy. This is often achieved using drugs called iron chelators. Of the three chelators in clinical use, Desferrioxamine (DFO) is the most effective iron binding compound, but an onerous administration regimen limits its clinical use. Nanotechnology approaches offer an attractive alternative method for delivery DFO efficiently.

Aims: To examine the efficacy of nanoparticulate formulations of DFO (DFO-NP) in iron removal and to develop targeted nanoparticles for delivering DFO to specific organs.

Approaches: A variety of DFO-NP formulations will be developed by using a range PLGA polymers and novel DFO derivatives with improved pharmacokinetic properties. Their efficiency in removing iron will first be tested in cell lines, and the most efficient formulations will subsequently be trialled in established murine models of iron loading (parenterally loaded wild-type mice, beta-thalassaemia intermedia mice and haemochromatosis mice). To develop targeted therapies for iron removal, the most effective DFO-NPs will be decorated with ligands that specifically target cardiomyocytes and hepatocytes, cells particularly prone to iron loading. The efficacy of these agents will be tested in animal models. To provide a platform for the efficient oral delivery of DFO, NP-based chelator formulations will be prepared using ligands that target molecules on the surface of intestinal enterocytes. The efficiency of delivery will be examined in mouse models. In all of these studies, a range of experiments will be carried out to assess the safety and tolerability of the NP formulations.

These studies will lay the foundation for a new generation of iron removing therapeutics that can be applied to iron loading disorders, as well as to a range of other conditions where excess iron has been implicated in pathogenesis.

Techniques to be used include nanoparticle preparation and characterisation, cell culture, mouse studies, and a range of biochemical and molecular analysis techniques.

A novel nanoparticulate iron supplement and its effect on the gastrointestinal tract

- This project can be modified to suit Honours, PhD or Clinical students

Background: Iron deficiency and iron deficiency anaemia are major global health issues. Currently available iron supplements based on ferrous iron salts can lead to gastrointestinal side effects. We have developed a new type of oral iron supplement (IHAT) that has been shown in animal studies to be as effective as conventional treatments, but without their limitations. This project will involve investigating the effect of IHAT on the gastrointestinal tract of mice to ensure its safety and to provide preliminary data for future clinical trials in humans.

Aims: The overall goals of this project are to investigate in detail how IHAT is taken up by intestinal enterocytes, to examine the effect of oral IHAT on healthy gut epithelial cells

and the intestinal microbiome, to determine the effect of oral IHAT on intestinal inflammation and to examine the effect of oral IHAT on intestinal tumourigenesis.

Approaches: There are several potential components to this project. Characterising the uptake of oral IHAT by intestinal enterocytes will be carried out using knockout animal lines and isolated intestinal loops to determine which proteins and pathways are essential for IHAT absorption. The effect of oral IHAT on gut epithelial cells will be determined by examining markers of inflammation and oxidative stress in enterocytes from wild-type mice. The effect of oral IHAT on the intestinal microbiome of wild-type mice will also be examined using 16s rRNA sequencing. As currently available oral iron supplements are contraindicated in patients with inflammatory bowel disease as they exacerbate symptoms, the effect of oral IHAT will be examined in several mouse models of this disease. The extent of inflammation will be determined by both histological scoring of the intestine and the expression of inflammatory cytokines. Animal models also suggests that currently available iron supplements increase the risk of intestinal tumours. As such various aspects of intestinal tumourigenesis will be examined in mice fed diets containing either ferrous iron or IHAT with particular emphasis on colon cancer development and progression.

Techniques to be used include mouse breeding and dietary manipulation, microscopy and immunohistochemistry, gene and protein expression studies, microbiome analysis and trace element analysis.

Mechanisms of intestinal iron absorption in early infancy

- This project can be modified to suit Honours, PhD or Clinical students.

Background: Iron is an essential nutrient at any stage of life, however, it is particularly important for the rapid growth and development that occurs soon after birth. In young infants, intestinal iron absorption is extremely efficient, but following weaning, it declines dramatically to adult levels. Our studies to date have suggested that iron absorption during suckling is dependent on the iron transport protein ferroportin (Fpn), as it is in adults, but systemic signals that are able to reduce absorption post-weaning are ineffective in neonates. This provides a novel strategy for maximizing iron intake at a time of high demand, while retaining the capacity to regulate internal iron trafficking and respond to various insults, such as infection. In this project the mechanisms underlying this hypo-responsiveness will be investigated.

Aims: To investigate the mechanism by which intestinal Fpn does not respond to systemic signals in early postnatal life and to determine how the iron homeostasis of neonates responds to infection and inflammation.

Approaches: Most of the studies to be carried out will use the mouse as a model, but some of the work will utilize intestinal biopsies from human infants. Initial studies will assess in detail the response of the intestine and spleen (as the internal organ that shows the highest level of Fpn-dependent iron release) to systemic inflammatory signals and infection with Pseudomonas aeruginosa. This work will be carried out in mice before and after weaning. The distribution and expression of Fpn will be studied, as will iron trafficking into and around the body. Fpn will be isolated from pre- and post-weaning gut and analysed by contemporary proteomic methods to detect post-translational modifications. The effects of any modifications will be examined in cells transfected with either wild-type Fpn or Fpn in which the modified residues have been mutated. We will also examine human infant intestinal biopsies for these modifications. Understanding the factors responsible for the high absorption in neonates provides the potential for modifying absorption pharmacologically.

Techniques to be used include mouse breeding and phenotypic analysis, in vivo iron kinetic analysis, microscopy, immunohistochemistry, proteomic analysis, protein-protein interaction studies, cell transfection and protein expression.

