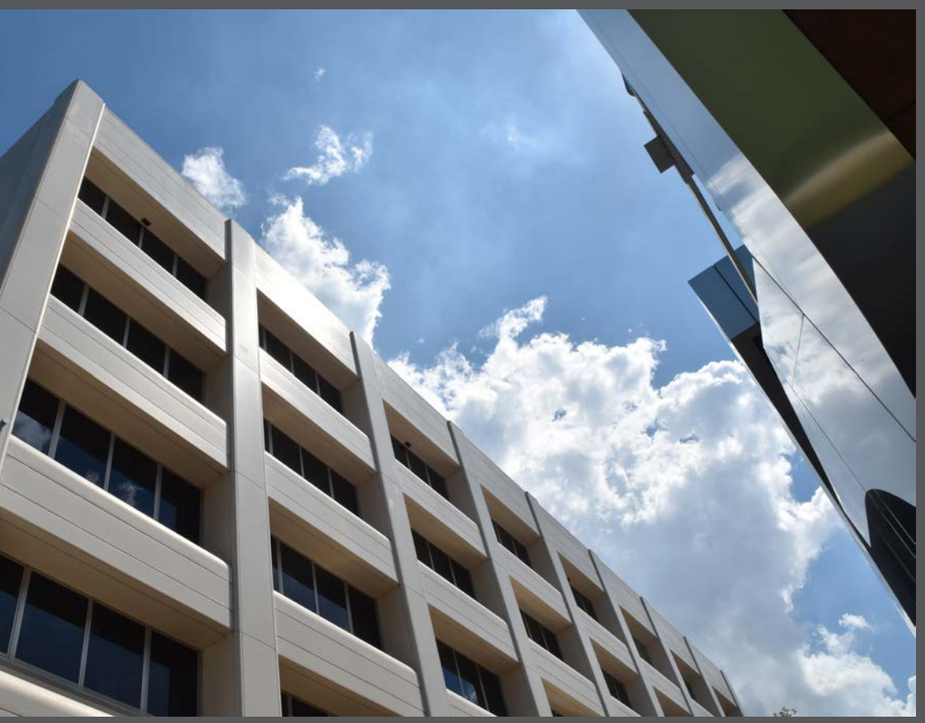
Centenary Institute

Honours, Masters and PhD Student Projects

The Centenary Institute is located in the Camperdown-Ultimo health precinct with the University of Sydney, The Charles Perkins Centre, Royal Prince Alfred Hospital and University of Technology Sydney as our neighbours.



Using this booklet
Projects listed are run through the following Disciplines at the University of Sydney or University of Technology Sydney.

— Discipline of Infectious Disease and Immunology, University of Sydney
— Discipline of Pathology, University of Sydney
— School of Medical Sciences, University of Sydney
— School of Life Sciences, University of Technology Sydney

The Centenary Institute could be your launching pad to a rewarding career in medical research!

As an independent and internationally recognised Medical Research Institute we offer a perfect balance of challenge, independence and opportunity in a supportive environment that will enable you to pursue a fulfilling career in medical research.

What we do
Discovery biology
Why
To master diseases
What makes us different
Others study problems we solve them
Our goal
Humanity without diseases

Key attractions

— World-leading researchers and clinicians
— State-of-the-art technology
— Track record of publications in high profile journals
— Career development and mentoring

Life at Centenary

We have a collegiate approach to student engagement and offer a number of initiatives to improve, encourage and support the education of our students and their time with us.

— Self-directed student and post-doc associations
— Mentoring program and events
— Supportive education office
— Inclusion and Gender Equity Committee open to all staff
— Social Committee

Projects

New therapies for treating corneal blindness

Theme
Cancer Innovations
Supervisor
Associate Professor Guy Lyons
Program/Laboratory
Cancer Progression
Suitable for
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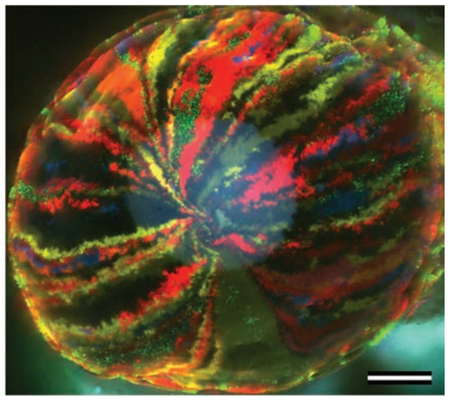
School
School of Medical Science
University of Sydney
Key words
Cell biology, computational biology, eye, image analysis, microscopy, stem cells, transplantation

Project overview

Our corneas are our windows to the world, and defects in the cornea account for 4 million cases of blindness worldwide. The outermost layer of cells, the corneal epithelium, has a protective role, and is continually replenished by stem cells located in the thin rim of tissue at the edge of the cornea, known as the limbus. These stem cells can be damaged by UV radiation, chemical splashes, physical trauma and pathogens, causing stem cell deficiency.

