# Beyond Boundaries



Heart Research Institute
Annual Review

2021

# Contents

Cover: Tiffany Goh, Cardiovascular Medical Devices Group
This page: Lauren Boccanfuso, Vascular Complications Group

# Our Mission

The HRI's mission is to prevent death and suffering from cardiovascular diseases, a complex array of diseases affecting the heart and blood vessels. We will address areas of unmet need in cardiovascular diseases, including coronary artery disease, stroke, peripheral artery disease, hypertension, heart failure, preeclampsia, congenital heart disease and pulmonary vascular disease, as well as metabolic complications such as diabetes.


Dr Sergey Tumanov, Arterial Inflammation and Redox Biology Group

## Specifically, our research programs will:

Provide greater understanding of the pathogenesis, development and early detection of cardiovascular diseases

Develop new drug therapies and devices to prevent and treat cardiovascular diseases and translate these through to clinical trials

Train the next generation of cardiovascular research leaders

Connect cardiovascular research communities to maximise collaboration and research translation.

### LOCATIONS

7 Eliza Street, Newtown, Sydney

Charles Perkins Centre,
The University of Sydney,
Camperdown, Sydney

### 14 SCIENTIFIC GROUPS

Arterial Inflammation and Redox Biology

Atherosclerosis and Vascular Remodelling

Cardiometabolic Disease

Cardiovascular Medical Devices

Cardiovascular Neuroscience

Cardiovascular-protective Signalling and Drug Discovery

Clinical Research

Coronary Diseases

Haematology Research

Heart Rhythm and Stroke Prevention

Microvascular Research

Thrombosis

Vascular Complications

Vascular Immunology

### CHAIR

Professor Len Kritharides

### HRI EXECUTIVE COMMITTEE

Dr Stephen Hollings
*Chief Executive Officer*

Professor Roland Stocker
*Director Science Strategy*

Emeritus Professor Carolyn Geczy
*Senior Executive Scientist*

Professor Ben Freedman
*Director External Affairs*

Professor David Celermajer
*Director Clinical Research*

Ms Elissa Dwyer
*Director, Human Resources*

Mr Adam Check
*Director, Fundraising and Philanthropy*

### DIRECTOR OF CARDIOVASCULAR RESEARCH, CHARLES PERKINS CENTRE

Professor Shaun Jackson

### HRI SCIENTIFIC EXECUTIVE COMMITTEE

Professor Roland Stocker
*Director Science Strategy*

Emeritus Professor Carolyn Geczy
*Senior Executive Scientist*

Professor Ben Freedman
*Director External Affairs*

Associate Professor Sanjay Patel
*Group Leader RPAH*

Associate Professor Mary Kavurma
*Group Leader HRI/Eliza Street*

Dr Anna Waterhouse
*Group Leader HRI/CPC*

Associate Professor Simone Schoenwaelder, HRI

### OUR PARTNERSHIPS

Sydney Local Health District and Sydney Health Partners

- Royal Prince Alfred Hospital
- Sydney Research

Charles Perkins Centre,
The University of Sydney

Australian Business
Number 41 003 209 952

827 collaborations over 44 countries

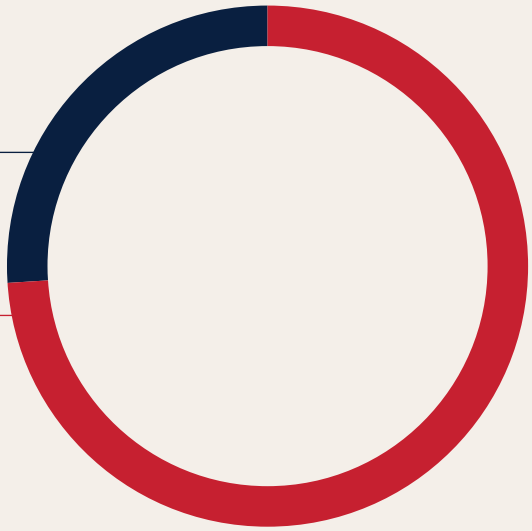
# HRI in 2021

# 2021 HRI Income

## Total Income
## $21,810,588

**Grants**
$5,773,756 (26%)

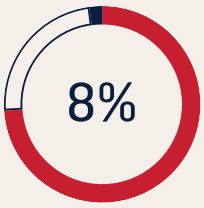
**Fundraising (incl Bequests)**
$16,036,832 (74%)