The uptake and toxicity of nanoparticles in the small intestine

- This project can be modified to suit Honours, PhD or Clinical students

Background: Nanotechnology is increasingly having an influence on many aspects of our lives, including health care. Nanoparticles come in a wide range of shapes, sizes and compositions, with different formulations suiting different applications. They have proved to be very effective in a range of applications, with their use as drug delivery and imaging agents being particularly notable. The oral delivery of substances using nanoparticles has received comparatively little attention and their mode of action/delivery and toxicity are incompletely understood.

Aims: The focus of this project is to assess the mechanism of action/uptake and potential toxicity of two types of nanoparticles in the small intestine. The first will be a nanoparticle system developed to deliver iron and folate as dietary supplements. The second type of nanoparticle will be one designed to deliver cytotoxic drugs and chemoprotective agents for tumour therapy.

Approaches: The nanoparticles themselves are currently being developed by collaborators in China. Our laboratory will assess their efficacy, mechanisms of action and toxicity. These will be examined initially in rat models, but the studies may be extended to strains of mice lacking critical components of intestinal transport pathways. Efficacy will be determined by measuring the delivery of the nanoparticle 'cargo' to the plasma and tissues, and by assessing nutrient status where appropriate (e.g. iron, folate levels). Light and electron microscopy will be used to follow the fate of the nanoparticles. Toxicity will be assessed morphologically and by measuring levels of oxidative stress in the gut. Since nanoparticles have the potential to alter gut microflora, 16S rRNA sequencing will be carried out to profile the gut microbiome before and after treatment. As part of these studies, a small intestine organoid culture system will be developed to enable the mechanism of nanoparticle interactions with the intestinal epithelium to be studied in greater detail. For example, inhibitors of membrane trafficking may be used in this system to determine whether they influence the interaction of the nanoparticles with the brush border membrane and/or their uptake into the cells.

Techniques to be used in this project include animal handling and phenotypic analysis, various types of microscopy, analysis of oxidative stress, microbiome analysis, and a range of more conventional biochemical, molecular and cell biology procedures.

Hepatic Fibrosis Group

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

Mechanism of inflammation-induced liver scarring (fibrosis) in cirrhosis associated with chronic liver disease

- PhD project but may also be considered for a Honours project

In this research proposal we hypothesise that the paracrine

release of tissue ferritin by damaged liver cells in chronic liver disease, causes an inflammatory response via ferritin endocytotic and signalling receptors on hepatic stellate cells (HSCs – liver fibroblasts), which drives hepatic fibrogenesis and cirrhosis, which may ultimately be associated with the development of hepatocellular carcinoma. While the association between inflammation and circulating ferritin in chronic liver injury is well established, we propose that rather than simply being a consequence of inflammation, elevated tissue-derived ferritin plays a role in mediating processes associated with hepatic injury. This study is designed to determine the identity of the HSC ferritin signalling and endocytotic receptors and thus the pathways which facilitate upregulated inflammation in hepatic fibrogenesis. We have identified a number of highly novel ferritin-binding proteins with signalling potential in HSCs. In this study we will characterise theses candidates and other potential cell surface/ intracellular binding proteins using confocal/live microscopy and proteomic analysis coupled with bioinformatic platforms.

We propose that HSCs are exposed to ferritin released from iron-damaged hepatocytes or following Kupffer cell phagocytosis of hepatocyte remnants/ apoptotic bodies. This study will assess the paracrine role of released hepatocellular ferritin in regulating HSC activation via ferritin receptor candidates. Physiological relevance will be demonstrated in animal models of injury/inflammation. Clinical significance will be demonstrated in human chronic liver disease by assessing the association between serum/liver ferritins and their receptors, and inflammation and hepatic fibrosis severity. These are highly novel and innovative studies which will identify proinflammatory ferritin-induced signalling pathways in HSC. Strategies designed to reduce the impact of liver disease in the future will have to rely on new treatments targeting such regulatory pathways. Our proposal will provide an important cornerstone for such advances.

Developing a novel blood test to improve the early diagnosis of liver cancer

Chronic liver disease morbidity and mortality is increasing alarmingly, due in large part to the growing epidemic of obesity which is associated with non-alcoholic fatty liver disease. By 2030 over 8 million Australians will be affected by chronic liver disease of various aetiologies. Untreated, chronic liver disease can progress to cirrhosis through liver scarring, or fibrosis. Cirrhosis represents permanent scarring of the liver. Cirrhosis is the common endpoint of all chronic liver disease. Cirrhosis is associated with life-threatening complications such as liver cancer (also known as hepatocellular carcinoma or HCC). Liver cancer is the 2nd largest cause of cancer death world-wide and now affects more people than ever before. Only 15% of people with HCC survive 5 years or more, however, early diagnosis of HCC is treatable (5-year survival is up to 90%). The key is early diagnosis but current blood tests are only positive in 50% of HCCs. A better diagnostic blood test is desperately needed for the early detection of HCC. This project investigates the potential role of serum microRNAs to detect early HCC diagnosis and examines the mechanistic role microRNAs play in the development and metastasis of HCC in chronic liver disease.

Can we stop the development of bone metastatic prostate cancer?

- Suitable for a PhD student.