This interdisciplinary project uses microscopic imaging of living corneal cells to identify the mechanisms by which the corneal epithelium responds to damage, and to develop new therapies for transplanting stem cells onto damaged eyes. This is complemented by a computational model of the corneal epithelium which enables us to simulate the effects of endogenous and environmental influences on epithelial cell dynamics.

Computer simulation (left) and fluorescence image of the corneal epithelium of a lineage-tracking mouse strain (right).
Images: Erwin Lobo, Naomi Delic



The evolution of cancer cell clones

Theme
Cancer Innovations
Supervisor
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Program/Laboratory
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School
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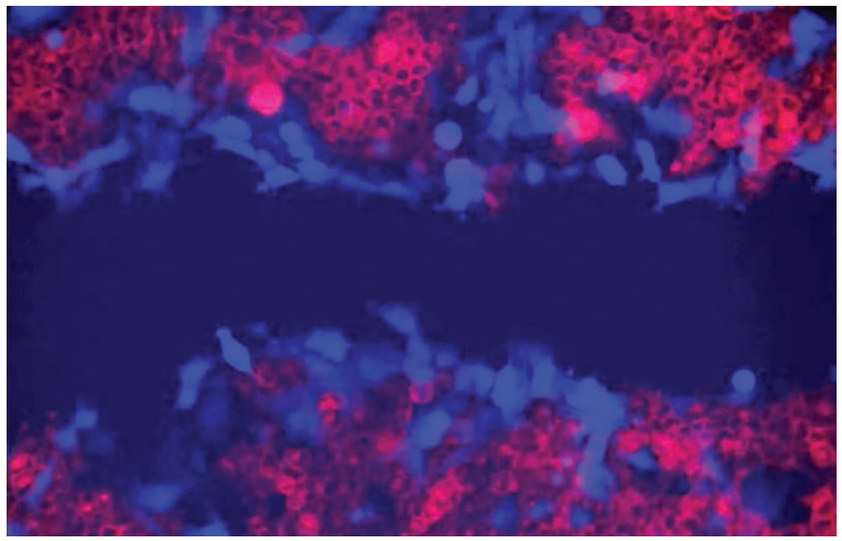
Key words
Cancer, cell biology, computational biology, CRISPR, epithelial-mesenchymal transition, evolution, gene editing, image analysis, metastasis, microscopy, molecular biology

Project overview

Cancers are caused by mutations in key regulatory genes that promote tumour growth and dissemination. Most tumours are multiclonal, being comprised of cells that have different mutations from other cells within the tumour. It is known that a high level of this genetic heterogeneity predicts poor patient outcomes, but the reason is not known. One possible reason is that different clones within a tumour have complementary mutations that enable them to behave more malignantly when they are together than when they are present as individual clones.

This project investigates the role of symbiotic interactions between clones of cells in driving tumour progression. It uses live cell microscopy, molecular analyses and gene editing to identify what types of genes can interact in different individual cells. Computer simulations are used to predict the effects of these cell-cell interactions on the population of cells as a whole, and how they affect the clonal evolution of the cells.

Two oral cancer clones expressing different oncogenes, tagged with red or blue fluorescent proteins, interacting to increase motility and growth. Image: Paul Sou



Why are men more likely to die from cancer compared to women? A case for the X chromosome.

Theme
Cancer Innovations
Supervisor
Dr Jessamy Tiffen, Dr Cindy Tseng and Dr Sara Alavi
Program/Laboratory
Epigenetics of Melanoma Program
Suitable for
PhD, Honours, Masters
Projects will be tailored to suit individual students accordingly

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School
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Key words
Melanoma, Cancer, Epigenetics, biological sex differences, Immunotherapy, targeted therapy, treatment resistance

Project overview

Background: Men are more than twice as likely to die from melanoma compared to women. Although several explanations have been suggested for this phenomenon, the puzzle remains incomplete. This project proposes that differences in genes located on sex chromosome may explain differences in the ability to combat cancer between males and females. To equalise the number of genes between sexes, one of the X chromosome gene copies in females undergoes inactivation. However, between 10 and 20% of X-linked genes 'escape' from inactivation, effectively doubling their expression in females compared to males, in a tissue specific manner.

The Project: The project builds on our extensive preliminary data that have identified new X-linked epigenetic regulators that escape inactivation and are more highly expressed in women compared to men. Many are involved in immune responses but the precise mechanisms of how they may protect females against infections and cancer remain a mystery. The successful candidate will explore how gain or loss in the expression of genes encoding these regulators in melanoma cells may lead to worse disease in males compared to females.

