This booklet contains the projects that will be supervised at Centenary Institute in 2021.

If you have any questions of a general nature, please contact our Student Recruitment Officer.

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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
At the Centenary Institute, researchers are bringing renewed health and hope to Australians and people around the world.

We are home to world-leading researchers in cancer, inflammation and cardiovascular disease.

As an independent and internationally recognised Medical Research Institute the Centenary Institute has state-of-the-art facilities and researchers at the top of their field. Centenary offers a perfect balance of challenge and support that will enable you to expand your skills and knowledge as you consider your future in science.

Notably the Centenary Institute has a long history of helping students graduate with 1st Class Honours, an extensive PhD program and Post-doctorate opportunities for those who wish to further develop their research skills.

Location
There are other benefits to joining Centenary and the first is location. We are located in the heart of the Camperdown-Ultimo health and education precinct - consisting of an active and geographically condensed hub of research, teaching, training and industry organisations specialising in medicine and healthcare.

Campus life is close at hand with our building on the border of the University of Sydney and next door to the Charles Perkins Centre, a multidisciplinary research centre committed to improving global health outcomes.

At Centenary you will be at the centre of the latest and most-up-to-date medical research taking place in Australia, our geography facilitating potential linkages and collaboration opportunities - plus you’ll be close to all of the advantages that University life has to offer.

Affiliation
Centenary is also closely affiliated with the Royal Prince Alfred Hospital, the University of Sydney and University of Technology Sydney. Many of our researchers are specialist clinicians at the hospital and lecturers at the Universities.

This provides Centenary students and post-doctorates with a ready-made network of some of the brightest minds in basic, applied and clinical medical research.

At Centenary we know that connection and collaboration is key - both to success in the present and to a successful future too. Benefit from the knowledge, the contacts and the professional expertise that our leading researchers can provide.

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.

Education Committee
The Education Committee’s general purpose is to provide advice on the education strategy for the Institute. It also plans, coordinates and implements activities that assist in the continuing education and development of Centenary researchers and support staff.

The Education Committee coordinates the regular seminar series within the Institute, develops and delivers public lectures and also helps organise Colloquia and Symposiums.

Inclusion and Gender Equity Program
Our Inclusion and Gender Equity Program provides a forum for staff to raise and discuss issues relating to inclusion and gender equity and champions initiatives that will help support and progress equity at Centenary.

Student Committee
The Student Committee advises on student related issues, coordinates events and engages with supervisors and potential students to promote student opportunities and recruitment at Centenary.

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Facilities
At Centenary you will be able to access state-of-the-art research equipment. Hands-on as well as theory training is provided to all Honours, Masters and PhD students by experienced facility staff.

Flow Cytometry
Our many BD Analysers allow you to take quantitative measurements of thousands of individual cells or particles. The 10-Laser LSR can even differentiate up to 20 different parameters within a single cell, which is something only very few labs in the world are able to do. We also have the CyTOF which is a mass cytometer - the first instrument of its kind in Australia.

Imaging Cytometry
The advantage of using the Imaging Cytometry is to analyse a large amount of cells (high throughout) in a consistent and unbiased manner. The AMNIS ImageStream X Mk2 allows many hundreds of cell images to be captured per second.

Microscopy
Our imaging systems include the Leica SP8 Confocal, the LAS Matrix Screener software and a water immersion pump allow for high content screening even when performing long-term live cell imaging. The other imaging systems are equipped with high precision stages, high quality objectives, and some are equipped with cameras.

Intravital Microscopy
Our most advanced microscopes available are three LaVision Biotech multi-photon imaging stations that can be used for deep tissue imaging in vitro or in vivo. These systems are the only ones in Australia that can utilise up to three different femto-second laser sources.

Software
For the analysis of flow cytometry data, we provide access to the FlowJo Single Cell Analysis Software. Images are used to analyse and observations quantified in order to generate meaningful outcomes. We provide access to a wide range of Image Analysis softwares.

Animal House
The Animal Facility is responsible for providing quality animals for research. Comprised of highly skilled staff who perform routine husbandry and welfare checks, as well as procedures training and researcher service requests.

Zebrafish Facility
Our 100 tank zebrafish facility is stocked with a range of transgenic and mutant zebrafish concentrated on the investigation of inflammation and vascular biology.
**MEET OUR RESEARCHERS**

### Research Laboratories

- **Dr Richard Bagnall**
  Head - Bioinformatics and Molecular Genetics Laboratory

- **Dr David Bowen**
  Joint Head - Liver Immunology Program

- **Associate Professor Anthony Don**
  Head - Lipid Metabolism and Neurochemistry Laboratory

- **Dr Daniel Hesselson**
  Head - Directed Evolution Laboratory

- **Dr Stefan Oehlers**
  Head - Immune-vascular Interactions Laboratory

- **Dr Mainthan Palendira**
  Head - Human Viral and Cancer Immunology Laboratory

- **Dr Yanfei (Jacob) Qi**
  Head - Lipid Cell Biology Laboratory

- **Dr Ulf Schmitz**
  Head - Computational BioMedicine Laboratory

- **Clinical Associate Professor Devanshi Seth**
  Head - Alcoholic Liver Disease Laboratory

- **Dr Xiangjian Zheng**
  Head - Cell Signalling Laboratory

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### Project Supervisors

- **Dr Chuck Bailey**
  Gene and Stem Cell Therapy Program

- **Associate Professor Patrick Bertolino and Associate Professor David Bowen**
  Liver Immunology Program

**Chuck Bailey** trained as a molecular and cellular biologist and has nearly 20 years experience in studying molecular mechanisms of normal biology, genetic disease and cancer. In 2001 he joined the Gene and Stem Cell Therapy Program headed by Professor John Rasko at the Centenary Institute studying the molecular genetics of human amino acid transporter disorders. His work lead to the discovery of the genetic causes of 3-of-5 principal inherited amino acid transport disorders in humans.

He was appointed as a Senior Research Fellow in 2007 and now leads a group within the Program in studying the role of transcription factors in cancer causation. By understanding fundamental gene regulatory mechanisms in normal biology, he is applying this knowledge to elucidating aberrant transcription factor function in cancer.

Dr Bailey uses the latest molecular, cellular, genetic and proteomic techniques in his research. Recently, he is applying this approach to improve the gene therapy efficiency of adeno-associated viral vectors. He is examining the pathway of AAV uptake into the cell to identify host entry factors that may participate in this process.

**Patrick Bertolino** is considered one of the leading experts in Liver Immunology internationally, and is acknowledged as the leader in this field in Australia.

He has worked in the same field for the last 20 years in internationally recognised research institutes, and has been trained by first class immunologists. During this time, he has developed unique transgenic mouse models and has acquired a leading reputation in liver immunology.

This reputation derives from original landmark papers that have transformed the field, and are now part of current paradigms. These include the first demonstration of naïve CD8 T cell activation in the liver, the first evidence of direct interaction between circulating T cells and hepatocytes, the role of intrahepatic T cell activation in tolerance, and the discovery that liver-activated T cells are deleted in the lysosomes of hepatocytes.

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Visit our website to learn more about our Laboratories and staff – [www.centenary.org.au/our-researchers](http://www.centenary.org.au/our-researchers)
David Bowen is a Gastroenterologist and Hepatologist at the AWM Morrow Gastroenterology and Liver Centre and the Australian National Liver Transplantation Unit, RPAH, and the Head of the MD Research Program at Sydney Medical School.

His research program is helping to improve our understanding of the liver and its impact on immune responses, both wanted and unwanted. Although the liver’s tolerogenic effects are beneficial in transplantation, they can be detrimental during infections such as hepatitis B, hepatitis C and malaria. These diseases can use the liver as a means of persisting, which can often lead to chronic infection.

Dr Bowen’s work is also providing some important clues to improve the success of human gene therapy and improve outcomes in liver transplantation. Having already shown that the liver, like the lymph nodes, can activate T cells, a key cell of the immune system, he is now investigating how the liver induces immune tolerance and how immunity can be enhanced in this organ.

David Bowen additional roles

Associate Professor Medicine, Central Clinical School, University of Sydney and Head MD Research Program, Sydney Medical School.

Warwick Britton is Emeritus Professor of Medicine at the University of Sydney, head of the Tuberculosis Research Program at the Centenary Institute, and Research Director for Sydney Local Health District and RPAH.

He has longstanding research in the immunology of mycobacterial infections and the control of tuberculosis and leprosy, including the development of novel protective vaccines and drugs against TB. He is principal investigator on the NHMRC-funded Centre for Research Excellence in Tuberculosis Control on both sides of the border that promotes TB research and collaborations, training and translation within Australia and the Asia-Pacific, including Vietnam, Indonesia and Papua New Guinea. He is involved in ongoing research in Vietnam and a new MRFF funded project to control drug resistant and latent TB in the Pacific (PEARL).

Professor Britton has received continuous research funding from the National Health and Medical Research Council of Australia since 1991 and has published 289 papers with >15,000 citations. He has supervised and co-supervised 27 PhD, 2 Masters and 30 Honours research students and mentored 24 post-doctoral scientists on his laboratory.

Warwick Britton additional roles

Research Director, Sydney Local Health District

Emeritus Professor of Medicine, Central Clinical School, University of Sydney

Peter Choi is an emerging researcher in the field of cardiovascular research. He received his PhD from the University of Sydney in 2016 and joined UTS in 2020 with Chancellor’s Postdoctoral Research Fellowship. His research focuses on identifying therapeutic targets for the commonest stroke in children: Cerebral Cavernous Malformation (CCM).

His recent work includes development of a novel micro-CT imaging, identified the gut microbiome as a critical stimulant of CCM and repurposed an-FDA approved drug to treat experimental CCM.

Mat Francois, heads the David Richmond Laboratory for Cardiovascular Development: Gene Regulation and Editing at the Centenary Institute. He leads a research team with a focus on identifying new and innovative therapeutic approaches targeting vascular diseases.

The research activity of the laboratory focuses on the transcriptional control of endothelial cell specification during vascular development in different organs (heart, skin) during embryogenesis and also during cancer metastasis.

The group is developing a novel approach combining developmental genetics (mouse and fish model system), biochemistry, genomics and biophysics (molecular imaging using super resolution microscopy) to understand and target transcription factors mode of action with small molecule inhibitors. One direct outcome of the current research activity is the discovery and development of a new class of anti-angiogenic drugs.
Jennifer Gamble is an internationally recognised research leader in the field of endothelial cell function. She holds the Inaugural Wenkart Chair of the Endothelium and leads the Vascular Biology Program.

Her interests lie in understanding endothelial cell function particularly in the area of inflammation and how dysfunction can influence disease. Her initial publication in this area established the endothelium as a dynamic organ, central to the control of the inflammatory processes.

The current studies in the Vascular Biology Program are under the broad area of “Understanding ageing of the endothelium and its impact on vascular function”. One of the major diseases being investigated is Alzheimer’s Disease. It is known that changes in the blood brain barrier occur early in disease progression with one of the changes seen in both humans and mouse models of Alzheimer’s Disease (AD) being vascular leak. Her team is investigating endothelial cell ageing and how this may influence the integrity of the blood brain barrier and AD progression, with the hope of exposing new therapeutic targets.