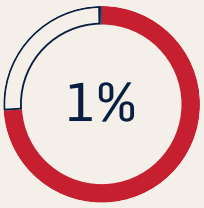
## Students Trained or Mentored

| | |
|---|---|
| Honours | 22 |
| Visiting Honours | 01 |
| Masters | 01 |
| PhD | 10 |
| Visiting PhD | 12 |
| Summer Scholars | 19 |
| Visiting Students | 08 |
| Winter Scholars | 01 |
| Work Experience | 02 |

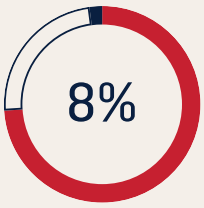
## 2021 Grant Income by Funding Body



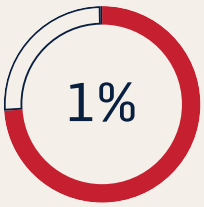

National Health & Medical Research Council
**$1,813,284**



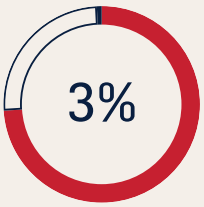

Universities
**$275,500**



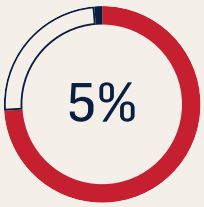

NSW Department of Health
**$1,782,421**




National Heart Foundation
**$267,500**




Research Block Grants
**$690,466**




Other
**$944,585**

**123** Discoveries published in peer-reviewed journals

**378** Citations by external world-wide researchers to work published by HRI researchers in 2021

**64** Scientific projects currently being undertaken

Download a full list of HRI publications and presentations here.

# Chair's Report

CHAIR

**Professor Len Kritharides**

MBBS, PhD, FRACP, FCSANZ, FAHA, FESC, FACC

## RENEWAL AND ADAPTATION

Biological systems are under continuous renewal. Cells grow, divide, clear debris, create and repair organelles and membranes, and replenish fuel supplies, while adapting to changes in their external environment. Biological processes in more complex organisms such as plants, animals and humans do this, integrating the response across different cell types and different tissues, while also adapting to changing social environments.

Organisations are in many respects like complex biological systems. They need to maintain and grow their business as usual, respond to changes in their external environment, while continually looking for opportunities to renew themselves. Renewal at an organisational level takes careful planning and commitment to follow through at all levels. The process of review and renewal is a special opportunity that sets the groundwork for the next five years, 10 years, or even longer. The Heart Research Institute (HRI) has had several cycles of growth and renewal in its 30-odd year history and is about to embark on its next cycle.

The "COVID-years" of 2020–2022 have served up many societal and organisational challenges. At HRI, "biological" adaptation to external circumstance required careful review of how we worked, where we worked (Eliza St, Charles Perkins Centre, Royal Prince Alfred Hospital (RPAH), and indeed working from home) and what we worked on. HRI and its staff adapted brilliantly, carrying on exciting work throughout this period, maintaining an enviable record of staff safety, and still ensuring all health guidelines were met. Special thanks to our CEO Dr Stephen Hollings and his management team, and all our HRI staff and scientists for this achievement. This period has, however, brought into stark relief the challenges of having our scientists on three campuses – Eliza St, Charles Perkins Centre and RPAH.

Despite these external circumstances, a number of grant successes were achieved (pages 18–19). Four of our scientists (Assoc Prof Rachel Cordina, Dr Anna Waterhouse, Assoc Prof John O'Sullivan and Prof Ben Freedman) were awarded NSW State Government Cardiovascular Research

**The Board has recognised for some time that for HRI to continue to adapt successfully to the changing external research landscape, careful reflection, planning and organisational change would be needed.**

Capacity Program grants, Assoc Prof John O'Sullivan and Dr Xuyu (Johnny) Liu were awarded Heart Foundation and Drug Discovery Initiative grants respectively, and grants investigating stroke led by Profs Shaun Jackson and Ben Freedman, and COVID-19 led by Dr Freda Passam, were other notable successes.