Role of portal tract myeloid cells in human liver diseases

Theme
Infectious Diseases and Immunity
Supervisor
Associate Professor Patrick Bertolino and Associate Professor David Bowen
Program/Laboratory
Liver Immunology Program
Suitable for
PhD, Honours or Masters

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Key words
Liver, T cells, tolerance immunity, portal tracts, macrophages, dendritic cells

Project overview

The liver has paradoxical immune properties: while it is known for its ability to induce antigen-specific immune tolerance, there are many examples of effective immune responses in this organ. While the liver's tolerogenic properties have been the focus of many studies and are relatively well characterised, pathways leading to intrahepatic immunity are poorly understood. Our recent studies in mice have revealed that liver resident myeloid cells (dendritic cells and macrophages) play a critical role in this response as they serve to amplify the initial CD8 T cell response generated in lymphoid tissues. These liver myeloid cells are mostly detected in portal tracts, structure within the liver that enclose afferent blood vessels of the liver as well as bile ducts and lymphatic vessels. These structures form a distinctive network in the liver tissue where leucocytes infiltrating the liver accumulate in inflammation and infection. These findings suggest that portal tracts represent a lymphoid compartment within the liver specialised in promoting effective immunity.

This project aims to characterise the myeloid cells detected in the portal tracts in human liver at steady state and in various liver diseases in order to assess whether disease pathogenesis is associated with specific myeloid cells types.

Methodologies used for the project: Flow cytometry, immunostaining of liver sections, confocal fluorescent microscopy imaging and image analysis.

Project 1

Irresistible therapies to eliminate intracellular pathogens

Project 2

Training Neutrophils to strategically use their weaponry

Theme
Infectious Diseases and Immunity
Supervisor
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School
School of Medical Sciences, University of Sydney

Key words
Hepatitis B virus, HIV, HTLV-1, Mycobacterium tuberculosis, inflammatory diseases, host-pathogen interactions

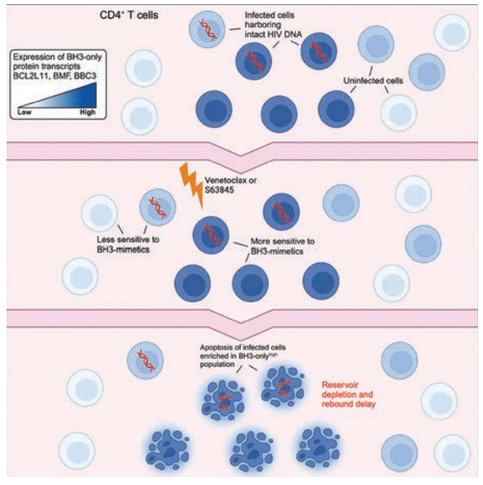
Project overview

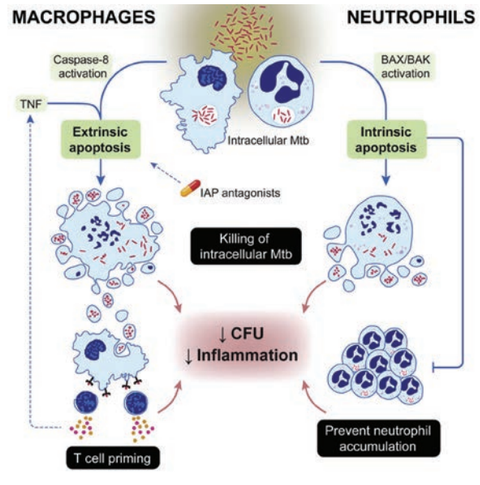
The Pellegrini lab is focused on making key discoveries around host-pathogen interactions that will inform the creation of novel antimicrobial therapies to combat resistant pathogens.

Based on several publications (Cell Rep Medicine 2023 August https://doi.org/10.1016/j.xcrm.2023.101178, Immunity 2021 54:1758 and Gastroenterology 2022 163:1643) we will continue to develop compounds and drug candidates that preferentially kill infected human cells as a mechanism to eliminate chronic intracellular organisms such as hepatitis B virus, HIV, HTLV-1, *Mycobacterium tuberculosis* and other bacterial intracellular organisms. Additionally, we are examining mechanisms of taming neutrophils. These cells are critical for human health, you can't survive without them, but they can also be responsible for many life-threatening inflammatory diseases.

Two projects are available for potential PhD and Postdocs:

1. Examining the efficacy of pro-apoptotic promoters in eliminating intracellular infections
2. Understanding the molecular pathways responsible for neutrophil degranulation and netosis.