Jennifer Gamble additional roles
Wenkart Chair of Endothelium Medicine, Central Clinical School, University of Sydney.

Mark Gorrell trained in cell biology, protein biochemistry, virology, parasitology and immunology at Australian National University, University of Melbourne and Johns Hopkins University.

His research is focussed upon liver scarring and cancer prevention and treatment, chronic liver disease pathogenesis, diabetes, and protein and enzyme biochemistry and cell biology related to the proteases DPP4, DPP9 and fibroblast activation protein (FAP).

His research was important in the development of DPP4 - targetted therapies for type 2 diabetes, which are now used to treat millions of patients. His research experience includes small RNA viruses, transcriptomics and proteomics. He current research includes SARS-CoV-2 protein biochemistry.

Inside the Centenary Institute, he chairs the postgraduate research committee, is an Academic Leader Research Education and is a Commercialisation Committee member.

Outside the Centenary Institute, he is active in the International Proteolysis Society, the Gastroenterological Society of Australia, NHMRC grant reviews, and editorial boards of journals including Scientific Reports.

Mark Gorrell Liver Enzymes in Metabolism and Inflammation Program

Daniel Hesselson heads the Directed Evolution Laboratory. He trained in Molecular Genetics in Alberta, Canada before completing his PhD in Wisconsin, US.

He was a postdoctoral fellow at the University of California before moving to the Garvan Institute in 2012. There his work pursued the experimental advantages of the zebrafish model system to develop new approaches for tackling the growing diabetes epidemic as laboratory Head.

He also held the position of Conjoint Lecturer, St Vincent’s Clinical School, Faculty of Medicine, UNSW Sydney.

DanielHesselson Directed Evolution Laboratory

Gang Liu is the leader of fibrosis programme in Centre for Inflammation at Centenary Institute and University of Technology Sydney (UTS). He is also a lecturer in School of Life Science at UTS to teach year 2 Immunology.

Dr Liu obtained his PhD in immunology and microbiology at Hunter Medical Research Institute and the University of Newcastle (UoN) in 2016. His PhD study is on tissue remodelling and fibrosis in lung disorders. He did his first postdoc training in the same group on mast cell regulate inflammation/airway remodelling in COPD. He then started his postdoc fellow position from 2017-2019 in priority research centre for digestive health and neurogastroenterology at UoN. His research was focusing on understanding of gut-lung axis in mucosal diseases and how microbiota changes affects gut diseases, such as inflammatory bowel disease.

His current research is to understand the mechanism of tissue remodelling and fibrosis in different lung diseases and identify novel therapeutic targets of lung fibrotic diseases. He also extends the fibrotic studies to the diseases in other organs, such as liver, kidney and gut.

Dr Gang Liu Centenary UTS Centre for Inflammation

Dr Daniel Hesselson heads the Directed Evolution Laboratory. He trained in Molecular Genetics in Alberta, Canada before completing his PhD in Wisconsin, US.

He was a postdoctoral fellow at the University of California before moving to the Garvan Institute in 2012. There his work pursued the experimental advantages of the zebrafish model system to develop new approaches for tackling the growing diabetes epidemic as laboratory Head.

He also held the position of Conjoint Lecturer, St Vincent’s Clinical School, Faculty of Medicine, UNSW Sydney.

Daniel Hesselson heads the Directed Evolution Laboratory.
Guy Lyons is a cell biologist who has appointments with the Centenary Institute, University of Sydney and RPA Hospital. His research aims to understand the pathogenesis of diseases that affect the stratified epithelial tissues that protect us from our environment, including those that cover the mouth, skin and eye. The mechanisms that regulate and enable these epithelial cells to form a multilayered structure are poorly understood, but important to a range of diseases. He has a particular interest in the mechanisms by which sunlight makes these tissues susceptible to conditions such as cancer, corneal blindness and viral infections. He uses microscopy of living tissues and advanced image analysis methods to investigate these diseases in combination with genetic and molecular analyses.

Stefan Oehlers trained with the zebrafish as a model of human immunity at the University of Auckland (PhD) and Duke University (postdoc, supported by an NHMRC CJ Martin Fellowship) before moving to Sydney to start an independent lab at the Centenary Institute. His Immune-Vascular Interactions Laboratory primarily seeks to understand how pathology-associated changes to the vasculature affect inflammation. He has an extensive publication record in the fields of mycobacterial infection and inflammatory bowel disease, with additional interests in atherogenesis and diseases with a shared granuloma-like pathotype. Dr Oehlers is currently a University of Sydney Fellow with the Marie Bashir Institute and a holder of a NSW Health Early-Mid Career Fellowship.

Devanshi Seth is an internationally recognised leader in alcohol and liver research. She is a Principal Scientist at the Royal Prince Alfred Hospital (RPAH) and Centenary Institute. In 2008 she established a unique Alcohol-Liver Disease Research Program in Australia to focus on this critical human health area using multiple approaches (genetics, clinical, cellular, molecular). Dr Seth has >175 publications/presentations, is the recipient of several awards, media releases and radio interviews, funding of >AU$ 6.5mil, including the prestigious National Institutes of Health (NIH)/National Institute on Alcohol Abuse and Alcoholism (NIAAA), USA and Australia India Strategic Research Fund (AISRF). Dr Seth is the founder and leader of the multinational GenomALC Consortium at the forefront of research in this field. With her leadership, GenomALC established the world’s largest database and bio-bank of thousands of drinkers, a significant global resource for future alcohol/liver research. The group has recently published novel genetic and clinical risk factors associated with alcohol-induced cirrhosis in drinkers. Dr Seth champions the Equity Diversity and Inclusion at the Centenary Institute (founder & ex-Chair of Gender Equity Program, current member; USYD (SAGE-SAT member), Research Society on Alcoholism, USA (Diversity and Inclusion Committee) and Franklin Women (Peer Advisory Committee).

Ulf Schmitz has an appointment as Conjoint Senior Lecturer at the Sydney Medical School. His laboratory develops integrative workflows combining various computational disciplines with experimentation to address questions around non-coding RNAs, post-transcriptional gene regulation and cancer biology. Using machine learning, mathematical modelling, and molecular dynamics simulations he investigates mechanisms of post-transcriptional gene regulation. He found that synergistic target regulation by microRNAs is a widespread phenomenon of post-transcriptional gene regulation – a mechanism that can be exploited to sensitize aggressive tumour cells to chemotherapy. He also develops multi-omics data analysis pipelines to investigate patterns of alternative splicing and other forms of gene regulation in normal biology and in various cancers. He has also identified intron retention as a well conserved form of alternative splicing that mediates cell-specific gene regulation. Aberrant intron retention has been described in multiple human cancers. He aims to identify regulators and consequences of intron retention as well as cross-talk with other forms of post-transcriptional gene regulation.
Sj Sijie Shen is a research officer as part of Prof. Philip Hansbro’s group at the Centenary Institute/University of Technology Sydney Centre for Inflammation. His research of interest is in respiratory and gastrointestinal tract diseases, with a major focus on the interaction between host immunity and microbiomes. Dr Shen has a special interest in the role diet plays in immune responses and disease progression.

The focus of Dr Shen’s research is on the investigation of how the gut and lung crosstalks and communicates under normal homeostasis and during disease. In particular, he wishes to understand how the community of gut bacteria (gut microbiome) affects chronic respiratory diseases including severe asthma and chronic obstructive pulmonary disease (COPD). Furthermore, his research will explore how the gut microbiome can be modified to protect against or treat these respiratory diseases.

Dr Shen’s prior studies have culminated in his current research. He examined the effects of dietary fibre and short-chain fatty acids in Allergic Bronchopulmonary Aspergillosis and Eosinophilic Oesophagitis as part of B.Biomes.Sci (Honours) (Monash University, 2014). In extension, his PhD research assessed the interplay between the gut microbiome and neutrophils in a mouse model of colitis (Monash University, 2019).

Dannel Yeo heads the Li Ka Shing Cell and Gene Therapy Initiative Group which investigates liquid biopsies in cancer and undertakes cellular immunotherapy clinical trials in solid cancers. The lab focuses on improving patient management and investigating novel treatments using patient samples from a range of solid cancers including pancreatic, lung and mesothelioma.

Dannel received his PhD from the University of Melbourne in cancer cell biology and cancer mouse models in pancreatic cancer. He then undertook a postdoctoral position under the direction of Prof Sean Grimmond at the University of Melbourne Centre for Cancer Research where he generated and utilised 3D culture organoids from pancreatic cancer patient resected tissue and biopsies for precision and personalised medicine.

Dannel also has appointments at the University of Sydney, Royal Prince Alfred Hospital and Chris O’Brien Lifehouse.

Hui Emma Zhang received a Master of Applied Science in Australian Centre of Microscopy and Microanalysis and a PhD in protease and cancer biology in the University of Sydney. She has over ten years’ biomedical research experience in various fields such as Alzheimer’s disease, diabetes, cancer and liver diseases. She trained in cell biology, protein biochemistry, cancer biology and immunology.

Her research seeks to understand the pathogenesis of liver cancer and to medically exploit the protease-based approach for the treatment of liver cancer. She has studied the unique protease named DPP9 for eight years and has published many novel and significant discoveries on DPP9. Her lab has developed genetically modified mouse strains and cell lines targeting DPP9. Her lab has also established new liver cancer mouse models to recapitulate human liver cancer development.

Hui Emma Zhang has an appointment as Conjoint Lecturer at the Faculty of Medicine and Health in the University of Sydney.
Take your first step into a career in medical research with the Centenary Institute. Housing state-of-the-art imaging, cytometry and animal facilities, you will hone new skills and learn the latest techniques from internationally renowned researchers whilst building the foundations for a future that could see you make breakthroughs that save lives.

“Centenary Institute is like a big family, people are very welcoming and friendly here. During an experiment, you may need to visit different labs for various equipment, which provides chances to chat with colleagues and make friends. It is very well organised. I am very happy to be part of it.”

“Centenary is a great place to further explore your interest in science. Research can be challenging, but there’s always someone to help you out at Centenary.”

Carrie Huang, Honours Student and Cecy Xi, PhD Student Liver Enzymes in Metabolism and Inflammation Program

centenary.org.au/students

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**Honours Projects**

**Student Research Projects for 2021**

**Molecular modeling of cancer-associated mutations in tumour suppressor genes**

The ‘master weaver’ protein CTCF, is mutated in endometrial cancer, as well as colorectal, stomach, breast and haemopoietic cancers. Our group was the first to demonstrate that the ubiquitous zinc finger (ZF) protein CTCF acts as a tumour suppressor gene. Missense mutations in CTCF are enriched in the DNA-binding ZF region.

We have shown that mutations in the ZF region can result in a loss- or gain-of-function in CTCF, which has implications for cancer development. We are currently modelling ‘hotspot’ mutations on published CTCF ZF structures to assess the impact of those mutations. In addition, we will develop homology models for the ZF domain of CTCF-Like protein (CTCFL, also known as BORIS). CTCFL which shares 80% homology with CTCF within its ZF domain is aberrantly expressed in more than half of all cancers. Both factors have overlapping and unique DNA binding characteristics.