Project Supervisors:
Prof Grant Ramm
Dr Carolina Soekmadji

The development and progression of prostate cancer are controlled by the androgen receptor (AR), a ligand-regulated transcription factor. Current therapy for advanced prostate cancer has focused on the inhibition or disruption of the AR signalling axis. Androgen deprivation therapy (ADT) is focused on inhibiting the nuclear activity of AR. While this is effective, ADT is associated with multiple side effects including osteoporosis, decreased libido, and erectile dysfunction. Unfortunately, while this treatment is initially effective in most patients, the tumour recurs in many patients within 2 years. Extracellular vesicles (EVs), such as exosomes, are vesicles secreted by cells to mediate communication with

surrounding cells and can be isolated from blood. We recently discovered that EVs can influence the AR signalling axis in prostate cancer. This project aims to characterise the role of EVs in regulating the development of bone metastatic prostate cancer. This project involves vesicle isolation and characterisation, co-culture and imaging of prostate cancer and bone cells in 2D and 3D, pathway analysis, and isolation of blood-derived vesicles for a potential biomarker.

Mucosal Immunology

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Tolerance induction with a hookworm protein and prevention/treatment of allergic asthma

Nearly one billion people globally suffer from allergies, representing a considerable social and economic impact, significant morbidity and reduced quality of life. Allergic diseases most commonly develop in infancy, meaning that children are exposed to life-long treatments that can cause considerable and irreversible side effects. Compelling evidence suggests that sensitisation occurs within the first two years of life when the gut microbiome establishes. Over this period, a delicate balance linking the microbiome and the immune system exists, which, if perturbed, results in heightened allergen-specific Th2 responses. These observations imply a "window of susceptibility" for the development of sensitisation that could be explored as an intervention opportunity to prevent atopy.

We have recently described that a hookworm recombinant protein, named Anti-Inflammatory Protein (AIP)-2, is able to suppress allergic responses in both mice (in vivo) and humans (ex vivo), and to promote sustained immune regulation in mice. We have found that AIP-2 administered via breastmilk (BM) within the first week of life, modified the composition of the gut microbiome and protected pups from asthma onset into adulthood. Our central hypothesis is that AIP-2 and BM co-factors prevent sensitisation by modifying the immune and microbiome landscape promoting sustainable tolerance.

Determine the composition of AIP-2-shaped breastmilk and define the microbiome, metabolome and immune landscape of AIP-2-nursed pups

- This project is suitable for a PhD student

Project description: Research on human BM has shown that bioactive factors influencing the infant immune system are primarily composed of proteins, essential fatty acids and micronutrients. Furthermore, it was recently reported that 30% of the infant gut microbiome originates from mother's BM, suggesting that AIP-2 likely influences the composition of BM and transmission of key microbial species to the neonate. Therefore, a comprehensive analysis of AIP-2-shaped BM nutritional and microbiome content is pivotal to understand how AIP-2 induces tolerance in pups.

Using a mouse model of tolerance induction, this project will require the use of bioinformatics to integrate data from microbial 16S rRNA sequencing, mass spectrometry, and nuclear magnetic resonance spectrometry (NMR).

Neonate mice will be treated with AIP-2 supplemented with the most abundant/relevant BM components and their role will be evaluated in a model of allergic asthma.

Determine the role of microbiome, immune factors and short-chain fatty acids in AIP-2-induced tolerance

- This project is suitable for a PhD student

Project description: To better understand the contribution of BM microbiome, protein, essential fatty acid and SCFAs in mediating AIP-2 tolerance in pups, a selective depletion/inhibition approach will be used.

This project relies mainly on the use of a mouse model of neonatal tolerance

and antibiotics, receptor antagonists, monoclonal antibodies, and genetically modified mice to determine the role of specific microbiome, cytokines (and other soluble proteins), and short-chain fatty acids in mediating tolerance with AIP-2 in pups.

A combination of animal handling, assessment of allergic disease, flow cytometry and complex immune assays will be required for this project.

Influence of parasite infection on microbiome and metabolite composition in mother/baby dyads from hookworm endemic areas

- This project is suitable for a PhD student

To support our hypothesis that unlike the Western lifestyle, parasites, such as hookworms, modulate maternal microbiome and promote infant bacterial colonization with key bacterial species that are critical for immune tolerance, we will perform a comparison study between a mother and baby cohort located in Papua New Guinea (PNG)) and Brisbane (QLD). This project seeks to examine infant microbiome colonisation via BM and enrol pregnant women to perform a longitudinal microbiome study of the child through the first year of life.

Project description: BM and stool from both mother and baby will be collected at 1 month post-partum, and from the child at 6 month and 12 month of age. Socio-health and dietary details will be collected at the time of recruitment and at each sample collection time point. Faecal samples from PNG will be further screened to determine the presence and burden of soil-transmitted helminths (STH). Faecal and BM samples from both locations will be analysed two-ways for microbial sequencing (16S rRNA) and metabolite content by nuclear magnetic resonance spectrometry.

This project relies heavily on the use of bioinformatics.

Development of a hookworm recombinant protein for the suppression of allergic responses

- This project is suitable for a PhD student, or can be modified to suit Honours or Clinical students

Project description: We have shown that the main cellular target of AIP-2 in both mice and human leukocytes is dendritic cells (DC). Selective inhibition of specific endocytosis pathways suggest that uptake likely involves a receptor. To understand the nature of interaction of AIP-2 with DC and the downstream effects, we need to:

(i) determine which organelle(s) in human DCs colocalize with AIP-2
(ii) identify AIP-2's putative receptor on DCs
(iii) validate findings (Surface Plasmon Resonance, confocal microscopy)

(iv) determine the transcriptome and proteome dynamics induced by AIP-2/receptor interaction

Organoid Research Group

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Impact of macrophages on cardiac maturation

- PhD project only

Background: There are resident macrophages in the heart and they are one of the most populous cell types present after endothelial cells, cardiomyocytes and fibroblasts. Recently, high profile publications have shown that macrophages play an important role in regulation of pacemaker activity and conduction. Additionally, during disease processes they have been shown to induce a fibrotic response in resident fibroblasts. However, little is know about their role in cardiac

development and maturation where there are profound changes in the phenotype and gene expression of resident macrophages. Furthermore, in human cardiac organoid models in vitro, the top differential expression difference compared with the adult heart is a signature from the resident macrophage population and signalling components.