Prof Jackson was Scientific Director at the HRI for approximately seven years until 30 June, 2021. During his tenure there was a significant expansion in the range of research undertaken at HRI, especially in areas related to thrombosis, and in the commercialisation of research. Highlights include Prof Jackson being awarded a National Health and Medical Research Council (NHMRC) Investigator grant in 2019, and a $2.7M grant from the Medical Research Future Fund (MRFF) to conduct a phase IIa clinical trial of a new drug to treat stroke in 2021. The presence of HRI at the Charles Perkins Centre certainly expanded during this time, and a number of successful early and mid-career scientists were recruited to HRI. A very important contribution of Prof Jackson was his work with Prof Graham of the Victor Chang Cardiac Research Institute to lead the NSW Government Cardiovascular Disease Research Capacity Building initiative worth $150M over 10 years.

Manisha Patil, Vascular Complications Group, and Dr Sergey Tumanov, Arterial Inflammation and Redox Biology Group

During 2021 HRI benefited from the scientific leadership of Prof Carolyn Geczy (Senior Executive Scientist throughout the year) and Prof Roland Stocker (Chair of the Scientific Executive Committee and Director Science Strategy since July 2021). They have led the expansion and role of the HRI Scientific Executive Committee, have represented HRI scientists at HRI Board meetings, and, working closely with the management team, they have brought a number of excellent initiatives to fruition and improved scientist engagement throughout all levels of HRI.

The Board has recognised for some time that for HRI to continue to adapt successfully to the changing external research landscape, careful reflection, planning and organisational change would be needed. As part of this process, an external Scientific Review of HRI, co-ordinated by Prof Stocker, was commissioned in 2021, and took place early 2022. The review undertaken by an outstanding panel of independent scientists conveyed a sense of excitement at emerging opportunities, but also provided clarity about opportunities for growth and development. The Board will be working closely with HRI scientists to address the recommendations of the report. Most important among these is the appointment of a new Scientific Director.

This year also saw renewal at the Board level. Joining the Board in 2021 were Mr Merrick Howes, Emeritus Prof Merilyn Sleigh, Dr Kate McBride, and The Hon Peter McGauran AM. The Hon Bruce Baird AM, Dr Teresa Anderson AM, and I come off the Board in early 2022. Prof Stephen Simpson AC, Mr Tony Pollitt, Mr Richard Rassi, Mr Rod Halstead and Prof Andrew Boyle will all remain on the Board. I thank past and present HRI Board Governors who have worked tirelessly on HRI's behalf.

Our donors, here in Australia, and overseas in the UK and in New Zealand, have provided us with exceptional support throughout HRI's history. However, the ongoing support received over the past two difficult years has been nothing short of exceptional. To our donors, our fundraising team, and our management team led by Dr Stephen Hollings, thank you.

After 13 years on the Board, including four and a half years as Chair, I am stepping off the Board and am delighted to be handing over the position of Chair to The Hon Peter McGauran. Peter brings a great history of distinguished public service and enthusiastic commitment to medical research to the role. As this is my last Annual Report, I would like to use this opportunity to thank our donors, the HRI Board, HRI scientists, HRI administrative staff and HRI members for the wonderful opportunity to work with everyone during this time.

# Scientific Review

DIRECTOR SCIENCE STRATEGY

**Professor Roland Stocker**

SENIOR EXECUTIVE SCIENTIST

**Emeritus Professor Carolyn Geczy**

After a challenging year in 2020, issues related to COVID-19 impacted all aspects of HRI research effort again in 2021. This limited the ability of researchers to perform their experiments and to have the personal contacts that are so vital to the exchange of ideas and collaborative interactions necessary to achieve the critical research outputs that are essential for high impact publications and peer-reviewed grant success. Despite this, our scientists have found ways to maintain their productivity and push the boundaries, although the sustained nature of virtual meetings and restricted work hours and conditions made this demanding. The wellbeing of our staff and operational flexibility, together with safe work practices and testing around COVID-19, have been important considerations to support staff in this environment.

Notwithstanding, there were some significant scientific achievements during 2021 that give a much-needed boost moving forward. Prof Roland Stocker was awarded the 2021 Basic Science Award from the Society for Free Radical Research Europe. Distinguished Prof Annemarie Hennessy was appointed Pro-Vice Chancellor Health and Medicine of Western Sydney University, and President of the International Society for the Study of Hypertension in Pregnancy. Drs Mary Kavurma and John O'Sullivan were appointed Associate Professors in the Faculty of Medicine and Health, The University of Sydney.