We will examine which residues are critical for binding of CTCF and CTCFL to the same DNA target sites and which ZF residues confer DNA binding specificity. This will provide important insight into the sibling rivalry that exists between CTCF and CTCFL in normal biology and cancer.

**School at:** Pathology

**Keywords:** protein structure, mutation, cancer, transcription factor

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**Understanding the role of CTCF genetic deletion in aggressive endometrial cancer**

CTCF is essential for the normal organisation of DNA in cells. Our team has discovered that CTCF is genetically deleted at high rates in the most aggressive and deadly types of endometrial cancer (Marshall, et al., 2017). CTCF deletion predominantly occurs in the Type II serous subtype of endometrial cancer and is associated with poorer overall survival in patients with serous tumours. Additionally, we have shown that CTCF deletions also occur in the clear cell subtype and this may be associated with tumour relapse and/or metastasis.

Our culturing of endometrial cancer cell-lines as 3D spheroids has shown that a functional consequence of CTCF deletion results in a loss of cell polarity – an early event in endometrial cancer pathology. Our analysis of gene expression data in CTCF heterozygous endometrial tumours has revealed a widespread dysregulation of transcription.

In this project we will examine those genes and biochemical pathways that are dysregulated in CTCF mutant endometrial cancers. We will investigate the impact of these genes on cell polarity in 3D spheroids which will give us important insights into early pathophysiological events underlying endometrial cancer.

**School at:** Pathology

**Keywords:** endometrial cancer, mutation, mouse models, cell biology

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**Keywords:** leukaemia, mutation, transcription factor, and contribute to cellular transformation.

...proliferation, differentiation and survival of CLL cells how acquired genetic lesions in MGA alter the...promotes chronic lymphocytic leukaemia disease resistance.

MGA inactivation through chromosomal deletion or the gene encoding the transcription factor Max Gene rearrangements. Recent reports have identified mutations, chromosomal deletions, amplifications in CLL can be heterogeneous, and include point...result in their transformation into cancerous cells that can live longer and grow faster than normal B cells. Similar to many blood cancers, genetic alterations in CLL can be heterogeneous, and include point mutations, chromosomal deletions, amplifications and rearrangements. Recent reports have identified the gene encoding the transcription factor Max Gene Associated (MGA) to be recurrently deleted in CLL. MGA inactivation through chromosomal deletion or point mutation occurs in 4% of CLL, but this increases to 16% as CLL disease progresses to chemotherapy resistance.

Our hypothesis is that genetic inactivation of MGA promotes chronic lymphocytic leukaemia disease progression. We will test this hypothesis by analysing how acquired genetic lesions in MGA alter the proliferation, differentiation and survival of CLL cells and contribute to cellular transformation.

**School at:** Pathology

**Keywords:** leukaemia, mutation, transcription factor, mouse models

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**Supervisor: Dr Chuck Bailey**

Gene and Stem Cell Therapy Program: Head - Professor John Rasko AO

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**Supervisor: Associate Professor Patrick Bertolino and Associate Professor David Bowen**

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**● The role of MGA mutation in chronic lymphocytic leukaemia (CLL)**

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in senior Australians. Every year nearly 1000 Australians are diagnosed with CLL and typically 80% of all new diagnoses are in patients over the age of 60 years.

CLL is a slow developing cancer affecting B cells. Genetic mutations acquired in these B cells result in their transformation into cancerous cells that can live longer and grow faster than normal B cells. Similar to many blood cancers, genetic alterations in CLL can be heterogeneous, and include point mutations, chromosomal deletions, amplifications and rearrangements. Recent reports have identified the gene encoding the transcription factor Max Gene Associated (MGA) to be recurrently deleted in CLL. MGA inactivation through chromosomal deletion or point mutation occurs in 4% of CLL, but this increases to 16% as CLL disease progresses to chemotherapy resistance.

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**School at:** Pathology

**Keywords:** leukaemia, mutation, transcription factor, mouse models

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**Modulation of host entry factors to improve AAV-mediated gene therapy**

Recombinant adeno-associated virus (rAAV) has gained widespread use as a gene delivery vector for corrective gene therapies due to its lack of association with any human disease and its ability to safely and efficiently deliver a genetic payload into a broad range of tissues.

For liver-specific genetic diseases, current rAAV modalities have not provided the necessary high-level transduction efficiencies and humoral neutralisation properties necessary for curative outcomes in diverse patient groups.

Improved transduction efficiency of rAAV vectors has been achieved by engineering capsids with higher affinity or cell-specific tropism and increased resistance to neutralising antibodies. Increasing AAV-mediated therapeutic efficacy by modulating host entry factors remains unexplored.

KIAA0319L was recently shown to be an essential host entry factor for most AAV serotypes, however the biology and normal function of KIAA0319L is poorly understood. This is an exciting project as it will use a combination of bioinformatics, biochemical and proteomic strategies to functionally characterise the host determinants that regulate KIAA0319L expression and distribution.

**School at:** Pathology

**Keywords:** gene therapy, adeno-associated virus, host factor, KIAA0319L

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**Investigating the role of monocyte-derived macrophages in liver structure and homeostasis**

Macrophages play a key immune role but are also considered as key regulators of pathology and healing responses as they secrete factors promoting or inhibiting inflammation and tissue fibrosis.

Liver resident macrophages include Kupffer cells (KCs) as well as ‘liver capsular macrophages’ (‘LCMs’) recently discovered by the host laboratory. KCs and LCMs have a distinct phenotype and ontogeny. While LCMs are CX3CR1+ and derived from blood monocytes, KCs are embryonically derived and CX3CR1-. LCMs form a network that is intimately related to the collagen framework of the liver capsule, and play a potential role in its integrity. Advancing our knowledge on the role of these two types of macrophages in normal liver tissue, and in mediating inflammation and fibrosis during pathology is critical for the development of new treatments.

This project aims to characterise the role of macrophages in the structure of the liver using a unique mouse line recently generated by the group. This line selectively lacks monocyte-derived macrophages and displays abnormal liver development.

**Techniques:** high resolution confocal microscopy, state of the art imaging, and flow cytometric techniques.

**School at:** Infectious Diseases and Immunology

**Keywords:** macrophages, liver, T cells, inflammation

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**How does silica dust make TB worse?**

The lung is one of the most important organs exposed to environmental pollution and pathogens. Lung inflammation and disease is a leading cause of death and disability globally, and an overlooked area is the intersection of silicosis and tuberculosis (TB).

Well-known as a disease of miners and stonemasons, silicosis has resurfaced in the sandstone basin which cups the Sydney region and continues to afflict millions of workers in hazardous occupations around the world. Silicosis predisposes to TB and patients with silicosis who develop active TB have poor outcomes. As 25% of the world’s population is infected with Mycobacterium tuberculosis, this is a serious problem.

The mechanisms by which silicosis impacts the body’s defenses against mycobacteria are poorly understood. This project will use a mouse model of silicosis and mycobacterial infection to examine how silicosis affects innate (dendritic cell and macrophage) and adaptive immune responses. The student will be part of a stimulating research team and develop skills in immunology, cellular biology and flow cytometry.

**School at:** School of Medical Sciences

**Keywords:** immunology, infectious diseases, tuberculosis, environment, inflammation
Supervisor: Dr Jaesung Peter Choi  
Centenary UTS Centre for Inflammation: Head - Professor Phil Hansbro  

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● Finding safe and effective therapies targeting sex hormones and the microbiome for the commonest cause of stroke in children: cerebral cavernous malformation (CCM)

Cerebral cavernous malformations (CCMs) are vascular lesions of the central nervous system that affect 1 in 200 people. CCM lesions are prone to bleeds and are the major cause of stroke and sudden death in children. Recent treatment for CCM is limited to high-risk neurosurgery. As such there is an urgent need for novel non-invasive, druggable treatment options.

Just as men have earlier onset and more severe cardiovascular diseases than women, recent clinical observations and our preliminary data in mouse models demonstrate a greater CCM burden in males. The male predisposition to CCM is likely to reflect an impact of sex hormone metabolism and action. Hence, the project aims to elucidate the role that sex hormones in its pathogenesis. Furthermore, we recently identified the gut microbiome as a critical stimulant of CCM. Interestingly, gut microbiota differs between males and females and microbiota influence sex hormone metabolism and action.

The biological question is centred around the molecular control of cell fate during lymphatic endothelial cell specification by a novel transcriptional effector. The work will involve wet and dry lab approach to understand how this new gene modulates the program of lymphatic endothelial cell differentiation on a genome wide scale. Techniques used will cover a broad range of skills from phenotyping vascular networks using confocal microscopy to gene editing with crispr/cas9 and genomics and transcriptomics approaches.

The primary objective of this project is to develop a research study with general and specific in vitro techniques in stem cells and in vivo approaches in early stage mouse embryo to study the molecular basis of cell fate decision during embryogenesis.

This work will take advantage of cutting edge approaches based on single molecule approaches to study the role of different components of the transcriptional machinery in stem cells. Two types of complementary approaches will be used in parallel either based on live imaging methods or on fixed cells with super resolution microscopy. Further the work will be complemented by genomic and transcriptomic approaches to correlate changes in gene output with molecular activity imaged in a cell.

The biological question is centred around the molecular control of cell fate during lymphatic endothelial cell specification by a novel transcriptional effector. The work will involve wet and dry lab approach to understand how this new gene modulates the program of lymphatic endothelial cell differentiation on a genome wide scale. Techniques used will cover a broad range of skills from phenotyping vascular networks using confocal microscopy to gene editing with crispr/cas9 and genomics and transcriptomics approaches.

The project aims to:
1. Confirm the identity of aged (senescent) perivascular macrophages in AD.
2. Investigate the consequence of the senescent perivascular macrophages on BBB function.

Student Research Projects for 2021

Alzheimer's Disease: Determining the role of aged perivascular macrophages in blood-brain barrier dysfunction

Alzheimer’s Disease (AD) is an age-related disease that affects brain function. Breakdown of the blood-brain barrier (BBB) results in neuroinflammation involved in cognitive decline, a feature of AD.

In a mouse model of AD, we have identified aged vascular cells. These cells are thought to be perivascular macrophages, which are known to regulate BBB permeability and neuroinflammation.

The project aims to:
1. Confirm the identity of aged (senescent) perivascular macrophages in AD.
2. Investigate the consequence of the senescent perivascular macrophages on BBB function.

Scientist associated with this project: Dr Kaka Ting  
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School at: Infectious Diseases and Immunology  

Keywords: alzheimer's disease, macrophages, aged immune response
Alzheimer's Disease: How age effects the blood vessels in the brain

Ageing is one of the greatest risk factors for cardiovascular disease including Alzheimer's Disease. Cellular ageing, referred to as cellular senescence, is an irreversible process activated in response to stress that is characterised by permanent cell cycle arrest, an active metabolic state and changes to the inflammatory phenotype of the cell.

Endothelial cells are unique in showing both pro-inflammatory and anti-inflammatory senescence phenotypes. We have evidence to suggest that this dual phenotype maybe regulated through changes in the metabolic state of the cell.