Novel drugs for multi-drug resistant Tuberculosis

Theme
Infectious Diseases and Immunity
Supervisor
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Tuberculosis Research Program
Suitable for
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School
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Key words
Tuberculosis, molecular microbiology, cellular immunology, stem cell biology, confocal microscopy, experimental M. tuberculosis infection

Project overview

Tuberculosis continues to be the commonest cause of death from a single pathogen globally, with over 1.5 million deaths and 10 million new cases each year. The development and spread of multi-drug resistant MDR and extensively strains of *M. tuberculosis* contributes to this global epidemic. In collaboration with Professor Richard Payne (School of Chemistry) we are developing and testing new compounds as drug leads to address this problem. After *Mycobacterium tuberculosis* infects alveolar macrophages in the human lung, the mycobacteria enter a phase of "dormancy" or low replicative state characterised by a defined "dormancy" transcriptional pattern and metabolic adjustment to different nutrients. The infected macrophages are surrounded by lymphocytes to form granulomas that may limit access of antimicrobials to the bacilli. New in vitro assays are required that more accurately reflect this phase of mycobacterial growth to determine if the drug leads will be active against dormant mycobacteria in human lungs.

This PhD student project will develop and use new assays to examine the effectiveness of novel drug leads against drug-sensitive and drug-resistant isolates of *M. tuberculosis.* These include:

1. In vitro human granulomas to test the capacity of drugs to penetrate the granulomas to kill the intracellular mycobacteria;
2. Metabolic culture conditions that reflect intracellular infection in the lung with chemiluminescent *M. tuberculosis;*
3. Time-to-kill assays to test the ability of drug leads to prevent drug tolerance.
4. Human lung organoids that will be an important platform for drug testing..

The activity in these assays will be compared with the effectiveness of known and experimental drug leads against *M. tuberculosis* in an murine model of infection.

Opportunities: The project will provide extensive training in molecular microbiology, cellular immunology, stem cell biology, confocal microscopy, and experimental *M. tuberculosis* infection. The student will be part of a collaborative network across the Centenary Institute and the University of Sydney.

New TB vaccines to control the global TB epidemic

Theme
Infectious Diseases and Immunity
Supervisor
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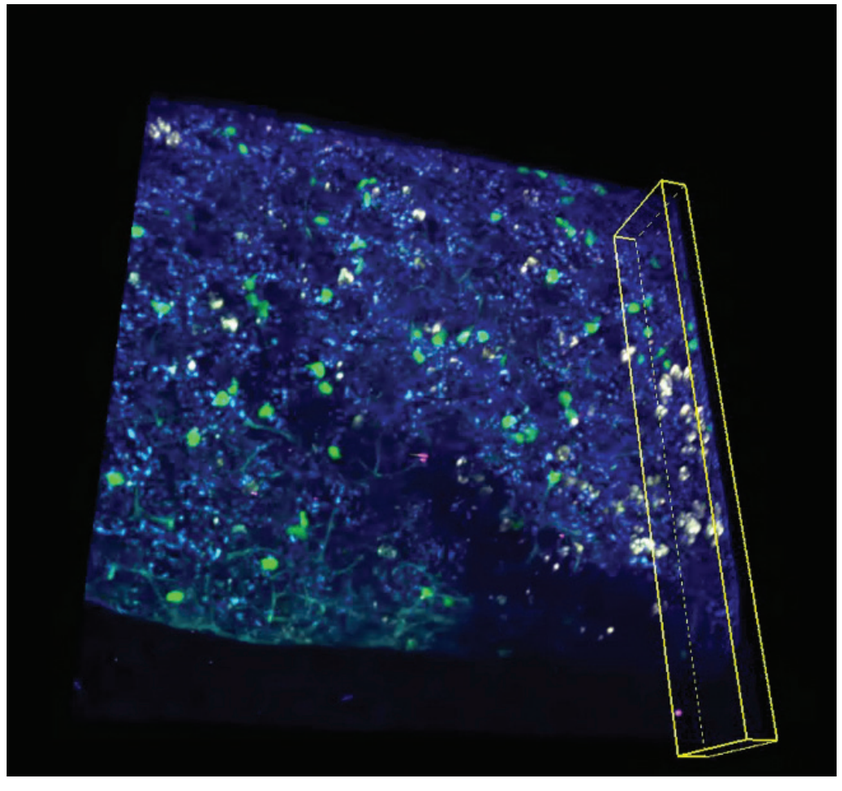
Key words
Tuberculosis, vaccines, cellular immunology, flow cytometry and cytokine assays, scRNAseq technology, bioinformatics, experimental infection

Project overview

Tuberculosis continues to be the commonest cause of death from a single pathogen globally, with over 1.5 million deaths and 10 million new cases each year. The current BCG vaccine partially protects young children against severe forms of TB, but it is less effective in adolescents and adults. Therefore, new vaccines are urgently needed that prevent the infectious form of pulmonary TB disease and to boost BCG-induced immunity. The WHO Stop TB Program recognises that more effective TB vaccines are essential to reduce transmission. The "Advancing Vaccine Adjuvant Research for Tuberculosis" program has been funded by the US National Institute of Health at the Centenary Institute and the University of Sydney to evaluate the effectiveness of novel adjuvants in combination with *Mycobacterium tuberculosis* protein antigens to protect against pulmonary TB.