HRI researchers made intense efforts to obtain grant funding, with some outstanding successes. Early career researcher fellowships funded by the NSW Health Cardiovascular Research Capacity Program were awarded to Dr Anna Waterhouse and Assoc Profs Rachel Cordina and John O'Sullivan, and a Senior Fellowship to Prof Ben Freedman. Dr Arnold (Lining) Ju received a National Heart Foundation Future Leaders grant. Dr Freda Passam launched a new project investigating links between the AstraZeneca COVID-19 vaccine and blood clots that received significant attention across 374 pieces of media with a total reach of almost 31 million people.

In line with the current push by the Australian Government to translate basic research findings to clinical applications, Prof Shaun Jackson's awarded Targeted Translation Research Accelerator project, in collaboration with Prof Richard Payne (Chemistry, The University of Sydney) and colleagues, aims to develop novel antithrombotic therapies for improved treatment of acute ischaemic stroke. Prof Jackson also received a National Medical Research Future Fund (MRFF) Cardiovascular Health Mission grant to proceed with phase IIa trials in humans that will test the

safety and tolerability of another drug developed by the group to treat stroke. Media interest in this award reached a historical high for HRI, with the story featured across 279 media outlets and amounting to a readership reach of 32.5 million. A second MRFF grant to detect preventable ischaemic stroke related to atrial fibrillation (AF) through screening, builds on Prof Ben Freedman and colleagues' pivotal research in Australia and internationally. It will fund a Clinical Trials & Cohort Study using ECG to enable more effective treatment for people with known AF, thereby reducing incidence of stroke.

A new initiative to support collaborative research between our researchers and HRI UK and with HRI NZ was developed. HRI NZ awarded $NZD1M shared by three grants to HRI researchers for cardiovascular research that will benefit New Zealand; HRI UK awarded £1M to be shared by six research grants to HRI researchers for cardiovascular research that will benefit the UK. This funding, starting in 2022, has provided a boost of morale, particularly to our early career researchers, that will positively sustain research outputs. More details of these and other grant successes appear in Notable Awards on pages 18–19 and Research and Media Highlights on pages 12–17.

HRI research was published in 124 papers during 2021, with seven across the prestigious journals *Nature, Nature Communications, Nature Metabolism* and *Nature Protocols*. Although conference travel was curtailed, many investigators presented their work virtually, which allowed our researchers to present on the national and international stage, an important feature of showcasing our research, and for building collaborations and networks.

**A new initiative to support collaborative research between our researchers and HRI UK and with HRI NZ was developed.**

A summary of presentations by HRI researchers in 2021 can be downloaded at www.hri.org.au/reports. New educational seminars to our students and young researchers, in addition to our regular research seminars and collaborative seminars with the cardiovascular community, are proving popular. The success of the two-day Sydney Cardiovascular Symposium, hosted in collaboration with the Victor Chang Cardiac Research Institute, was a notable end-of-year event and a credit to the organisers, Drs Melissa Farnham and Jessica Maclean.

Postgraduate and undergraduate students contribute significantly to the research environment and to research

Dr Anita Ayer, Arterial Inflammation and Redox Biology Group

outputs by HRI. During 2021, HRI held a successful virtual Careers Open Day, and welcomed 18 honours students (two from New Zealand) and three PhD students (two from New Zealand), a successful recruitment after the committed endeavours of several staff members. Five students were awarded Honours degrees; one, Taqi Shaik (Arterial Inflammation and Redox Biology Group) was awarded the University Medal by The University of Sydney.

Emphasis on commercialisation of research has increased because of the strategic alliances required by some major granting bodies to undertake translation of research results into clinical applications and a team has been put in place to assist with this.

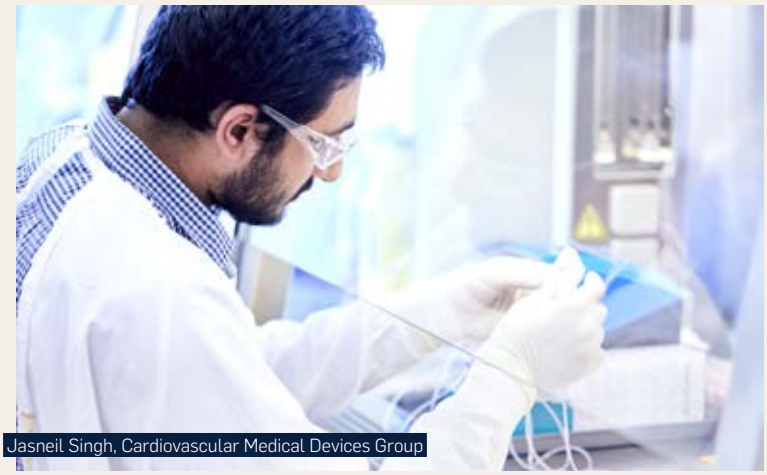
COVID-19 has impacted research productivity in several ways, including accessibility of supplies and reagents. We are grateful for the continued efforts to maintain the research effort, particularly during the difficulties experienced during this time, by our Scientific Support teams, and for their dedication in keeping our workplace safe. Continued COVID-19 testing of staff and regular Town Hall meetings to inform staff have been important. These have allowed research staff and students to access the laboratories to continue key experiments, although working from home continued through virtual meetings.