Aim: To determine the impact of incorporating human macrophages on the biology and function of human cardiac organoids.

Approach: Human monocytes (commercially available) will be added to our human cardiac organoids. We will use different analysis techniques to determine their impact on biology (single cell RNA sequencing and single organoid proteomics) and function (force of contraction analyses, impaling electrode electrophysiological measurements and response to adrenaline). Using these approaches we hope to identify key regulators of macrophage-cardiac interactions under both resting and activated macrophage phenotypes.

Outcome: Elucidating the impact of macrophages on human cardiac organoid biology and function is important for deciphering the cell-cell crosstalk in the regulation of the maturation process to advance our in vitro organoid models. Additionally, it has the potential to unlock new therapeutic targets for treatment of cardiovascular disease.

Respiratory Immunology

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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 maternal diet on the severity of infant viral bronchiolitis

Viral bronchiolitis is an infection of the small airways (bronchioles) characterised by the infiltration of neutrophils, oedema, and shedding on 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.

Regulation of HMGB1 and IL-33 release from airway epithelial cells

High-mobility group box 1 (HMGB1) and interleukin-33 are constitutively expressed in the nucleus. However, both proteins can translocate to the cytoplasm and if released into the extracellular environment, act as cytokines to induce functional responses in local cells. The processes that regulate the release of these two proteins (also described as ‘alarmins’) remains poorly described, however we have recently identified a role for the purinergic receptor P2RY13, and a recently described form of programmed cell death termed necroptosis. This project will interrogate the role of these two pathways in regulating alarmin release using experimental mouse models and in vitro culture models of primary airway epithelial cells.

Microbiome and immune cell development in early life

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

Eicosanoids and viral exacerbations of chronic obstructive pulmonary disease (COPD)

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

Cell death pathways and the induction of type-2 inflammation

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

ER stress pathways in respiratory disease

Stress of the endoplasmic reticulum can be a protective mechanism that promotes antiviral immunity. However, we have preliminary data that suggests that excessive ER stress can cause severe morbidity and potentially mortality during an acute pneumovirus infection in mice. This project will seek to unravel the cellular and molecular pathways that underlie this process.

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

One major focus is understanding genetic and epigenetic variation in various cancers. Cancers studied include melanoma, ovarian cancer, breast cancer and oesophageal cancer. Ultimately this work will lead to 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 work ongoing to identify the specific genes involved in both eye disease and in underlying quantitative risk factors.

Genetics of keratinocyte cancer

Project Description:
Genetics, together with sun exposure, play an important

role in the development of skin cancers, particularly keratinocytic cancers (Squamous Cell Carcinoma and Basal Cell Carcinoma). While keratinocytic cancers are rarely deadly, their high incidence still results ~600 deaths are year, and are the most expensive cancer in Australia (> $500 million p.a.).

The Q-Skin cohort is a large (~20,000 people) cohort dedicated to exploring skin cancer. We have genetic data on >17,000 people, and are currently undertaking large scale genome-wide association studies of keratinocytic cancer. A range of methods can leverage this data to better understand keratinocyte cancer.

Aims: To use computational statistics approaches to identify risk factors for keratinocytic cancer, improve prediction and explore the overlap with other traits.

Approaches: Prediction models will be developed from genome-wide association study data, and calibrated against Q-Skin to determine their efficacy. Mendelian randomisation will be used to determine if potential risk factors associated with keratinocyte cancer are causal. The overlap of Keratinocyte cancer with other traits (e.g. melanoma, pigmentation) will be explored to both identify new genetic risks, and improve prediction models. Fine-mapping, bioinformatics, and post-GWAS approaches (e.g. gene-based tests).

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

Genetics of skin traits

Project Description: Through large cohort studies based at QIMR Berghofer Medical Research Institute, including the Queensland Study of Melanoma: Environmental and Genetic Associations (Q-MEGA), the Queensland Twin Registry (QTwin), and the QSkin skin cancer study (N ~ 20,000), and from large international datasets (e.g. UK Biobank, N > 500,000) we have a large body of data linking genetics to skin biology. Through this we are able to assess the genetics of skin cancers, including melanoma, skin ageing, pigmentation, and mole count.

These traits interact, and recent methods such as Multi-trait analysis of GWAS, MTAG, have shown that combining related traits can dramatically increase discovery of new genes. We wish to combine this data to greatly increase this data to improve our understanding of skin biology.

Aims: Through advanced statistical genetics techniques perform combined analysis of skin traits, identifying new genetic risks and generating improved prediction models.

Approaches: The overlap of these traits will be explored to identify new genetic risks common to all traits. Prediction models will be developed from the combined data, and calibrated against datasets in hand.

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

Melanoma genetics – moving beyond risk

Project Description: Melanoma is responsible for >1,800 deaths a year in Australia Melanoma risk has a complex etiology, with environmental (ultraviolet radiation, UVR) and genetic factors both important. ~58% of the variability in melanoma risk in populations is due to genes.

While research into the genetics of melanoma risk is well in hand through work undertaken at QIMR Berghofer. the environmental and genetic factors influencing melanoma survival are far less well understood. The Swedish Family Cancer

database clearly shows familial aggregation and hence heritability of mortality from melanoma, and as a proof of principle we have shown genetic variants in PARP1 leads to markedly worse survival (hazard ratio >2). Our unpublished work shows melanoma tumour depth is heritable. Survival is influenced by tumour depth, number of tumours, histological type and anatomical site, making it important to perform GWAS within these phenotypes; this data is in hand. While immunotherapy improves melanoma survival there is substantial variability in response. Host variation in immune responses are strongly genetically determined supporting a role for the germline in response.