This project will investigate this possibility and uncover the molecular pathway that controls the metabolic switch.

Associated Scientist: Dr Paul Coleman
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School at: School of Medical Sciences
Keywords: ageing, metabolism, inflammation

Proteases in the pathogenesis of chronic liver injury and cancer

Primary liver cancer is the 4th leading cause of cancer related deaths. We are addressing the urgent need to develop a greater understanding of pathogenesis for improved therapeutics. The pathogenesis of chronic liver injury and cancer is driven by chronic cell death and proliferation and inflammation. Cirrhosis generally precedes cancer in the liver.

Proteases are important in cancer pathogenesis and suit drug development. We primarily study fibroblast activation protein (FAP) and DPP9 as proteases associated with cancer pathogenesis.

I discuss with each student their interests, skills and aspirations in order to design a suitable project within these topics:

1. Liver complications of diabetes and chronic fatty liver.
2. Liver cirrhosis and cancer.
3. Protein biochemistry and inhibitors of FAP and DPP9.
4. Diagnosis of fibrosis in chronic liver disease and predicting treatable patients.
5. Potential therapies for cancer and NASH.

Training: We use sophisticated techniques in immunohistochemistry, flow cytometry, qPCR, immunoblotting, protease assays, ELISA and confocal microscopy. Projects can be in cell lines, mouse models or with specimens from RPA hospital.

School at: School of Medical Sciences
Keywords: cirrhosis, NASH, cancer, liver, DPP4, fibrosis, mouse, human
HONOURS PROJECTS

Supervisor: Dr Gang Liu
Centenary UTS Centre for Inflammation: Head - Professor Phil Hansbro
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- Understanding the role of extracellular matrix proteins in regulating lung fibrosis

Lung fibrosis is a progressive, debilitating, and severe lung disease, which is characterised by damage to lung tissues, and idiopathic pulmonary fibrosis (IPF) is one of the major lung fibrosis diseases in humans. It is characterised by lung tissue remodelling and fibrosis, where normal lung tissue is interspersed with interstitial fibrosis, honeycomb cysts and fibroblast foci.

In lung injury, extracellular matrix (ECM) proteins are secreted into the connective tissue to serve as scaffolds for tissue repair and regeneration. However, ECM proteins continue to be produced and deposited in lung tissues in IPF, and the process becomes irreversible. Current treatments to lung fibrosis have limited effect to reduce and inhibit lung fibrosis development in IPF.

Our recent studies have identified some key ECM proteins that targeting these proteins can reduce lung fibrosis and inflammation in an experimental model of lung fibrosis. In this research project, we aim to understand the mechanism of the ECM proteins regulate lung fibrosis in IPF.

School at: UTS School of Life Sciences

Keywords: lung fibrosis, idiopathic pulmonary fibrosis, animal models, extracellular matrix proteins

Supervisor: Dr Gang Liu
Centenary UTS Centre for Inflammation: Head - Professor Phil Hansbro
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- Novel treatments of alpha-1 antitrypsin gene deficiency induced chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive pulmonary disease defined by emphysema and severe breathing difficulties. It is the 3rd commonest cause of chronic morbidity and death.

In traditional COPD, proteases function to clear debris and damaged tissues from the lungs. However, when not properly controlled they have aberrant activity degrading elastin and various forms of collagen leading to lung damage.

It is well-known that deficiencies in A1AT lead to an imbalance in protease-anti-protease activity resulting in tissue damage and emphysema. More than 80% of the human genome produces RNAs that are not translated, and many of them are long non-coding (lnc) RNAs.

In this project, we aim to understand how lncRNA regulates A1AT deficiency-induced COPD and explore a potential treatment.

School at: UTS School of Life Sciences

Keywords: Alpha-1 antitrypsin, COPD, PCR, CRISPR

Supervisor: Associate Professor Guy Lyons
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- How the cornea responds to UV radiation

The cornea is covered by a multi-layered (stratified) sheet of clear epithelial cells, which protects it from pathogens and the environment. Like the skin, the cornea is exposed to damaging ultraviolet radiation (UVR) from sunlight.

This project will investigate how UVR affects stratification of the corneal epithelium and its barrier function against viruses such as coronaviruses. It will use advanced microscopy and image analysis methods to visualise the epithelial cells of living corneas as they divide, migrate and stratify.

The corneas from novel reporter strains of genetically modified mice will be used to locate and measure signalling responses in the living tissue, and probed with pathway-specific drugs to determine their importance.

School at: Pathology

Keywords: eye, cancer, COVID-19, UV radiation, microscopy

Supervisor: Associate Professor Guy Lyons
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- Genes and cell-cell interactions in tumour progression

Cancer cells within a tumour often have different mutations from neighbouring cells. This genetic heterogeneity enables novel cell-cell interactions to occur that are not possible in homogenous tumours. This opens up exciting new possibilities for understanding the pathogenesis of cancer and strategies for treating it.

To explore these interactions between cancer cells, we have identified clones of cells that interact to promote cancer cell growth in an experimental model of oral cancer.

This project will investigate the molecular genetic basis for this interaction, using cell culture, image analysis, deep sequencing and mouse models.

School at: Pathology

Keywords: cancer, oral, skin, microscopy
Our research group uses the zebrafish model system to better understand and treat this disease. The zebrafish is an emerging model for the study of infectious diseases that complements existing mouse infection models in the Tuberculosis Research Program at the Centenary Institute.

Mycobacterial infection results in the formation of complex aggregates of immune cells known as granulomas, and these can be readily visualised in zebrafish. These granulomas behave similarly to the ones found in humans and other mammalian hosts, and they provide a unique opportunity to study the interactions between host immune cells and mycobacteria in a real-time, in vivo system.

This project will expand these findings by determining the effects of vascularisation on host and bacterial growth in zebrafish infection models.

DNA rearrangement leading to fusion genes is a hallmark of cancer. A number of these fusions are used as biomarkers and therapeutic targets in different cancer types; prominent examples include BCR-ABL1 for chronic myeloid leukemia and MYC-IGH for Burkitt’s lymphoma.

Traditionally, DNA rearrangement and gene fusion was attributed largely to chromosomal translocations. However, recent years have produced conclusive evidences that two or more transcripts can fuse at the transcription level irrespective of chromosomal translocations.

In this project, we will analyse long-read sequencing patterns of competitive post-transcriptional gene regulation. Toward this, we will identify gene-regulatory network modules using a data integration approach to determine patterns of competitive post-transcriptional gene regulation.

In a large-scale analysis of alternative splicing across 2,500 human tissue samples and cell lines we generated a wealth of data regarding gene-, cell type-, tissue-, and disease-specific intron-retention events. This data is in parts accessible through a rudimentary web interface: http://mirnana.centenary.org.au/irfinder/database/

In this project we will develop a sophisticated database and web interface design to provide an efficient and rich user experience facilitating a rapid success in the hunt for information about intron retention. The new IRBase 2.0 will provide data in interactive graphs and customized data retrieval options.

In this project we will construct a mathematical model of competitive post-transcriptional gene regulation. Perturbations to the highly calibrated system of gene regulation can have severe consequences and cause diseases including cancer. MicroRNAs can regulate dozens of target genes and intron retention has been found to be another mechanism of post-transcriptional gene regulation affecting hundreds of genes.

In our project, we will use a combination of in vitro cell culture assays, zebrafish infection experiments and mouse physiology using a combination of in vitro cell culture models in the Tuberculosis Research Program at the Centenary Institute.

Mycobacterial Program: Head - Professor Warwick Britton AO, Immune-Vascular Interactions Laboratory: Head - Dr Stefan Oehlers

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HONOURS PROJECTS

Alphabetical by supervisor surname.

Student Research Projects for 2021

28
Core transcriptional networks in cell trans-differentiation

Core transcriptional networks are essential drivers and determinants of cell-fate transitions. To date, our mechanistic understanding of these essential regulatory layers is very limited, especially in the context of trans-differentiation, despite being one of the most promising therapeutic cell replacement strategies in regenerative medicine.

In this project, we will reconstruct gene-regulatory networks involving non-coding RNAs and mRNAs that drive trans-differentiation of human cells and identify key alternative splicing events during cell-fate transitions.

School at: School of Medical Sciences

Keywords: bioinformatics, systems biology, next generation sequencing data analysis

Role of lipid metabolism in alcohol-induced liver cirrhosis

Risky drinking continues to be a major concern in Australia. The major medical consequence of risky drinking is alcohol-induced liver cirrhosis (AC). Our discovery of a novel variant in FAF2 gene (lipid droplet/ metabolism) associated with the risk of AC in drinkers, is significant because it fits well with the current knowledge of other single nucleotide polymorphisms (SNPs) in genes (PNPLA3, TM6SF2 and HSD17B13) also linked to lipid biology. Build-up of lipid droplets in the liver due to heavy drinking can cause inflammation, leading to cirrhosis in some drinkers.

My group is interested to understand the mechanisms of action of these genes in the development of cirrhosis. We will use our established zebrafish model of alcohol-induced liver injury. Function of risk genes and their mechanisms driving disease development will be studied using gene-editing (Crispr-Cas9), transgenics and state-of-art imaging technology. It will advance knowledge on the role of lipid biology genes in chronicity of AC development. Importantly, it will generate a list of new drug targets.

School: School of Medical Sciences

Keywords: cirrhosis, SNPs, lipid, alcohol, genetics, zebrafish, crispr

Modulating the gut microbiome to influence the progression of lung diseases

Dr Shen is a postdoctoral researcher in Professor Phil Hansbro’s group at the recently established UTS/ Centenary Centre for Inflammation, based at the Centenary Institute.

His research aims to provide deeper insights into the “gut-lung axis”. The project will explore how our lifestyle and environment alters the bacteria in the gut (the gut microbiome) to influence lung inflammation during severe asthma and chronic obstructive pulmonary disease (COPD). The major aim of this project is to delve deep into understanding the mechanisms by which bacteria interacts with and influences host immune cells and responses in the gut, and how this modulates inflammation in the lungs. This project will utilise well-established animal models combined with cutting-edge techniques for research.

Dr Shen received his PhD in medicine/immunology from Monash University in 2019. His research shows that host immune and environmental factors change the gut microbiome in severe asthma and chronic obstructive pulmonary disease (COPD). The major aim of this project is to delve deep into understanding the mechanisms by which bacteria interacts with and influences host immune cells and responses in the gut, and how this modulates inflammation in the lungs. This project will utilise well-established animal models combined with cutting-edge techniques for research.

School at: UTS School of Life Sciences

Keywords: microbiome, gut, lung, respiratory, COPD, bacteria, asthma

Circulating tumour cells to monitor cancer patients

Circulating tumour cells (CTCs) are tumour cells that have been released from the primary tumour tissue to form metastases by travelling through the blood and lymphatic system. Capturing and analysing these rare cells is now possible using our next generation liquid biopsy platform.

We are able to identify, capture and characterise these CTCs. Hence, this platform has the potential to provide ‘real-time’ cancer monitoring throughout all stages of a patient’s cancer journey and identify potentially effective treatments in cancers such as pancreatic cancer, lung cancer, and mesothelioma. Potential research topics include:

1. Evaluate CTCs to predict patient response and guide patient management.
2. Characterise CTCs using genetic, cellular and imaging techniques.
3. Establish and characterise patient-derived CTC organoid cultures.
4. Evaluate CTCs and other blood biomarkers as a diagnostic marker to improve early detection.