We also acknowledge the consistent efforts of our operations and management teams led by Dr Stephen Hollings, who faced many challenges during 2021 that often demanded more than could be expected under normal circumstances. We thank the Fundraising team for their outstanding efforts during 2021, particularly the media attention attracted by several HRI scientists. Congratulations go to the members of the Brand, Communications and Digital team, who won a Public Relations Institute of Australia (PRIA) Silver Award for the 'Help prevent heart attack' fundraising appeal.

We greatly appreciate our many valued donors who have contributed to keeping HRI at the forefront of research. Your support, interest and generosity are important in so many facets of our mission to maintain our research excellence.

# 2021 Research & Media Highlights

Cardiovascular-protective Signalling and Drug Discovery Unit



Jasneil Singh, Cardiovascular Medical Devices Group

## CARDIOVASCULAR MEDICAL DEVICES HIGHLIGHTS

- Blood clots that form on medical devices can halt their function, and the clots can break off and lodge in the patient's body, causing further damage, eg, a stroke, deep vein thrombosis or a lung embolism. The Group created lab-based model systems to evaluate clot structure on materials with different properties and found that materials that are more wettable had less dense clot structures. These clots could also be more easily broken down using a protein that breaks down clots. This information could be useful to understand which clots in medical devices can be broken down and which clots break off, providing the potential to personalise treatment of medical device clots for patients. It could also help in the design of medical devices that do not cause blood clots.
- The success of blood contacting implants hinge on their ability to minimise thrombosis and encourage healing. In the body, the blood vessel cells prevent blood clotting, but in artificial vascular grafts used to replace diseased vessels, the regeneration of this anti-thrombotic cell layer on the graft material is key to long-term success. In partnership with the Rnjak-Kovacina Lab (UNSW) and Bilek Lab (USYD), previously inert silk graft materials were functionalised with the vascular protein perlecan, creating a bioactive surface to encourage vessel cell growth and inhibit thrombosis. The Group found that this new silk material promoted vessel cell growth and minimised thrombus formation. This bioactive silk graft material is a promising approach to prevent thrombosis while enhancing graft healing.

## HEART RHYTHM AND STROKE PREVENTION HIGHLIGHTS

- The Group gave presentations on self-screening for atrial fibrillation (AF) in general practices at both the Cardiac Society of Australia and NZ meeting, and the largest and most prestigious world meeting by the European Society of Cardiology.
- The World Heart Federation (WHF) published an update of its Roadmap on AF in Global Heart. WHF is the global peak body of over 200 national and continental heart foundations, cardiac and civil societies, and patient organisations from over 100 countries. Prof Freedman co-chaired this Roadmap and is the first author. It provides a comprehensive global plan to overcome roadblocks in AF management, addresses health inequalities such as Indigenous health and roadblocks in low-middle income countries, and advocates a greater reliance on eHealth and mHealth solutions, which are a feature of the Group's research. Prof Freedman gave international presentations on this Roadmap (all virtual due to COVID-19 restrictions), in Japan, China, Europe, the UK, Venezuela and Argentina.
- The Heart Rhythm Congress (UK) named a new lecture the "Professor Ben Freedman Lecture" – the first lecture was given in October 2021 by Prof Freedman and will be repeated annually.

## ARTERIAL INFLAMMATION AND REDOX BIOLOGY HIGHLIGHTS

- The Group published a seminal paper in the prestigious journal *Nature Communications* describing a novel paradigm for cellular signalling in 'inflamed' arteries based on specific and selective redox changes to activate key target proteins.
- Prof Roland Stocker was awarded the "Basic Science Award" from the Society for Free Radical Research Europe, in recognition of extraordinary achievements in the field of arterial redox signalling controlling blood pressure during inflammation.