Aims: Perform large scale genetic analyses of melanoma outcome, survival and treatment response. Use these datasets to develop prediction model and explore the role of traits influence melanoma survival (e.g. tumour histology).

Approaches: Genome-wide association studies (GWAS), meta-analysis of GWAS, and post-GWAS analyses (e.g. fine-mapping, bioinformatics, gene-based tests). Development of prediction models.

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

Eye disease genetics

Project Description: 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 makes understanding the molecular mechanisms fundamental to improve screening and develop better therapies. Although we have discovered many specific genes influencing glaucoma, we have also shown that most have still be to be found

Aims: To identify more loci explaining why some people get glaucoma and some do not. To translate genetic findings into improved screening and into better therapies.

Approaches: We already have custody of very large scale genetic data sets (genome wide association studies, exome/genome sequencing), with further data collection underway. The student will employ a range of statistical genetic approaches to interrogate these data and to determine the genes and pathways underlying glaucoma. Statistical approaches for prediction will be investigated.

Suitable background: The post is ideally suited to someone with an undergraduate or Masters degree in genetic epidemiology, epidemiology, statistics or bioinformatics. Experience in the analysis/ manipulation of large datasets and a good knowledge of computing is desirable. Experience in ophthalmic genetics advantageous but not essential. Non-statistical applicants must be able to demonstrate some knowledge of statistics. For statistical applicants, some knowledge of genetics is desirable.

Knowledge of pathophysiology (in particular, the brain circuits involved in the mood disorders), biological and social risk factors.

Mental Health

The 2007 National Survey of Mental Health and Wellbeing found that an estimated 3.2 million Australians (20 % of the population aged between 16 and 85) had a mental disorder in the 12 months prior to the survey. The Burden of Disease and Injury in Australia (2003) study indicated that mental disorders constitute the leading cause of disability burden in Australia.

Mental illnesses encompass disorders of mood, thinking, perception, communication and function. They can occur throughout the lifespan and be disabling and distressing. The focus of the Mental Health Research Program at QIMR Berghofer is to combine genomic, epidemiological and neuroscience approaches to advance the understanding and treatment of mental illnesses. The promise of this approach is personalised therapies for mental illnesses, based on improved knowledge of pathophysiology (in particular, the brain circuits involved in the mood disorders), biological and social risk factors.

Mental Health and Neurological Disorders we research

- Anxiety
- Attention Deficit Hyperactivity Disorder
- Autistic Spectrum Disorder
- Bipolar Disorder
- Dementia
- Depression
- Eating Disorders
- Migraine
- Personality Disorders
- Schizophrenia

Neurogenomics Group

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Our group investigates and validates genome-wide transcriptomic data to provide insight into how the human brain functions. For this we employ cutting-edge technologies such as:

- Induced pluripotent stem cells (iPSCs)
- Next generation sequencing (NGS)
- Advanced bioinformatic analyses

Understanding how the human brain works has historically been restricted due to the lack of a suitable human model and the ability to interrogate the entire transcribed human genome. Recent innovations in iPSC technology has permitted an unprecedented view into the biology of human cellular function as many cell types, including brain cells, can be derived from these 'stem' cells.

Furthermore, the emergence of powerful bioinformatic capabilities has extraordinarily advanced the field of genomics and transcriptomics over the last decade. We are exploring, using a combination of iPSC and NGS technologies; particularly how mRNAs, long non-coding RNAs and small RNAs combine to underpin human cognitive advancement and psychiatric disease.

What makes us human? How has newly evolved regulatory sophistication occurred? How can we understand and treat psychiatric disease? We seek to answer important and exciting questions in human biology using the brain as a model.

What makes us human?

- This project can be modified to suit Honours, PhD or Clinical students
- Suitable for both wet lab or bioinformatics projects

Genome sequencing of our closest primate relatives such as the chimpanzee, bonobo and gorilla found ~4% of the human genome to be unique. Much of this human-specific sequence is dynamically transcribed, highly enriched in the brain and derived from non-coding, repeat-containing sequences, such as transposable Alu elements and subtelomeric regions; and proposed to have significantly impacted recent human, and especially brain, evolution.

However, the functions of human-specific transcripts in the brain are poorly understood, due to:

(1) A suitable human model of functional and modifiable neural cells and

(2) Their difficult-to-analyse inherent repeatability.

Our lab circumvents these problems by using cutting edge technologies in both research and bioinformatics:

Wet lab: This project will exploit induced pluripotent stem cell (iPSC) technology that has recently revolutionised the field of human neuroscience, as a large range of human neural cells can be derived from iPSCs. IPSCs allow effective exploration of human neural mechanisms utilising non-cell line, functional, reproducible and modifiable neural cells. Human-specific transcripts involved in neural activity, uncovered through bioinformatic analyses, will be targeted for molecular manipulation in iPSCs and resulting cellular consequences will shed light on the signalling pathways intricately linked to the evolution of human brain function.

Bioinformatics: Next generation sequencing (NGS) enables a genome-wide, unbiased view of the entire transcriptome. Cutting-edge bioinformatic analysis, including new approaches for circumventing repeat-mapping problems, will enable a comprehensive view of the dynamic transcriptome.

In both wet lab and bioinformatic projects we will also include disease-associated models such as schizophrenia, bipolar disorder and epilepsy, while also exploring changes during human aging and linking these conditions to newly evolved human brain functions.