Skills/tools: Mammalian cell culture (3D), cell biology assays, western blot, RT-qPCR, microscopy, immunofluorescence, cell picking, mouse models

School at: Pathology

Keywords: cancer, translational medicine, liquid biopsy, circulating tumour cells
Investigating CAR-T therapy for pancreatic cancer

Chimeric antigen receptor-engineered T-cell (CAR-T) therapy is an exciting new cellular immunotherapy for the treatment of cancer.

Isolated patient T-cells are modified to target a specific tumour surface antigen and then injected back into the patient. CAR-T therapy is now approved for blood cancers but the same success has not been observed in solid cancers.

Novel CAR-T therapies will be evaluated in pancreatic cancer using the latest cancer model systems including 2D cells, 3D organoids and mice models. To test the efficacy of CAR-T cells, cytotoxicity and immune activation/persistence will be evaluated, and mechanisms of resistance will be explored.

Skills/tools: mammalian cell culture, cell biology assays (including cellular impedance assays, live cell imaging), isolating T cells, lentivirus gene transfer, immune phenotyping (by flow cytometry), RT-qPCR, cytokine analysis (ELIZA), and mouse models.

School at: Pathology

Keywords: cancer, immunotherapy, CAR-T

Proteases in liver cancer

Primary liver cancer is the 4th leading cause of cancer related deaths and there is an urgent need to develop improved medical therapy. Our team is the first to find that the protease DPP9 is a druggable target in hepatocellular carcinoma (HCC). DPP9 inhibition has shown anti-cancer actions in acute myeloid leukaemia and lung cancer. This project aims to better understand the roles of DPP9 in the pathogenesis of HCC.

Projects will be these, or similar based on student interests:
1. To elucidate molecular mechanisms of DPP9 using liver cancer cell lines.
2. To generate cell-specific DPP9 depletion in mice to study the role of DPP9 in the immune system.
3. To measure growth of orthotopic tumours in DPP9 inhibitor treated mice.

Skills that the student can learn: cell culture, histopathology, immunohistochemistry, immunoblotting, qPCR, flow cytometry, confocal microscopy.

School at: Pathology

Keywords: protease, liver cancer, inflammation, DNA repair

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Masters Projects

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“I love the positive and supportive environment and the resources and laboratories are absolutely top-notch. The best thing? My supervisors help me a lot. They’re always willing to listen, to advise and to share the fantastic knowledge that they’ve gained over years of hard work and effort. I love working here!”

Darren Liu, Masters Student
Lipid Cell Biology Laboratory

centenary.org.au/students
Molecular modeling of cancer-associated mutations in tumour suppressor genes

The ‘master weaver’ protein CTCF, is mutated in endometrial cancer, as well as colorectal, stomach, breast and haemopoietic cancers. Our group was the first to demonstrate that the ubiquitous zinc finger (ZF) protein CTCF acts as a tumour suppressor gene. Missense mutations in CTCF are enriched in the DNA-binding ZF region.

We have shown that mutations in the ZF region can result in a loss- or gain-of-function in CTCF, which has implications for cancer development. We are currently modelling ‘hotspot’ mutations on published CTCF ZF structures to assess the impact of those mutations. In addition, we will develop homology models for the ZF domain of CTCF-Like protein (CTCFL, also known as BORIS), CTCFL which shares 80% homology with CTCF within its ZF domain is aberrantly expressed in more than half of all cancers. Both factors have overlapping and unique DNA binding characteristics.

We will examine which residues are critical for binding of CTCF and CTCFL to the same DNA target sites and which ZF residues confer DNA binding specificity. This will provide important insight into the sibling rivalry that exists between CTCF and CTCFL in normal biology and cancer.

School at: Pathology

Keywords: protein structure, mutation, cancer, transcription factor

Understanding the role of CTCF genetic deletion in aggressive endometrial cancer

CTCF is essential for the normal organisation of DNA in cells. Our team has discovered that CTCF is genetically deleted at high rates in the most aggressive and deadly types of endometrial cancer (Marshall, et al., 2017). CTCF deletion predominantly occurs in the Type II serous subtype of endometrial cancer and is associated with poorer overall survival in patients with serous tumours. Additionally, we have shown that CTCF deletions also occur in the clear cell subtype and this may be associated with tumour relapse and/or metastasis.

Our culturing of endometrial cancer cell-lines as 3D spheroids has shown that a functional consequence of CTCF deletion results in a loss of cell polarity – an early event in endometrial cancer pathology. Our analysis of gene expression data in CTCF heterozygous endometrial tumours has revealed a widespread dysregulation of transcription.

In this project we will examine those genes and biochemical pathways that are dysregulated in CTCF mutant endometrial cancers. We will investigate the impact of these genes on cell polarity in 3D spheroids which will give us important insights into early pathophysiological events underlying endometrial cancer.

School at: Pathology

Keywords: endometrial cancer, mutation, mouse models, cell biology

The role of MGA mutation in chronic lymphocytic leukaemia (CLL)

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in senior Australians. Every year nearly 1000 Australians are diagnosed with CLL and typically 80% of all new diagnoses are in patients over the age of 60 years.

CLL is a slow developing cancer affecting B cells. Genetic mutations acquired in these B cells result in their transformation into cancerous cells that can live longer and grow faster than normal B cells. Similar to many blood cancers, genetic alterations in CLL can be heterogeneous, and include point mutations, chromosomal deletions, amplifications and rearrangements. Recent reports have identified the gene encoding the transcription factor Max Gene Associated (MGA) to be recurrently deleted in CLL. MGA inactivation through chromosomal deletion or point mutation occurs in 4% of CLL, but this increases to 16% as CLL disease progresses to chemotherapy resistance.

Our hypothesis is that genetic inactivation of MGA promotes chronic lymphocytic leukaemia disease progression. We will test this hypothesis by analysing how acquired genetic lesions in MGA alter the proliferation, differentiation and survival of CLL cells and contribute to cellular transformation.

School at: Pathology

Keywords: leukaemia, mutation, transcription factor, mouse models

Modulation of host entry factors to improve AAV-mediated gene therapy

Recombinant adeno-associated virus (rAAV) has gained widespread use as a gene delivery vector for corrective gene therapies due to its lack of association with any human disease and its ability to safely and efficiently deliver a genetic payload into a broad range of tissues.

For liver-specific genetic diseases, current rAAV modalities have not provided the necessary high-level transduction efficiencies and humoral neutralisation properties necessary for curative outcomes in diverse patient groups.

Improved transduction efficiency of rAAV vectors has been achieved by engineering capsids with higher affinity or cell-specific tropism and increased resistance to neutralising antibodies. Increasing AAV-mediated therapeutic efficacy by modulating host entry factors remains unexplored.

KIAA0319L was recently shown to be an essential host entry factor for most AAV serotypes, however the biology and normal function of KIAA0319L is poorly understood. In this project, we will use a combination of biochemical, genetic and proteomic strategies to functionally characterise the host determinants that regulate KIAA0319L expression and distribution.

School at: Pathology

Keywords: gene therapy, adeno-associated virus, host factor, KIAA0319L
Cerebral cavernous malformations (CCMs) are vascular lesions of the central nervous system that affect 1 in 200 people. CCM lesions are prone to bleeds and are the major cause of stroke and sudden death in children. Current treatment for CCM is limited to high-risk neurosurgery. As such there is an urgent need for novel non-invasive, druggable treatment options.

Just as men have earlier onset and more severe cardiovascular diseases than women, recent clinical observations and our preliminary data in mouse models demonstrate a greater CCM burden in males. The male predisposition to CCM is likely to reflect an impact of sex hormones and the microbiome play in the prominent sex hormone metabolism and action.

Hence, the project aims to elucidate the role that sex hormones and the microbiome play in the prominent sex difference in CCM. This could reveal a potential use of steroids, precision antibiotics/probiotics, and repurposing existing drugs as non-invasive therapeutic options for CCM.

School at: UTS School of Life Sciences

Keywords: stroke, cardiovascular diseases, mouse, microbiome, cerebral cavernous malformation

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MASTERS PROJECTS

Supervisor: Dr Gang Liu
Centenary UTS Centre for Inflammation: Head - Professor Phil Hansbro
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● Understanding the role of extracellular matrix proteins in regulating lung fibrosis

Lung fibrosis is a progressive, debilitating, and severe lung disease, which is characterised by damage to lung tissues, and idiopathic pulmonary fibrosis (IPF) is one of the major lung fibrosis diseases in humans. It is characterised by lung tissue remodelling and fibrosis, where normal lung tissue is interspersed with interstitial fibrosis, honeycomb cysts and fibroblast foci.

In lung injury, extracellular matrix (ECM) proteins are secreted into the connective tissue to serve as scaffolds for tissue repair and regeneration. However, ECM proteins continue to be produced and deposited in lung tissues in IPF, and the process becomes irreversible. Current treatments to lung fibrosis have limited effect to reduce and inhibit lung fibrosis development in IPF.

Our recent studies have identified some key ECM proteins that targeting these proteins can reduce lung fibrosis and inflammation in an experimental model of lung fibrosis. In this research project, we aim to understand the mechanism of the ECM proteins regulate lung fibrosis in IPF.

School at: UTS School of Life Sciences

Keywords: lung fibrosis, idiopathic pulmonary fibrosis, animal models, extracellular matrix proteins

Supervisor: Dr Gang Liu
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● Novel treatments of alpha-1 antitrypsin gene deficiency induced chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive pulmonary disease defined by emphysema and severe breathing difficulties. It is the 3rd commonest cause of chronic morbidity and death.

Alpha 1 anti-trypsin (A1AT) deficiency is the major genetic predisposition to COPD. Endogenous proteases function to clear debris and damaged tissues from the lungs. However, when not properly controlled they have aberrant activity degrading elastin and various forms of collagen leading to lung damage.

It is well-known that deficiencies in A1AT lead to an imbalance in protease-anti-protease activity resulting in tissue damage and emphysema. More than 80% of the human genome produces RNAs that are not translated, and many of them are long non-coding (lnc) RNAs.

In this project, we aim to understand how lncRNA regulates A1AT deficiency-induced COPD and explore a potential treatment.

School at: UTS School of Life Sciences

Keywords: Alpha-1 antitrypsin, COPD, PCR, CRISPR

Supervisor: Associate Professor Guy Lyons
Immune Imaging Program: Head - Professor Wolfgang Weninger
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● How the cornea responds to UV radiation

The cornea is covered by a multi-layered (stratified) sheet of clear epithelial cells, which protects it from pathogens and the environment. Like the skin, the cornea is exposed to damaging ultraviolet radiation (UVR) from sunlight.

This project will investigate how UVR affects stratification of the corneal epithelium and its barrier function against viruses such as coronaviruses. It will use advanced microscopy and image analysis methods to visualise the epithelial cells of living corneas as they divide, migrate and stratify.