Prof Shaun Jackson on The House of Wellness

## THROMBOSIS HIGHLIGHTS

- Prof Shaun Jackson and Assoc Prof Simone Schoenwaelder filed a patent for "Treatment of thrombosis and associated disorders with an anti-platelet agent".
- To accelerate the Group's stroke research, a successful Christmas fundraising appeal to raise $30,000 for a state-of-the-art macroscope was developed, and Dr Jessica Maclean was interviewed by Science Reporter Gabrielle Rogers for 9News. An order for the macroscope has been placed, with delivery expected for 2022. Read more here.
- Dr Maclean was awarded a Kanematsu Research Award 2021 from the Royal College of Pathologists of Australasia (RCPA) Foundation as well as a Thrombosis and Haemostasis society of Australia and New Zealand (THANZ) Scientific & Education Trust Grant and an NSW Cardiovascular Research Network (CVRN) Professional Development Award to attend a Cert IV in Leadership and Management.
- Channel 7's The House of Wellness show invited Prof Shaun Jackson to talk about stroke, and why research into the next generation of stroke treatment is so vital. View the segment here.

Dr Xuyu Liu, Cardiovascular-protective Signalling and Drug Discovery Unit

**The Cardiovascular-protective Signalling and Drug Discovery Unit was awarded the USyd Drug Discovery Initiative and Cardiovascular Initiative Partnership Award.**

## CARDIOVASCULAR-PROTECTIVE SIGNALLING AND DRUG DISCOVERY HIGHLIGHTS

- The dietary lipids that the Unit discovered from broccoli sprouts have, for the first time, enabled the use of new druggable proteins in the ubiquitome, in platelets. The Unit's contribution to this work was recognised by The University of Sydney with the award of the USyd Drug Discovery Initiative and Cardiovascular Initiative Partnership Award. This research also secured seed funding through an HRI NZ grant ($400,000) to make further strides toward clinical translation with NZ rising star biophysicists Dr Kai Chen and Dr Wanting Jiao, from the Victoria University of Wellington.
- Dr Xuyu Liu was appointed Review Editor for *Frontiers in Medical Technology*, attributed to his research impact in antithrombotic discovery. Dr Liu was also appointed a Royal Australian Chemical Institute (RACI) USYD Ambassador and participated in coordinating interstate early-career researcher and postgraduate student conferences.
- The Unit was invited to provide an authoritative review and perspective on the current and future roles of peptide chemistry in innovative drug discovery for a leading journal in chemistry, *Frontiers in Chemistry*.

## MICROVASCULAR RESEARCH HIGHLIGHTS

- The Unit contributed to the publication of two papers, one in *Current Opinions in Nephrology and Hypertension* and the other in *Nature Communications*. These publications highlighted the emergence and detailed the mechanisms of novel signalling pathways in the arteries.
- The Unit was awarded a competitive grant ($235,405) by HRI UK to interrogate how septic shock pathologically alters arterial membrane potential and calcium signalling. This grant was in collaboration with Drs Adam Greenstein and Harry Pritchard of the University of Manchester, UK.
- Key contributions were also made by the Unit to Australian cardiovascular research symposiums through invited speaker presentations by Dr Chris Stanley at the Australian Vascular Biology Society annual conference and as a co-panel chair discussing the "Impacts of COVID-19 on the heart" as part of the Sydney Cardiovascular Symposium.

## VASCULAR IMMUNOLOGY HIGHLIGHTS

- Publications in 2021 demonstrated for the first time the pharmacology of aspirin in pregnant women, and the barriers to aspirin use in our communities. This has provided robust data with which to advise women about the risks of preeclampsia as well as the benefits of preventive treatment.
- The team received a significant National Health and Medical Research Council grant via Western Sydney University, which will be used to create a new Molecular and Cell Biology Unit, headed by Dr Chia-Chi (Jat) Liu.