Psychiatric Genetics

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Our research focuses on investigating the genetic and environmental factors that influence mental health conditions and the impact of non-psychiatric conditions on mental health. We work on many common mental health conditions and psychiatric traits including child and youth mental health, depression, anxiety and addiction.

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

- Project is suitable for PhD or subsections could be Honours projects

Project Description:
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 nation-wide cohort of children with ADHD this project will examine the cost and impact of ADHD to families and the community.

The project will require a strong background in statistics and research methodology. Applicants with backgrounds in Psychology/Psychiatry, Statistics or Public Health are preferred.

Potential sub-projects include

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

The role of genomics in understanding psychiatric and neurological disease

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. Applicants with backgrounds in Psychology, Psychiatry, Statistics or Public Health are preferred.

Health and wellbeing in people with bipolar disorder

- Suitable for Honours. PhD students interested on the topic are invited to contact Sarah Medland to discuss on related projects.

Bipolar disorder is a lifelong and severe psychiatric illness characterized by recurrences of episodes of depression and hypomania or mania. Lithium is a 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.

Systems Neuroscience

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Systems Neuroscience is an approach to brain sciences that seeks the fundamental principles of brain organisation, dynamics and function across a hierarchy of spatial and temporal scales. It is a rapidly growing field that differs considerably from the traditional reductionist paradigm in neuroscience that seeks purely sufficient causes for local phenomena. In contrast, systems neuroscience seeks unifying explanations for emergent phenomena.

The work of our group embodies these principles across three broad domains – empirical, computational and clinical neuroscience. The overarching aim of this work is to contribute towards unifying models of brain architecture, dynamics and cognitive (dys)function. These models then inform the design of brain imaging experiments into major mental illnesses.

Brain dynamics following (un-) successful ageing

- Suitable for Honours or PhD student

Supervisor:
Dr Leonardo Gollo

The brain exhibits structural adaptations as we age. The functional consequences of such structural changes remain poorly understood. The goal of this project is to characterize changes in brain dynamics associated with ageing. This is a crucial step to identify disruptions in brain dynamics that lead to cognitive impairments. Applicants should be highly motivated and should have a strong background in physics, computer science, neuroscience or a related discipline, and interest in Neuroscience is required.

Computational models of brain network dynamics

- Suitable for Masters or PhD student

Supervisor:
Dr Leonardo Gollo

The human connectome project is one of the largest and most ambitious scientific projects and has the goal of understanding the “Google map” of the brain – namely the complex network connections that underlie cognitive function. Applications are sought for a PhD project in the Systems Neuroscience Group, investigating the roles of neural and glial networks in shaping neuronal dynamics. The successful student will investigate the dynamics of fast large-scale neuronal networks, and how they interact with the slower glial network employing computational modelling and graph theory. The project will focus on computational and mathematical studies of network dynamics, although there is also ample opportunity to study human connectomic data and be involved in local neuroimaging projects. Applicants should be highly motivated and should have a strong background in physics, computer science, neuroscience or a related discipline. Interest in Neuroscience and programming experience are required.

Simultaneous EEG-FMRI: Functional MRI brain networks related to EEG NF Neurofeedback learning

Project Supervisor/s:
Professor Michael Breakspear
Dr. Johan van der Meer

Electroencephalographic (EEG) neurofeedback (NF) is a technique by which subjects

can learn to gain behavioural control over their brain signals. It is increasingly used as therapeutic intervention for various psychiatric disorders [1-4]. However, NF training has behavioural transfer effects associated with successful EEG regulation only in a subgroup of participants. EEG-NF has been proposed to rely on the dynamics of large-scale functional brain networks, and to normalize pathological network states [1]. Although functional network analysis of EEG-NF based on magnetic resonance imaging (fMRI) would be ideal for testing this idea, direct investigation so far has not been performed, mainly due to large artefacts in the EEG co-registered with fMRI.

The aim of this project is to identify specific functional brain networks involved in NF learning and to characterize their plastic changes with respect to both learning efficiency and possible cognitive transfer effects of NF training. As a follow-up, we can exploit this knowledge to optimize the efficiency and the desired transfer effects of NF learning using combined EEG/fMRI-NF, for example by reinforcing recruitment of specific functional networks during learning. This project will provide grounds for improved NF based therapies and cognitive enhancement training applying to a wider range of patients. As a first step, we will focus on the up- and downregulation of global EEG alpha power by NF to address the following questions:

Are there different functional networks associated with active alpha power regulation, as compared to spontaneous alpha fluctuations during rest?

Are there configurations and plastic changes of functional networks related to NF learning of alpha power regulation?

Are there inter-individual differences in the functional networks explaining differences in the efficiency of NF learning?

Can we associate the recruitment of particular functional networks with transfer effects of NF training on cognitive performance?

To answer these questions, we are going to carry out EEG alpha-NF simultaneously with functional magnetic resonance imaging (fMRI) by employing a newly developed EEG artefact reduction technique using carbon wire loops (CWL). This technique will permit real-time EEG-NF in combination with MRI/EEG functional network analysis, which has not been achieved before. We will characterize functional networks involved in different stages of NF learning, and relate inter-individual differences of learning efficiency and transfer effects on working memory or mental rotation to different functional network characteristics.

1. Niv et al. (2013) Efficacy and potential mechanisms of neurofeedback. Pers and Indiv Diff 54, 676-686.

2. Birbaumer et al. (2009) Neurofeedback and brain-computer interface clinical applications. Int Rev Neuro Biol 85, 107-117.