The corneas from novel reporter strains of genetically modified mice will be used to locate and measure signalling responses in the living tissue, and probed with pathway-specific drugs to determine their importance.

School at: Pathology

Keywords: eye, cancer, COVID-19, UV radiation, microscopy

Supervisor: Associate Professor Guy Lyons
Immune Imaging Program: Head - Professor Wolfgang Weninger
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● Genes and cell-cell interactions in tumour progression

Cancer cells within a tumour often have different mutations from neighbouring cells. This genetic heterogeneity enables novel cell-cell interactions to occur that are not possible in homogenous tumours. This opens up exciting new possibilities for understanding the pathogenesis of cancer and strategies for treating it.

To explore these interactions between cancer cells, we have identified clones of cells that interact to promote cancer cell growth in an experimental model of oral cancer.

This project will investigate the molecular genetic basis for this interaction, using cell culture, image analysis, deep sequencing and mouse models.

School at: Pathology

Keywords: cancer, oral, skin, microscopy

Alphabetical by supervisor surname.
Supervisor: Dr Stefan Oehlers

Mycobacterial Program: Head - Professor Warwick Britton AO; Immune-Vascular Interactions Laboratory: Head - Dr Stefan Oehlers

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Keywords: Infection & immunity, cardiovascular & respiratory diseases, vascular biology, zebrafish

School at: Centenary Institute.

Our research group uses the zebrafish model system to better understand and treat this disease. The zebrafish is an emerging model for the study of infectious diseases that complements existing mouse infection models in the Tuberculosis Research Program at the Centenary Institute.

Mycobacterial infection results in the formation of complex aggregates of immune cells known as granulomas, and these can be readily visualised in zebrafish. These granulomas behave similarly to tumours in many ways including the way they recruit leaky blood vessels to the site of infection. We have shown that angiogenesis was attributed largely to chromosomal translocations. However, recent years have produced conclusive evidences that two or more transcripts can fuse at the transcription level irrespective of chromosomal translocations.

In this project we will expand these findings by determining the effects of vascularisation on host and bacterial physiology using a combination of in vitro cell culture assays, zebrafish infection experiments and mouse models of pulmonary TB.

School at: Infectious Diseases and Immunology

Keywords: infection & immunity, cardiovascular & respiratory diseases, vascular biology, zebrafish

Supervisor: Dr Ulf Schmitz

Gene and Stem Cell Therapy Program: Head - Professor John Rasko AO; Computational BioMedicine Laboratory: Head - Dr Ulf Schmitz

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Keywords: bioinformatics, trans-splicing, single cell sequencing, long read sequencing, big data, cancer biology

School of Medical Sciences

Graphical user interface, data integration, data visualization

In a large-scale analysis of alternative splicing across 2,500 human tissue samples and cell lines we generated a wealth of data regarding gene-, cell type-, tissue- and disease-specific intron-retention events. This data is in part accessible through a rudimentary web interface: http://mimirna.centenary.org.au/irfinder/database/.

In this project we will develop a sophisticated database and web interface design to provide an efficient and rich user experience facilitating a rapid success in the hunt for information about intron retention. The new IRBase 2.0 will provide data in interactive graphs and customized data retrieval options.

School at: School of Medical Sciences

Keywords: alternative splicing, database design, graphical user interface, data integration, data visualisation

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School at: School of Medical Sciences

Keywords: alternative splicing, database design, graphical user interface, data integration, data visualisation

To this, we will integrate expression profiles of microRNAs and genes, retention profiles and predicted gene-regulatory interactions between (i) microRNAs and target genes, (ii) transcription factors and target genes, and (iii) microRNA-intron retention interactions. For a selected sub network relevant in cancer we will construct a mathematical model of competitive post-transcriptional gene regulation.

School at: School of Medical Sciences

Keywords: microRNA, alternative splicing, bioinformatics, systems biology

Supervisor: Dr Ulf Schmitz

Gene and Stem Cell Therapy Program: Head - Professor John Rasko AO; Computational BioMedicine Laboratory: Head - Dr Ulf Schmitz

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MCRON synthesis and expression in leukemia

In a large-scale analysis of alternative splicing across 2,500 human tissue samples and cell lines we generated a wealth of data regarding gene-, cell type-, tissue- and disease-specific intron-retention events. This data is in parts accessible through a rudimentary web interface: http://mimirna.centenary.org.au/irfinder/database/.

In this project we will develop a sophisticated database and web interface design to provide an efficient and rich user experience facilitating a rapid success in the hunt for information about intron retention. The new IRBase 2.0 will provide data in interactive graphs and customized data retrieval options.

School at: School of Medical Sciences

Keywords: alternative splicing, database design, graphical user interface, data integration, data visualisation

Our research group uses the zebrafish model system to better understand and treat this disease. The zebrafish is an emerging model for the study of infectious diseases that complements existing mouse infection models in the Tuberculosis Research Program at the Centenary Institute.

Mycobacterial infection results in the formation of complex aggregates of immune cells known as granulomas, and these can be readily visualised in zebrafish. These granulomas behave similarly to tumours in many ways including the way they recruit leaky blood vessels to the site of infection. We have shown that angiogenesis was attributed largely to chromosomal translocations. However, recent years have produced conclusive evidences that two or more transcripts can fuse at the transcription level irrespective of chromosomal translocations.

In this project we will expand these findings by determining the effects of vascularisation on host and bacterial physiology using a combination of in vitro cell culture assays, zebrafish infection experiments and mouse models of pulmonary TB.

School at: Infectious Diseases and Immunology

Keywords: infection & immunity, cardiovascular & respiratory diseases, vascular biology, zebrafish

School of Medical Sciences
Core transcriptional networks in cell trans-differentiation

Core transcriptional networks are essential drivers and determinants of cell-fate transitions. To date, our mechanistic understanding of these essential regulatory layers is very limited, especially in the context of trans-differentiation, despite being one of the most promising therapeutic cell replacement strategies in regenerative medicine.

In this project, we will reconstruct gene-regulatory networks involving non-coding RNAs and mRNAs that drive trans-differentiation of human cells and identify key alternative splicing events during cell-fate transitions.

School at: School of Medical Sciences

Keywords: bioinformatics, systems biology, next generation sequencing data analysis

Modulating the gut microbiome to influence the progression of lung diseases

Dr Shen is a postdoctoral researcher in Professor Phil Hansbro’s group at the recently established UTS/ Centenary Centre for Inflammation, based at the Centenary Institute.

His research aims to provide deeper insights into the “gut-lung axis”. The project will explore how our lifestyle and environment alters the bacteria in the gut (the gut microbiome) to influence lung inflammation during severe asthma and chronic obstructive pulmonary disease (COPD). The major aim of this project is to delve deep into understanding the mechanisms by which bacteria interacts with and influences host immune cells and responses in the gut, and how this modulates inflammation in the lungs. This project will utilise well-established animal models combined with cutting-edge techniques for research.

Dr Shen received his PhD in medicine/immunology from Monash University in 2019. His research shows that host immune and environmental factors change the gut microbiome and alter colitis.

School at: UTS School of Life Sciences

Keywords: microbiome, gut, lung, respiratory, COPD, bacteria, asthma

Proteases in liver cancer

Primary liver cancer is the 4th leading cause of cancer related deaths and there is an urgent need to develop improved medical therapy. Our team is the first to find that the protease DPP9 is a druggable target in hepatocellular carcinoma (HCC). DPP9 inhibition has shown anti-cancer actions in acute myeloid leukaemia and lung cancer. This project aims to better understand the roles of DPP9 in the pathogenesis of HCC.

Projects will be these, or similar based on student interests:

1. To elucidate molecular mechanisms of DPP9 using liver cancer cell lines.
2. To generate cell-specific DPP9 depletion in mice to study the role of DPP9 in the immune system.
3. To measure growth of orthotopic tumours in DPP9 inhibitor treated mice.

Skills that the student can learn: cell culture, histopathology, immunohistochemistry, immunoblotting, qPCR, flow cytometry, confocal microscopy.

School at: Pathology

Keywords: protease, liver cancer, inflammation, DNA repair
Embrace the independence to pursue your desire of discovery.

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Centenary has supported PhD candidates that have gone on to revolutionise medical practice and saving countless lives.

“As a clinician, it has been a really interesting transition into the research world but with the support of an amazing group of experienced researchers in the lab, I am thoroughly enjoying pursuing my PhD at Centenary.”

Dr Julia Isbister, PhD Student pictured with her Supervisor, Professor Chris Semsarian AM, Head of the Molecular Cardiology Program

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**Molecular modeling of cancer-associated mutations in tumour suppressor genes**

The ‘master weaver’ protein CTCF, is mutated in endometrial cancer, as well as colorectal, stomach, breast and haemopoietic cancers. Our group was the first to demonstrate that the ubiquitous zinc finger (ZF) protein CTCF acts as a tumour suppressor gene. Missense mutations in CTCF are enriched in the DNA-binding ZF region.

We have shown that mutations in the ZF region can result in a loss- or gain-of-function in CTCF, which has implications for cancer development. We are currently modelling ‘hotspot’ mutations on published CTCF ZF structures to assess the impact of those mutations.

In addition, we will develop homology models for the ZF domain of CTCF-Like protein (CTCFL, also known as BORIS). CTCFL which shares 80% homology with CTCF within its ZF domain is aberrantly expressed in more than half of all cancers. Both factors have overlapping and unique DNA binding characteristics.

We will examine which residues are critical for binding of CTCF and CTCFL to the same DNA target sites and which ZF residues confer DNA binding specificity. This will provide important insight into the sibling rivalry that exists between CTCF and CTCFL in normal biology and cancer.

**School at:** Pathology

**Keywords:** protein structure, mutation, cancer, transcription factor

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**Understanding the role of CTCF genetic deletion in aggressive endometrial cancer**

CTCF is essential for the normal organisation of DNA in cells. Our team has discovered that CTCF is genetically deleted at high rates in the most aggressive and deadly types of endometrial cancer (Marshall, et al., 2017). CTCF deletion predominantly occurs in the Type II serous subtype of endometrial cancer and is associated with poorer overall survival in patients with serous tumours. Additionally, we have shown that CTCF deletions also occur in the clear cell subtype and this may be associated with tumour relapse and/or metastasis.

Our culturing of endometrial cancer cell-lines as 3D spheroids has shown that a functional consequence of CTCF deletion results in a loss of cell polarity – an early event in endometrial cancer pathology. Our analysis of gene expression data in CTCF heterozygous endometrial tumours has revealed a widespread dysregulation of transcription.

In this project we will examine those genes and biochemical pathways that are dysregulated in CTCF mutant endometrial cancers. We will investigate the impact of these genes on cell polarity in 3D spheroids which will give us important insights into early pathophysiological events underlying endometrial cancer.

**School at:** Pathology

**Keywords:** endometrial cancer, mutation, mouse models, cell biology
The role of MGA mutation in chronic lymphocytic leukaemia (CLL)

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in senior Australians. Every year nearly 1000 Australians are diagnosed with CLL and typically 80% of all new diagnoses are in patients over the age of 60 years.