Dr Yen Chin Koay, Cardiometabolic Disease Group

## CARDIOMETABOLIC DISEASE HIGHLIGHTS

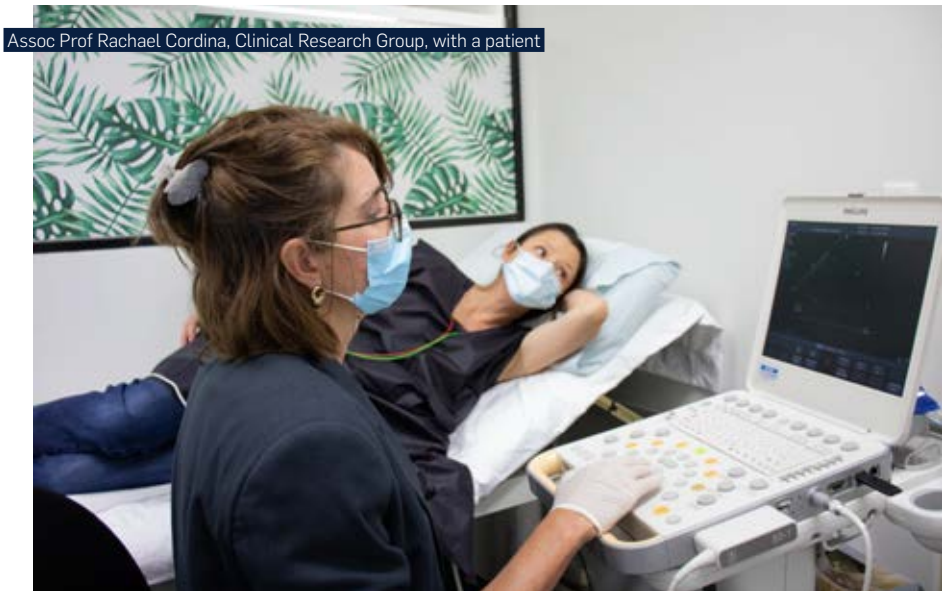
- Assoc Prof John O'Sullivan was awarded a Level 2 National Heart Foundation Future Leader Fellowship as well as a Vanguard Grant.
- The Group led two research publications in *Nature Communications* and two research publications in *Cardiovascular Research*. They were also awarded funding from the National Heart Foundation ($150,000) and NSW Office of Health and Medical Research ($750,000) to support their work in HFpEF, also known as stiff heart failure.


### INVESTIGATING THE LINK BETWEEN ASTRAZENECA COVID-19 VACCINE AND BLOOD CLOTS

*Appeared in The Australian, 10News, 7News and 9News, 2 August 2021, and featured 166 times across radio news networks*

Dr Freda Passam and the Haematology Research Group spearheaded a pilot study that screened patients 10 days after their first AstraZeneca COVID-19 vaccine injection to determine their risk of developing a rare blood clot from the vaccine. Dr Passam says, "Currently the only warning signs a blood clot may form are a headache or bad stomach pains within a month of the vaccine being administered. This research will alert us to the risk of clotting earlier and answer why it happens in some and not others."

Announcement of this project to the public was incredibly popular and resulted in 197 media mentions across radio, TV, print and digital media. View the full media report and video here.


Assoc Prof Rachael Cordina, Clinical Research Group, with a patient

### CLINICAL RESEARCH HIGHLIGHTS

The Group published over 30 papers in international literature, including practice and clinical guidelines, and recruited key staff to their two major congenital heart disease (CHD) projects, to advance their CHD registry and exercise work. Dr Rachael Cordina was promoted to Associate Professor level, and Drs Ben Moore and Michelle Lim, PhD students in the Group, were awarded their doctorates by The University of Sydney.

### ATHEROSCLEROSIS AND VASCULAR REMODELLING HIGHLIGHTS

- The Unit was invited to provide an expert review and views by esteemed journals *Cell Stem Cell* (2020), *Nat Metabolism* (2021) and *Arteriosclerosis, Thrombosis, and Vascular Biology* on cellular reprogramming in atherosclerosis.
- Dr Ashish Misra presented the Unit's findings at meetings of the Australian Atherosclerosis Society and the Cardiovascular Research Network, and at the Cardiovascular Research Centre, University of Edinburgh, UK. Dr Misra was awarded funding through Perpetual IMPACT and HRI UK grants to identify novel methods of atherosclerotic plaque regression.
- Alex Li completed his Honours project with distinction as part of his Bachelor of Biomedical Engineering and will continue his vital research through a PhD with the Unit, starting in 2022.


### WORLD'S LARGEST SCREENING PROJECT TO LAUNCH IN AUSTRALIA TO PREVENT DISABLING STROKES

*Appeared on 7News, 4 June 2021*

Prof Ben Freedman was interviewed by Senior Reporter Helen Wellings for 7News, which has an average of 1.4 million viewers each evening and is Australia's most-watched television news service, on the SAFER-AUS study. This will be the largest world study of screening for atrial fibrillation to prevent stroke, and the results will impact current screening guidelines to prevent stroke and improve stroke-related healthcare. HRI is collaborating with multiple partners on this pioneering project in Australia and the UK. View the full media report and video here.