3. Arns et al. (2014) Evaluation of neurofeedback in ADHD: The long and winding road. Biol Psych 95, 108-115

4. Choi et al. (2011) Is alpha wave neurofeedback effective with randomized clinical trails in depression? A pilot study. Neuropsychobiol 63, 43-51.

This project would suit an (international) Honors/Masters or PhD student who had as a part of their curriculum advanced programming, mathematics and/or signal analysis techniques (applied mathematics, physics, electrical engineering or similar curicullum).

Brain Modelling Group

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How brain dynamics emerge from energy constraints

- Suitable for PhD or Honours student

The brain consumes 20% of the body's energy despite constituting only 2% of the body's mass. Optimal brain functioning thus requires careful balancing of the brain's energy budget. This central organising principle has been extraordinarily successful in explaining brain structure, including brain network architectures that minimise wiring length and optimal

neural codes for efficient information representation. Despite these successes, most of the brain's energy expenditure is currently unexplained. The question of how metabolic constraints shape neuronal dynamics – particularly at the large scale – remains largely unanswered. A large part of the problem is that existing models of large-scale brain activity do not explicitly include metabolic variables and so are unable to address dynamical constraints on resources such as oxygen and energy. This project aims to develop a biophysical model to understand how the brain's need to optimise its energy resources shapes its activity. The project will involve close engagement with neurophysiological and neuroimaging data. 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).

Modelling brain dynamics across the lifespan

- Suitable for PhD or Honours students.

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 interests, examples **include:** how ageing brain structure changes our brain activity; how noninvasive brain stimulation perturbs brain network activity; how disorders such as epilepsy, schizophrenia, or ADHD may emerge from biologically-plausible changes to model parameters; how flashing lights can can drive nonlinear brain responses with application to migraine; and developing novel analysis methods for complex spatiotemporal dynamics. 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).

Novel methods for monitoring brain activity in preterm babies

- Suitable for PhD or Honours students.

A major challenge in neonatal intensive care is timely and efficient bedside monitoring of the preterm brain to guide optimal individual care. The overarching aim of this project is to clinically validate novel methods to noninvasively detect acute brain injury and form a prognosis for long-term outcome as early as the first hours after preterm birth. Electroencephalography (EEG) is widely used to monitor preterm brain health, but its diagnostic utility is limited by the need for subjective visual assessments of raw signals or simple trends. These are also prone to the many recording artefacts in intensive care units. We recently developed new metrics for analysing preterm brain activity that enable detection of injuries and prediction of neurodevelopment, earlier than had been possible before. This project will take the crucial next steps toward taking our new technology to the clinic. This will involve validating and refining our existing metrics using a newly-collected, large, multicentre dataset of preterm EEG with full clinical follow-up. There are also numerous technical challenges to solve so that our methods can work smoothly in the real-world intensive care environment. The outcome will be a validated brain monitoring toolbox for neonatal intensive care, ready for immediate implementation in brain monitors. This project would suit students with a background in physics, maths, statistics, machine learning, engineering, or a related discipline, with some experience in programming (e.g. in MATLAB).

Clinical Brain Networks

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Studying whole-brain networks in health and disease

- Suitable for Honours and PhD.

The brain can be conceptualised as a complex network. Recent findings highlight that psychiatric disorders including obsessive-compulsive disorders and schizophrenia are associated to abnormalities in macroscopic brain networks. Our group focuses on modelling brain network dysfunctions in mental disorders with the goal of optimizing patients' diagnosis and prognosis. Moreover, knowledge regarding altered brain network structure and function is used to develop new therapeutic interventions. Projects focus on modelling brain networks in pathologies and assessing the impact that non-invasive brain stimulation may have on network activity, in health and disease. These projects would suit students with a background in neuroscience, physics, maths, or a related discipline that have some experience in programming (e.g. in MATLAB).

Cellular and Molecular Neurodegeneration Group

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Biometals including copper, zinc, and iron, have essential roles in many areas of brain function including energy metabolism, and synaptic signalling. During ageing and brain disease, regulation of biometals is dramatically affected. This leads to impairment of brain cell function, in both neurons and surrounding cell types (glia) and contributes to neuronal cell death in disorders such as Alzheimer's, Parkinson's and motor neuron diseases.

Our research investigates how biometal regulation is altered during ageing and neurodegenerative disease (Alzheimer's disease and other disorders). We study the proteins involved in mis-regulation of biometals, how changes to biometals affect inflammation in the brain, and how this can be modified by novel therapeutic approaches. Our research has led to a new compound that is entering clinical trials for motor neuron disease, and we are developing another copper compound with novel effects on brain inflammation as a potential treatment for Alzheimer's.

To facilitate this research we harness a range of exciting new approaches including development of a 3D Alzheimer's 'brain on a chip', X-ray imaging of biometals at the Australian Synchrotron, iPSC-derived brain cells in collaboration with A.I. Virtanen Institute in Finland, and advanced metalloproteomics in collaboration with the Florey Institute in Melbourne.

3D Alzheimer's disease 'brain on a chip'

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

Alzheimer's dementia is a rapidly growing health issue for Australia and worldwide with an expected 136 million cases by 2050. The disease is characterized by accumulation of amyloid peptide and phosphorylated tau microtubule protein in the brain, together with an abnormal inflammatory response and neuronal cell death in affected brain regions. However, there is still little understanding of how these processes occur and why they are age-dependent. One of the major problems with trying to understand the disease and develop treatments is that there are no ideal cell models to allow detailed molecular and cellular studies.