CLL is a slow developing cancer affecting B cells. Genetic mutations acquired in these B cells result in their transformation into cancerous cells that can live longer and grow faster than normal B cells. Similar to many blood cancers, genetic alterations in CLL can be heterogeneous, and include point mutations, chromosomal deletions, amplifications and rearrangements. Recent reports have identified the gene encoding the transcription factor Max Gene Associated (MGA) to be recurrently deleted in CLL. MGA inactivation through chromosomal deletion or point mutation occurs in 4% of CLL, but this increases to 16% as CLL disease progresses to chemotherapy resistance. For liver-specific genetic diseases, current rAAV modalities have not provided the necessary high-level transduction efficiencies and humoral neutralisation properties necessary for curative outcomes in diverse patient groups.

Improved transduction efficiency of rAAV vectors has been achieved by engineering capsids with higher affinity or cell-specific tropism and increased resistance to neutralising antibodies. Increasing AAV-mediated therapeutic efficacy by modulating host entry factors remains unexplored. For example, KIAA0319L was recently shown to be an essential host entry factor for most AAV serotypes, however the biology and normal function of KIAA0319L is poorly understood. In this project, we will use a combination of biochemical, genetic and proteomic strategies to functionally characterise the host determinants that regulate KIAA0319L expression and distribution.

School at: Pathology

Keywords: gene therapy, adeno-associated virus, host factor, KIAA0319L

How does silica dust make TB worse?

The lung is one of the most important organs exposed to environmental pollution and pathogens. Lung inflammation and disease is a leading cause of death and disability globally, and an overlooked area is the intersection of silicosis and tuberculosis (TB).

Well-known as a disease of miners and stonemasons, silicosis has resurfaced in the sandstone basin which cups the Sydney region and continues to afflict millions of workers in hazardous occupations around the world. Silicosis predisposes to TB and patients with silicosis who develop active TB have poor outcomes. As 25% of the world’s population is infected with Mycobacterium tuberculosis, this is a serious problem.

The mechanisms by which silicosis impacts the body’s defenses against mycobacteria are poorly understood. This project will use a mouse model of silicosis and mycobacterial infection to examine how silicosis affects innate (dendritic cell and macrophage) and adaptive immune responses. The student will be part of a stimulating research team and develop skills in immunology, cellular biology and flow cytometry.

School at: School of Medical Sciences

Keywords: immunology, infectious diseases, tuberculosis, environment, inflammation

Finding safe and effective therapies targeting sex hormones and the microbiome for the commonest cause of stroke in children: cerebral cavernous malformation (CCM)

Cerebral cavernous malformations (CCMs) are vascular lesions of the central nervous system that affect 1 in 200 people. CCM lesions are prone to bleeds and are the major cause of stroke and sudden death in children. Current treatment for CCM is limited to high-risk neurosurgery. As such there is an urgent need for novel non-invasive, druggable treatment options.

Just as men have earlier onset and more severe cardiovascular diseases than women, recent clinical observations and our preliminary data in mouse models demonstrate a greater CCM burden in males. The male predisposition to CCM is likely to reflect an impact of sex hormones in its pathogenesis. Furthermore, we recently identified the gut microbiome as a critical stimulant of CCM. Interestingly, gut microbiota differs between males and females and microbiota influence sex hormone metabolism and action.

Hence, the project aims to elucidate the role that sex hormones and the microbiome play in the common sex difference in CCM. This could reveal a potential use of steroids, precision antibiotics/probiotics, and repurposing existing drugs as non-invasive therapeutic options for CCM.

School at: UTS School of Life Sciences

Keywords: stroke, cardiovascular diseases, mouse, microbiome, cerebral cavernous malformation
**Imaging transcription at single molecule resolution in a living cell**

The primary objective of this project is to develop a research study with general and specific in vivo techniques in stem cells and in vivo approaches in early stage mouse embryo to study the molecular basis of cell fate decision during embryogenesis. This work will take advantage of cutting edge approaches based on single molecule approaches to study the role of different components of the transcriptional machinery in stem cells. Two types of complementary approaches will be used in parallel either based on live imaging methods or on fixed cells with super resolution microscopy. Further the work will be complemented by genomic and transcriptomic approaches to correlate changes in gene output with molecular activity imaged in a cell. The biological question is centred around the molecular control of cell fate during lymphatic endothelial cell specification by a novel transcriptional effector. The work will involve wet and dry lab approaches to understand how this new gene modulates the program of lymphatic endothelial cell differentiation on a genome wide scale. Techniques used will cover a broad range of skills from phenotyping vascular networks using confocal microscopy to gene editing with crispr/cas9 and genomics and transcriptomics approaches. The project is directed to identification of changes in the vascular control of cell fate during lymphatic endothelial cell specification by a novel transcriptional effector. The work will involve wet and dry lab approaches to understand how this new gene modulates the genome-wide scale. Techniques used will cover a broad range of skills from phenotyping vascular networks using confocal microscopy to gene editing with crispr/cas9 and genomics and transcriptomics approaches.

**Molecular and cellular basis of lymphatic vascular development**

The primary objective of this project is to develop a research study with general and specific in vivo techniques in mouse or zebrafish model system to study the molecular and cellular biology of vascular development during embryogenesis. The biological question is centred around the molecular control of cell fate during lymphatic endothelial cell specification by a novel transcriptional effector. The work will involve wet and dry lab approaches to understand how this new gene modulates the program of lymphatic endothelial cell differentiation on a genome-wide scale. Techniques used will cover a broad range of skills from phenotyping vascular networks using confocal microscopy to gene editing with crispr/cas9 and genomics and transcriptomics approaches.

**Alzheimer's Disease: How age effects the blood vessels in the brain**

Alzheimer's Disease (AD) is an age-related disease that affects brain function. Ageing and its consequence to induce dysfunctional endothelial cells is one of the greatest risk factors for both AD and cardiovascular disease. We are studying the molecular consequences of ageing (cellular senescence) on endothelial cells and pericytes using single cell RNAseq analysis of mouse brain cells. The genes may expose novel insights into cellular ageing and potential targets for the development of senolytics, drugs designed to eliminate senescent cells and restore organ function.

**Calcified aortic valve disease: the role of the ageing**

Calcific aortic valve disease (CAVD) is the most common valvular heart disease in developed countries. However, the molecular mechanisms or targets for nonsurgical treatments, to prevent or slow the progression of CAVD, remain elusive. The incidence of CAVD increases with age, in an area of the aorta where blood flow is disturbed. Disturbed blood flow is associated with premature ageing of blood vessels and loss of the protective mechanisms against inflammation in the aorta. The project is directed to identification of changes in the aortic valve upon ageing using animal model and human tissue and the molecular signalling pathways that are altered with age.

**Student Research Projects for 2021**

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Alzheimer’s Disease: How age effects the blood vessels in the brain

Ageing is one of the greatest risk factors for cardiovascular disease including Alzheimer’s Disease. Cellular ageing, referred to as cellular senescence is an irreversible process activated in response to stress that is characterised by permanent cell cycle arrest, an active metabolic state and in changes to the inflammatory phenotype of the cell.

Endothelial cells are unique in showing both pro-inflammatory and anti-inflammatory senescence phenotypes. We have evidence to suggest that this dual phenotype maybe regulated through changes in the metabolic state of the cell.

This project will investigate this possibility and uncover the molecular pathway that controls the metabolic switch.

Associated Scientist: Dr Paul Coleman

E: p.coleman@centenary.org.au Pon: + 61 2 9565 6229

School at: School of Medical Sciences

Keywords: ageing, metabolism, inflammation

Proteases in the pathogenesis of chronic liver injury and cancer

Primary liver cancer is the 4th leading cause of cancer related deaths. We are addressing the urgent need to develop a greater understanding of pathogenesis for improved therapeutics. The pathogenesis of chronic liver injury and cancer is driven by chronic cell death and proliferation and inflammation. Cirrhosis generally precedes cancer in the liver.

Proteases are important in cancer pathogenesis and suit drug development. We primarily study fibroblast activation protein (FAP) and DPP9 as proteases associated with cancer pathogenesis.

I discuss with each student their interests, skills and aspirations in order to design a suitable project within these topics:

1. Liver complications of diabetes and chronic fatty liver.
2. Liver cirrhosis and cancer.
3. Protein biochemistry and inhibitors of FAP and DPP9.
4. Diagnosis of fibrosis in chronic liver disease and predicting treatable patients.
5. Potential therapies for cancer and NASH.

Training: We use sophisticated techniques in immunohistochemistry, flow cytometry, qPCR, immunoblotting, protease assays, ELISA and confocal microscopy. Projects can be in cell lines, mouse models or with specimens from RPA hospital.

School at: School of Medical Sciences

Keywords: cirrhosis, NASH, cancer, liver, DPP4, fibrosis, mouse, human

Blocking follistatin in ovarian cancer to prevent chemoresistance and recurrence

In the Directed Evolution laboratory, we harness the power of Darwinian selection to evolve proteins with new therapeutic activities. We have discovered that blocking follistatin activity could increase the sensitivity of ovarian cancer to primary chemotherapeutics.

Thus, we will evolve high affinity single-domain antibodies (nanobodies) against follistatin, to disrupt its signalling. This work will pave the way for new adjunctive therapies which could enhance the efficacy of primary chemotherapeutics in a wide range of cancers.

School at: School of Medical Sciences

Keywords: directed evolution, cancer, chemoresistance

Functional strategies to mitigate or eliminate PFAS from human and animal tissue

Per- and poly-fluoroalkyl substances (PFAS) are synthetic chemicals that resist heat and water, and have been widely used since the 1940s. Importantly, these compounds are highly stable in the environment and in some areas have penetrated ground water putting rural populations at risk of continued chronic exposure.

This project is part of a larger program to provide clear and experimentally validated evidence and meta-evidence for how PFAS exposure impacts human health, its biological mechanisms of action, and importantly how to treat individuals exposed to hazardous levels of PFAS.

Developing zebrafish embryos absorb PFAS from their aqueous environment and bioaccumulate these chemicals. We’ve discovered that embryos loaded with PFAS continue to endure toxic effects even once moved to an uncontaminated environment providing a high-throughput experimental system to identify small molecule treatments that stimulate PFAS elimination at the organism level. In this project we will perform unbiased small molecule screens to identify and validate novel potential treatments for PFAS exposure in humans.

School at: School of Medical Sciences

Keywords: environmental determinants of human health and treatment strategies
Supervisor: Dr Gang Liu
Centenary UTS Centre for Inflammation: Head - Professor Phil Hansbro

Understanding the role of extracellular matrix proteins in regulating lung fibrosis

Lung fibrosis is a progressive, debilitating, and severe lung disease, which is characterised by damage to lung tissues, and idiopathic pulmonary fibrosis (IPF) is one of the major lung fibrosis diseases in humans. It is characterised by lung tissue remodelling and fibrosis, where normal lung tissue is interspersed with interstitial fibrosis, honeycomb cysts and fibroblast foci.

In lung injury, extracellular matrix (ECM) proteins are secreted into the connective tissue to serve as scaffolds for tissue repair and regeneration. However, ECM proteins continue to be produced and deposited in lung tissues in IPF, and the process becomes irreversible. Current treatments to lung fibrosis have limited effect to reduce and inhibit lung fibrosis development in IPF.