This PhD student project will examine the ability of one of these adjuvants to stimulate early and diverse cellular immune responses that lead to long-term T cell memory and protection against aerosol infection with *M. tuberculosis* in a preclinical model. The early transcriptional responses induced by the adjuvant/protein combinations will be examined with single cell RNA sequencing technology.



Opportunities: The project will provide extensive training in cellular immunology, including advanced flow cytometry and cytokine assays, scRNAseq technology and bioinformatics, and experimental infection. The student will be part of an international network of scientists who are contributing to this important program for global health.

Image shows:
Pulmonary delivery of rIAV-TB vaccine induces GFP+ tissue resident memory CD4 T cells in the lungs.

Detection of GFP-p25 CD4 T cells by 2-photon microscopy. Flórido M, et al, Mucosal Immunology 2019

Project 1

Early identification of patients at-risk of cirrhosis and preventing chronic liver disease progression based on personalised risk

Project 2

Developing a novel nanoparticle system targeting lipid for drug delivery in fatty liver disease in zebrafish models

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Theme
Healthy Ageing
Supervisor
Clinical Professor Devanshi Seth
Program/Laboratory
Alcoholic Liver Disease Research Program
Techniques
CRISPR-Cas9, lipidomics (MS), Confocal-live imaging, Molecular genetics, genomics
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Key words
Alcohol, Liver Cirrhosis, Lipotoxicity, Lipid droplet biology, Genetics, Nanoparticle, Drug, delivery, Zebrafish models, Disease modelling, Adult human induced pluripotent stem cells, (iPSCs), Clinical translation, Personalised medicine

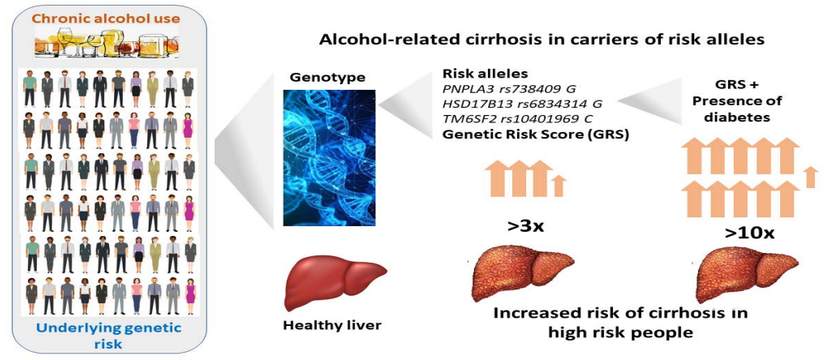
Project overview

Risky drinking continues to be a major ongoing concern in Australia. As 90% of alcohol is metabolised through the liver, those with drinking problems are at greater risk of developing alcohol-induced liver disease/cirrhosis (ALD/ALC). But who amongst the drinkers are at a greater risk of developing cirrhosis is unknown. Our multinational GenomALC Consortium recently developed a novel algorithm based on individualised genetic and clinical (diabetes) risks of patients to predict cirrhosis risk (J Hepatol 2022; Hepatol 2021; Am J Gastroenterol 2020).

We also reported world's largest meta-genome wide association study (GWAS) in ALC discovered novel (FAF2, SERPINA-1) and previously (PNPLA3, HSD17B13, TM6SF2) identified genetic risk factors (Hepatol 2021). Majority of these genes are involved in lipid biology, making lipids the genetic nexus of fatty liver, and are shared between ALD and non-alcoholic fatty liver diseases (NAFLD). To study mechanisms linking genetic susceptibility to lipotoxicity we have developed novel zebrafish genetic models of fatty liver showing increased hepatic triglyceride and inflammation (bioRxiv 2023).