To overcome this, we are developing a 3D Alzheimer's disease 'brain on a chip' platform. We grow human neural stem cells and human brain

macrophages in 3D cultures on an OrganoPlateTM culture platform (Mimetas, leaders in 'organ on a chip' technology). The aim is to generate amyloid accumulation and tau phosphorylation together with a neuro-immune response in the cultures more closely modelling the human Alzheimer's brain (compared to 2D cultures of animal cells). These cultures can be used to understand how amyloid and tau accumulate, what role neuroinflammation has in the disease process, incorporation of patient cells, and enhance development of potential therapeutics that would normally only be examined in large scale animal studies.

Techniques will include neural stem cell and inflammatory cell culture, molecular studies (i.e. cell transfections), microscopy (confocal imaging) and protein analysis (western blot).

Copper as a major epigenetic regulator of Late Onset Alzheimer's Disease (LOAD) gene expression

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

Alzheimer's disease is the leading form of dementia and is a rapidly growing health issue internationally. While the hallmark pathological features of Alzheimer's have been well characterized, there is still little understanding of the disease mechanisms that drive accumulation of amyloid peptide and tau microtubule protein in Alzheimer patient brains. New genetic susceptibility factors for late-onset Alzheimer's disease (LOAD) have recently been uncovered in genome wide association studies (GWAS). Meta analysis of single nucleotide polymorphisms (SNPs) within 74,000 people (>23,000 AD cases), determined that SNPs in 20 loci were significantly associated with LOAD. Expression of a number of these genes (ABCA7, BIN1, CD33, CLU, CR1 and MS4A6A: with functions in amyloid peptide clearance, tau interactions, cholesterol and inflammation) is consistently altered in Alzheimer brains compared to cognitively normal individuals. It is unclear how LOAD risk gene expression is regulated in AD patients without SNPs in those loci.

Epigenetic changes are sequence-independent heritable traits acquired during an individual's lifetime in response to environmental stimuli. Epigenetic modifications include chemical marks on histone proteins that package DNA into chromatin. Specific histone marks (such as acetylation, methylation, ubiquitination) direct gene expression or silencing. Alterations to histone acetylation have been extensively reported in Alzheimer's and some LOAD risk genes can be regulated by epigenetic mechanisms. However, the environmental regulation of these epigenetic factors is not known. Large meta-analyses have now confirmed a loss of total brain copper in Alzheimer's, and additional studies have shown that copper is an important regulator of epigenetic changes. This project investigates whether changes to copper regulation control expression of LOAD risk genes for Alzheimer's through epigenetic modulation. This is being explored in neurons, glia, and animal models of neurodegeneration.

The project will involve the growth of human neural stem cell cultures and microglia cultures and treatment to elevate or decrease copper levels in cells. The effect of this on neuronal, astrocyte and microglial epigenetics will be assessed by examination of histone acetylation patterns. The effects on LOAD gene expression will be determined by qRT-PCR. The project will additionally explore copper regulation of these genes in animal models that have natural excess or deficiency of copper in the brain. The project involves cell culture, PCR, western blot, ELISA, microscopy, and additional assays.

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 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 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 from 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 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 development of real-time, individual therapeutic approaches with major clinical benefit, including identifying patient-specific drugs, selection of 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 have major which make 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 anesthetic 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 a 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 the stem cells. These are 'mini-brains' that represent the 3-dimensional structure of a small part of a human brain and allow a much more accurate understanding of how brain cells work (or fail to work) in dementia. This will enable us to understand how brain cells are affected by dementia differently for each patient (i.e. derived neurons will retain patient-specific epigenetic markers) and will allow the screening of potential therapeutic drugs on an individual basis.

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

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

- studies genetic variation
- identifies differences in gene expression levels observed in brain and non-brain tissues
- finds associations between

genetic risk and brain anatomy.

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

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

What causes overlap between mental health disorders?

- PhD project but may also be considered for a Honours project
- Dry lab/biostatistics project (not suitable for clinical students)

Background: Large overlap between mental health disorders is observed. For example, a patient diagnosed with autism is more likely to develop schizophrenia, and those who suffer from depression have a higher chance of developing alcohol dependence. Genetic factors may contribute to the observed overlap.

The study aims to:

1. describe patterns of overlap between mental health disorders using large samples
2. describe the impact of genetic risk factors
3. determine causal relationships between disorders.

Our approach is to:

- conduct statistical analyses using large databases of patients and controls
- apply sophisticated modelling techniques to describe causal relationships.

Student Profile: We are seeking a highly motivated student with a strong interest in statistics and quantitative studies.

What we offer: A position in a dynamic research environment and the opportunity to conduct high-quality studies. Access to large-scale data sets through national and international collaborations. Be part of a successful research team.

What makes one at risk for having a mental health disorder? Investigating the regulatory role of genetic variants

- PhD project but may also be considered for a Honours project.
- Dry lab/bioinformatics project (not suitable for clinical students).

Background: The risk of developing a mental health disorder, such as schizophrenia, depression, autism, or drug/alcohol addiction is to a large extent influenced by genetic factors. More effective interventions could be developed if we understood the biological mechanisms of a disease. Large-scale genetic studies have revealed regions in DNA that contribute to disease risk, but the biological role of these regions is not yet well understood.

The study aims to:

1. Describe the functional role of genetic risk loci for mental health disorders.
2. Identify functional targets for pharmacological interventions.

Approach: To conduct bioinformatics analyses to determine the impact of transcriptomic regulation (i.e., gene expression and epigenetic markers) on the development of mental health disorders. We aim to identify functionally relevant elements in regions of the DNA that have an impact on disease risk.

Student profile: We are seeking a highly motivated student with a strong interest in statistics, bio-informatics, and quantitative studies.

What we offer: We offer a position in a dynamic research environment and the opportunity to conduct high-quality studies. Access to large-scale data sets through national and international collaborations. Be part of a successful research team.

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