Our recent studies have identified some key ECM proteins that targeting these proteins can reduce lung fibrosis and inflammation in an experimental model of lung fibrosis. In this research project, we aim to understand the mechanism of the ECM proteins regulate lung fibrosis in IPF.

School at: UTS School of Life Sciences

Keywords: lung fibrosis, idiopathic pulmonary fibrosis, animal models, extracellular matrix proteins

Novel treatments of alpha-1 antitrypsin gene deficiency induced chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a progressive pulmonary disease defined by emphysema and severe breathing difficulties. It is the 3rd commonest cause of chronic morbidity and death.

Alpha 1-antitrypsin (A1AT) deficiency is the major genetic predisposition to COPD. Endogenous proteases function to clear debris and damaged tissues from the lungs. However, when not properly controlled they have aberrant activity degrading elastin and various forms of collagen leading to lung damage.

It is well-known that deficiencies in A1AT lead to an imbalance in protease-anti-protease activity resulting in tissue damage and emphysema. More than 80% of the human genome produces RNAs that are not translated, and many of them are long non-coding (lnc) RNAs.

In this project, we aim to understand how lncRNA regulates A1AT deficiency-induced COPD and explore a potential treatment.

School at: UTS School of Life Sciences

Keywords: Alpha-1 antitrypsin, COPD, PCR, CRISPR

How the cornea responds to UV radiation

The cornea is covered by a multi-layered (stratified) sheet of clear epithelial cells, which protects it from pathogens and the environment. Like the skin, the cornea is exposed to damaging ultraviolet radiation (UVR) from sunlight.

This project will investigate how UVR affects stratification of the corneal epithelium and its barrier function against viruses such as coronaviruses. It will use advanced microscopy and image analysis methods to visualise the epithelial cells of living corneas as they divide, migrate and stratify.

The corneas from novel reporter strains of genetically modified mice will be used to locate and measure signalling responses in the living tissue, and probed with pathway-specific drugs to determine their importance.

School at: Pathology

Keywords: eye, cancer, COVID-19, UV radiation, microscopy

Genes and cell-cell interactions in tumour progression

Cancer cells within a tumour often have different mutations from neighbouring cells. This genetic heterogeneity enables novel cell-cell interactions to occur that are not possible in homogenous tumours. This opens up exciting new possibilities for understanding the pathogenesis of cancer and strategies for treating it.

To explore these interactions between cancer cells, we have identified clones of cells that interact to promote cancer cell growth in an experimental model of oral cancer.

This project will investigate the molecular genetic basis for this interaction, using cell culture, image analysis, deep sequencing and mouse models.

School at: Pathology

Keywords: cancer, oral, skin, microscopy
School at: School of Medical Sciences

Keywords: bioinformatics, systems biology, next generation sequencing data analysis

Role of lipid metabolism in alcohol-induced liver cirrhosis

Risky drinking continues to be a major concern in Australia. The major medical consequence of risky drinking is alcohol-induced liver cirrhosis (AC). Our discovery of novel variant in FAF2 gene (lipid droplet metabolism) associated with the risk of AC in drinkers, is significant because it fits well with the current knowledge of other single nucleotide polymorphisms (SNPs) in genes (PNPLA3, TM6SF2 and HSD17B13) also linked to lipid biology. Build-up of lipid droplets in the liver due to heavy drinking can cause inflammation, leading to cirrhosis in some drinkers.

My group is interested to understand the mechanisms of action of these genes in the development of cirrhosis. We will use our established zebrafish model of alcohol-induced liver injury. Function of risk genes and their mechanisms driving disease development will be studied using gene-editing (Crispr-Cas9), transgenics and state-of-art imaging technology. It will advance knowledge on the role of lipid biology genes in chronicity of AC development. Importantly, it will generate a list of new drug targets.

School: School of Medical Sciences

Keywords: cirrhosis, SNPs, lipid, alcohol, genetics, zebrafish, crisper

Core transcriptional networks in cell trans-differentiation

Core transcriptional networks are essential drivers and determinants of cell-fate transitions. To date, our mechanistic understanding of these essential regulatory layers is very limited, especially in the context of trans-differentiation, despite being one of the most promising therapeutic cell replacement strategies in regenerative medicine.

In this project, we will reconstruct gene-regulatory networks involving non-coding RNAs and mRNAs that drive trans-differentiation of human cells and identify key alternative splicing events during cell-fate transitions.

School at: School of Medical Sciences

Keywords: microRNA, alternative splicing, bioinformatics, systems biology

Deciphering the cross-talk between microRNAs and retained introns in cancer gene regulation

Perturbations to the highly calibrated system of gene regulation can have severe consequences and cause diseases including cancer. MicroRNAs can regulate dozens of target genes and intron retention has been found to be another mechanism of post-transcriptional gene regulation affecting hundreds of genes.

In this project we will identify gene-regulatory network modules using a data integration approach to determine patterns of competitive post-transcriptional gene regulation.

Toward this, we will integrate expression profiles of microRNAs and genes, intron retention profiles and predicted gene-regulatory interactions between (i) microRNAs and target genes, (ii) transcription factors and target genes, and (iii) microRNA-intron retention interactions. For a selected sub network relevant in cancer we will construct a mathematical model of competitive post-transcriptional gene regulation.

School at: School of Medical Sciences

Keywords: microRNA, alternative splicing, bioinformatics, systems biology

Bidirectional interaction between the cardiovascular system and infectious diseases

Our research group uses the zebrafish model system to better understand and treat this disease. The zebrafish is an emerging model for the study of infectious diseases that complements existing mouse infection models in the Tuberculosis Research Program at the Centenary Institute.

Mycobacterial infection results in the formation of complex aggregates of immune cells known as granulomas, and these can be readily visualised in zebrafish. These granulomas behave similarly to tumours in many ways including the way they recruit leaky blood vessels to the site of infection. We have shown that angiogenesis (dx.doi.org/10.1038/nature13967),vascular permeability (http://dx.doi.org/10.1093/nf/aji355), and haemostasis (http://dx.doi.org/10.1093/nf/aji355) aid mycobacterial growth in zebrafish infection models.

This project will expand these findings by determining the effects of vascularisation on host and bacterial physiology using a combination of in vitro cell culture assays, zebrafish infection experiments and mouse models of pulmonary TB.

School at: Infectious Diseases and Immunology

Keywords: infection & immunity, cardiovascular & respiratory diseases, vascular biology, zebrafish
Why do only some drinkers develop liver cirrhosis? Risk stratification of drinkers using genomics + clinical risk factors

Risky drinking continues to be a major ongoing concern in Australia despite public health measures. As 90% of alcohol is metabolised through the liver, vulnerable population, especially those with drinking problems, are at high risk of alcohol-induced liver cirrhosis (AC). There is limited information to predict who amongst the drinkers are at a greater risk of developing cirrhosis.

The project will utilize our multinational GenoMCC Consortium data from thousands of drinkers. We recently reported that algorithm combining a few genomic with clinical risk factors performed better than either alone in stratifying drinkers ‘at risk’ of developing AC.

We will generate predictive models and precision algorithm using machine learning (ML) tools as novel means in this disease to allow reliable identification and stratification of drinkers by disease risk. Understanding individual risks will revolutionise clinical management of patients with AC.

School: School of Medical Sciences

Keywords: cirrhosis, alcohol, genetics, coffee, diabetes, risk prediction, machine learning

Modulating the gut microbiome to influence the progression of lung diseases

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His research aims to provide deeper insights into the “gut-lung axis”. The project will explore how our lifestyle and environment alters the bacteria in the gut (the gut microbiome) to influence lung inflammation during severe asthma and chronic obstructive pulmonary disease (COPD). The major aim of this project is to delve deep into understanding the mechanisms by which bacteria interacts with and influences host immune cells and responses in the gut, and how this modulates inflammation in the lungs. This project will utilise well-established animal models combined with cutting-edge techniques for research.

Dr Shen received his PhD in medicine/immunology from Monash University in 2019. His research shows that host immune and environmental factors change the gut microbiome and alter colitis.

School: UTS School of Life Sciences

Keywords: microbiome, gut, lung, respiratory, COPD, bacteria, asthma

Circulating tumour cells to monitor cancer patients

Circulating tumour cells (CTCs) are tumour cells that have been released from the primary tumour tissue to form metastases by travelling through the blood and lymphatic system. Capturing and analysing these rare cells is now possible using our next generation liquid biopsy platform.

We are able to identify, capture and characterise these CTCs. Hence, this platform has the potential to provide ‘real-time’ cancer monitoring throughout all stages of a patient’s cancer journey and identify potentially effective treatments in cancers such as pancreatic cancer, lung cancer, and mesothelioma. Potential research topics include:

1. Evaluate CTCs to predict patient response and guide patient management.
2. Characterise CTCs using genetic, cellular and imaging techniques.
3. Establish and characterise patient-derived CTC organoid cultures.
4. Evaluate CTCs and other blood biomarkers as a diagnostic marker to improve early detection.

Skills/tools: Mammalian cell culture (3D), cell biology assays, western blot, RT-qPCR, microscopy, immunofluorescence, cell picking, mouse models

School: Pathology

Keywords: cancer, translational medicine, liquid biopsy, circulating tumour cells

Investigating CAR-T therapy for pancreatic cancer

Chimeric antigen receptor-engineered T-cell (CAR-T) therapy is an exciting new cellular immunotherapy for the treatment of cancer.

Isolated patient T-cells are modified to target a specific tumour surface antigen and then injected back into the patient. CAR-T therapy is now approved for blood cancers but the same success has not been observed in solid cancers.

Novel CAR-T therapies will be evaluated in pancreatic cancer using the latest cancer model systems including 2D cells, 3D organoids and mice models. To test the efficacy of CAR-T cells, cytotoxicity and immune activation/persistence will be evaluated, and mechanisms of resistance will be explored.

Skills/tools: mammalian cell culture, cell biology assays (including cellular impedance assays, live cell imaging), isolating T cells, lentivirus gene transfer, immune phenotyping (by flow cytometry), RT-qPCR, cytokine analysis (ELIZA), and mouse models

School: Pathology

Keywords: cancer, immunotherapy, CAR-T
Proteases in liver cancer

Primary liver cancer is the 4th leading cause of cancer related deaths and there is an urgent need to develop improved medical therapy. Our team is the first to find that the protease DPP9 is a druggable target in hepatocellular carcinoma (HCC). DPP9 inhibition has shown anti-cancer actions in acute myeloid leukaemia and lung cancer. This project aims to better understand the roles of DPP9 in the pathogenesis of HCC.

Projects will be these, or similar based on student interests:

1. To elucidate molecular mechanisms of DPP9 using liver cancer cell lines.
2. To generate cell-specific DPP9 depletion in mice to study the role of DPP9 in the immune system.
3. To measure growth of orthotopic tumours in DPP9 inhibitor treated mice.

Skills that the student can learn: cell culture, histopathology, immunohistochemistry, immunoblotting, qPCR, flow cytometry, confocal microscopy.

School at: Pathology

Keywords: protease, liver cancer, inflammation, DNA repair