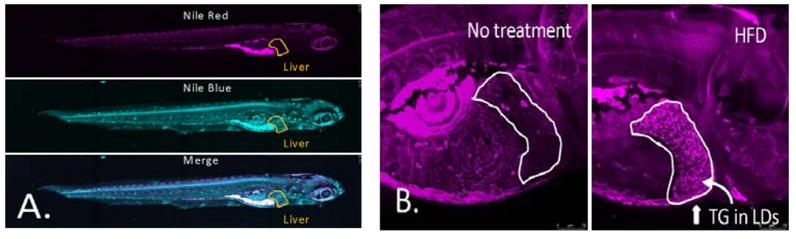
Project 1

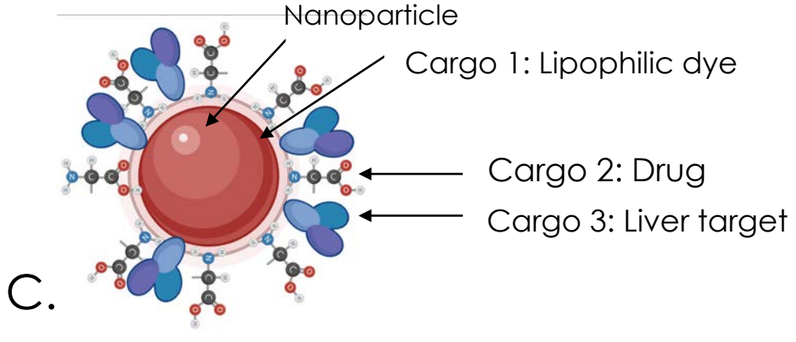
Utilizing our algorithm to identify early drinkers at-risk of cirrhosis in real life diverse populations, and providing interventions based on personalised risks to prevent progression of cirrhosis. Outcome: This world-first trial will change the treatment paradigm through personalised medicine for alcoholic liver disease patients.



Project 2

This interdisciplinary project combines nanotechnology, genetics, cell biology, dietary drugs and zebrafish disease models to study the roles of lipid droplet genes in disease progression and targeting them through drugs directed to liver specific cells. Outcome: IP generation for novel liver specific drug delivery system using nanoparticles. Live imaging with lipophilic dyes showing triglyceride (pink-Nile red) and fatty acids (turquoise-Nile blue) in zebrafish larvae (A) and increased triglyceride in CRISPR-Cas9 knockdown risk gene pnpla3 larvae hepatic lipid droplets (LDs) exposed to high fat diet (HFD) (B). Strategy to create liver targeting nanoparticle drug delivery system (C).





Novel targets and therapeutics for Alzheimer's Disease

Theme
Healthy Ageing
Supervisor
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Program/Laboratory
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School
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Key words
Alzheimer's disease, ageing, vascular, endothelial cells, dementia

Project overview

Alzheimer's disease is now considered a vascular disease, where breakdown of the blood brain barrier is an early step in the development of pathology. The vessels become fragile, they leak and microbleeds start being visible.

The project is focused on understanding the early events in the breakdown of the vascular barrier, how this may lead to deposition of amyloid in the brain and vessel wall and exposing new targets for the development of therapeutics which mend the damaged blood vessels.

It involves cell and molecular biology, high resolution imaging, animal models of disease, and proteomic analysis of human brain tissue.

Enhancing heart regeneration to treat cardiomyopathies

Theme
Biomedical AI
Supervisor
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Directed Evolution
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School
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Key words
Heart regeneration, directed evolution, AI, biological therapeutics

Project overview

The hallmark of many types of heart disease is an insufficiency of functional heart muscle cells or cardiomyocytes (CMs). These disorders, known as cardiomyopathies, lead to heart failure with a 5-year survival ≤50% (worse than all but one form of cancer), and currently there are no therapies to directly improve contractile function. Cardiomyopathies, therefore, represent an urgent unmet clinical need for innovative treatments to directly address the underlying pathophysiology by regenerating CMs and, thereby, to improve outcomes, wellbeing and survival. This project will increase the potency and specificity of a therapeutic approach that involves administration of a core cardiomyogenic transcriptional regulator, Krüppel-like factor-1 (KLF1). We will achieve this using PROTEUS, a world-leading platform for the evolution of human KLF1 developed by the Directed Evolution laboratory. Computational projects are also available that will use deep sequencing data to train AI models that aim to predict KLF1 "supervariants". The work in this area is evidence-based and has the potential to lead to simple, implementable therapies for treating cardiomyopathies.

Improving cancer patient outcomes through liquid biopsy, organoids and CAR-T cell therapy

Theme
Rare Diseases and Gene Therapy
Supervisor
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Dr Dannel Yeo
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Li Ka Shing Cell and Gene Therapy,
Gene and Stem Cell Therapy Program
Suitable for
PhD, Honours, Masters

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School
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Key words
Cancer, Liquid Biopsy, Organoids,
Cellular Immunotherapy, CAR-T cells

Project overview

Our laboratory aims to improve low surviving cancers (pancreatic cancer, small cell lung cancer, mesothelioma, appendiceal cancer, and liver cancer) through a personalised approach using liquid biopsy (circulating tumour cells) and patient-derived organoids (3D culture models). We utilize next generation liquid biopsy technology to detect and isolate rare cancer cells in the blood as a diagnostic and prognostic biomarker. Through single-cell characterisation, we can obtain molecular insights in a non-invasive manner. We also explore novel therapies such as targeted therapy and CAR-T cellular immunotherapy to target cancer vulnerabilities and obtain cures. We work closely with our clinical collaborators at Royal Prince Alfred Hospital and Chris O'Brien Lifehouse to ensure our findings have the best possible outcomes for cancer patients. Our translational research projects can be tailored to suit Honours, Masters or PhD degrees.

Modulating host entry factors to improve AAV-mediated gene therapy

Theme
Rare Diseases and Gene Therapy
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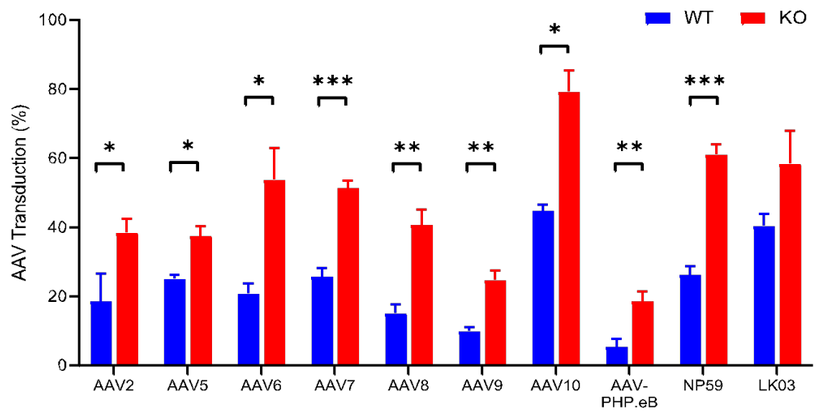
Key words
Gene therapy, adeno-associated virus, receptor, host factor

Project overview

Adeno-associated virus (AAV) is widely used as a gene therapy vector due to its tissue-tropism and safety profile. A growing number of AAV-based therapies are being approved for treatment of rare diseases; however, high doses are required in many cases. Improved transduction efficiency of AAV vectors has been achieved by engineering capsids with higher affinity, cell specificity and increased resistance to neutralising antibodies. Increasing AAV-mediated therapeutic efficacy by modulating host entry factors remains unexplored. KIAA0319L (aka AAV receptor (AAVR)) is an essential host entry factor for most AAV serotypes. We have identified other host factors that also regulate AAV uptake via AAVR trafficking. One such factor is WDR11, a protein involved in vesicle tethering during endosomal to Golgi trafficking. Genetic knockout of WDR11 increases AAVR surface expression leading to increased AAV transduction. Molecular genetic and cell biological techniques will be used to examine AAV uptake when expression of WDR11 and other host factors are modulated.

Figure 1 WDR11 knockout in eHAP cells increases transduction of many AAV serotypes



CTCF dysregulation and loss of cell polarity in epithelial cancers

Theme
Rare Diseases and Gene Therapy
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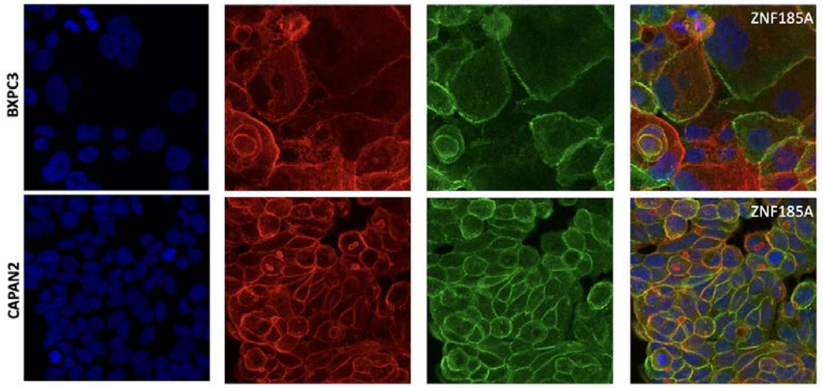
School
School of Medical Science
University of Sydney
Key words
Endometrial cancer, pancreatic cancer, tumour suppressor, transcriptional regulation, metastasis, mutation

Project overview

DNA binding by the tumour suppressor protein CTCF, an essential regulator of transcription and chromatin architecture, can be disrupted by somatic mutation leading to gene dysregulation. In epithelial cancers this can lead to loss of cell polarity, invasion and metastasis. During CTCF mutation or depletion, expression of the X-linked gene ZNF185 is upregulated. Upregulation of ZNF185 expression is a marker of poor prognosis in both pancreatic and endometrial cancers. Overexpression of ZNF185, a cytoskeletal remodeling protein, disrupts cell polarity via its interaction with the actin cytoskeleton This project will examine the impact of ZNF185 expression on cancer cell growth, invasion and chemoresistance in 3D organoid or spheroid cultures, as well as orthotopic xenograft models of pancreatic tumour growth in vivo. Further, ZNF185 interaction and co-localisation with key cytoskeletal binding partners will be determined. The expected outcomes of this project will be to develop novel therapeutic approaches for epithelial cancers by exploiting newly discovered cell vulnerabilities.

Techniques: Cell culture, Western blotting, lentiviral-mediated shRNA KD and overexpression, recombinant protein production, CoIP, mass spectrometry, flow cytometry, confocal microscopy, spheroid cultures, xenograft mouse models

Figure 1 ZNF185 plasma membrane expression observed in pancreatic cancer cell lines



Cardiovascular research at Centenary

At Centenary our world-recognised scientists are focusing their cardiovascular research on mechanisms that cause strokes and heart attacks. As well as the genes that are associated with causing sudden death in young people. We are working on new drugs that improve vascular treatments and outcomes in a number of blood vessel related diseases. Developing a clinical approach that better serves the community.

Agnes Ginges Centre for Molecular Cardiology

The Centre's research is focused on understanding the clinical and genetic basis of inherited heart disease. The team use a range of approaches including human gene discovery studies, basic cellular systems, animal models of human disease, and population-based psychosocial and public health studies.

The research involves state-of-the-art approaches including whole exome sequencing, mRNA and microRNA profiling, and RNASeq. Most importantly, the Centre has the key clinical resources, including well phenotyped individual patients and families, which form the basis of all our genetic studies.

Contact Professor Chris Semsarian AM on email c.semsarian@centenary.org.au for further information about student opportunities.

Bioinformatics and Molecular Genetics Laboratory

Our ability to read DNA sequence has far exceeded our ability to identify genetic variants which cause inherited diseases. To address this shortcoming, the Bioinformatics and Molecular Genetics Group develop new computer-based approaches and laboratory-based methods to identify and characterise disease-causing genetic variants, with a current focus on inherited heart diseases and sudden cardiac death in young people.

Contact Dr Richard Bagnall on email r.bagnall@centenary.org.au for further information about student opportunities.

Lipid Cell Biology Laboratory

Atherosclerosis is a chronic condition in which arteries harden and narrow due to a build-up of fatty plaque on the arterial wall. Although the use of blood cholesterol-lowering medications can be successful in halting or reducing this plaque build-up, atherosclerosis remains the leading cause of cardiovascular disease-related death worldwide. The Lipid Cell Biology Laboratory is studying how fat products within blood vessel cells affect vascular fitness and disease progression.

Contact Dr Jacob Qi on email j.qi@centenary.org.au for further information about student opportunities.

Inflammation research at Centenary

The Centenary Institute is dedicated to studying the mechanisms underlying inflammation, to understand how specific diseases develop and progress and can be treated. We consider that understanding inflammation is the key to unlocking a new armoury of treatments and cures for many of the deadliest and prominent diseases effecting humanity.

Centenary UTS Centre for Inflammation

Inflammation is increasingly being found to play crucial roles in the development of many major diseases, including Alzheimer's, heart disease, cancer, respiratory diseases, diabetes, tuberculosis and COVID-19.

The Centenary UTS Centre for Inflammation (CFI) is Australia's first research centre dedicated exclusively to studying the mechanisms underlying inflammation, to understand how specific diseases develop and progress and can be treated.

The Centenary UTS Centre for Inflammation brings together world-leading experts in a partnership between one of Australia's foremost medical research institutes and the country's top-rated young university. The Centre collaborates with a global network of other pioneering inflammation researchers, including at the universities of Manchester, Edinburgh and London in the United Kingdom, as well as other research institutes and universities (IMB/UQ, Hudson MRI, WEHI) and industry across Australia and globally.

In particular, the Centre focusses on respiratory diseases driven by inflammation which are among the leading causes of all deaths worldwide. The team are focussing on COPD, severe asthma, influenza, COVID-19, pulmonary fibrosis and lung cancer. In these diseases chronic or excessive inflammation results in tissue damage and current therapies are ineffective. The research has also expanded into other disease areas including cystic fibrosis, Mycobacteria and other infections and non-respiratory diseases (eg. gut, cardiovascular, brain, kidney, liver).

Contact Sarah Mulvey on email s.mulvey@centenary.org.au for further information about student opportunities.

Key Centenary contacts who can help you

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Enquiries regarding:
— Advice on applying for scholarships, awards and grants
— Advice on dealing with the USYD/UTS administration
— General advice on careers in academic and non-academic roles

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— Employment opportunities
— Recruitment
— Position descriptions
— Terms and conditions of employment

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Enquiries regarding:
— Student Association events and membership
— Student Life

Elinor Hortle
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Enquiries regarding:
— Post-doc Association events and membership
— Life at Centenary

Where to find us

But the easiest way to find us is
Follow Johns Hopkins Drive, off Missenden past RPA and we are at the end of the road. Or walk through the University of Sydney and we are next to the Charles Perkins Centre.

Centenary Institute