The Cardiometabolic Disease Group found that increases in nicotine levels were associated with a 2.3-minute increase in the time spent with oxygen saturations below 90 per cent.

## SILENT SLEEP DANGER FOR SMOKERS UNCOVERED IN WORLD-FIRST STUDY

*Appeared in The Australian, 10 November 2021; 7News, 6 November 2021; and on 2GB radio 11 November 2021*

Sleep apnoea occurs when a person's throat and upper airway become partly or completely blocked during sleep, causing short periods where breathing stops. One of the markers of severity of sleep apnoea is time spent with an oxygen saturation less than 90 per cent. The Cardiometabolic Disease Group found that increases in nicotine levels were associated with a 2.3-minute increase in the time spent with oxygen saturations below 90 per cent, meaning that for every cigarette a person smoked, they were more likely to have dangerously low levels of oxygen.

This story was covered across 175 pieces of media, in Australia (digital, print, radio and TV) and in the UK, NZ, USA, Germany and the UAE in digital articles. View the full media report and video here.

## CORONARY DISEASES HIGHLIGHTS

- The Group published 18 papers in journals including the *Journal of the American Heart Association*, *Cells*, and *Heart, Lung and Circulation*.
- The Group was also awarded grants from NSW Health for "Colchicine nanotherapy – a novel targeted drug delivery system for atherosclerosis" ($449,000) and from the Australia-India Strategic Research Fund for "Aortic and lung inflammation following COVID: a marker of cardiac events" ($351,068).
- An HRI UK grant for "Integrating transcriptomics with lineage tracing to identify novel candidates to stabilise atherosclerotic plaque" ($318,000) was awarded in conjunction with the Atherosclerosis and Vascular Remodelling Group.


Haematology Research Group

## HAEMATOLOGY RESEARCH HIGHLIGHTS

The Group was awarded a grant through the Medical Research Future Fund for their work investigating COVID-19 vaccine-associated thrombosis. Another grant was received through The University of Sydney Nano Institute Grand Challenge for their project "Organ-on-chip for blood clot assessment". The Group also published five papers in international journals including *Blood*, *Journal of Autoimmunity*, and *Antioxidants & Redox Signaling*.

## A NOVEL DIAGNOSTIC TEST FOR HEART ATTACK

*Appeared on News.com.au, 29 May 2021*

The Arterial Inflammation and Redox Biology Group, led by Prof Roland Stocker, is working on creating a world-first: a novel diagnostic test to help identify and potentially treat people who are at high risk of a heart attack due to the presence of unstable plaque in the arteries. This research was run by 14 digital news outlets, syndicated across News Limited sites, including the Daily Telegraph, Adelaide Advertiser, Courier Mail and Herald Sun. Prof Stocker was also interviewed by Sydney radio network 2SM on this work.

## CARDIOVASCULAR NEUROSCIENCE HIGHLIGHTS

- The Unit filed a provisional patent for a novel diagnostic for sleep apnoea. They also published three papers and delivered six conference posters and presentations, with Dr Melissa Farnham giving two conference presentations as an invited speaker.
- Two Honours students with the Unit completed and were awarded First Class honours. The Unit was also awarded the James N Kirby Foundation Grant to research how obstructive sleep apnoea causes disease, and the Franklin Women's Theresa Anderson Award.
- Dr Farnham was featured in the article "How to make your arteries younger" in the March 2021 edition of the *Australian Women's Weekly*.
- Dr Farnham was also interviewed on 2GB radio in September 2021 about her research on a ketogenic diet to help manage low blood sugar in diabetes, with the interview appearing across eight other local radio stations. View the full media report here.


Vascular Complications Group

## VASCULAR COMPLICATIONS HIGHLIGHTS

- High density lipoprotein (HDL), or the "good" cholesterol, can have beneficial effects in atherosclerosis and diabetes. However, its mechanism(s) of action are not fully elucidated. Using a physiological model of diabetes-accelerated atherosclerosis, the Group sought to examine the effects of reconstituted HDL (rHDL) on disease. The findings suggest that a targeted approach for rHDL therapy may be necessary, with rHDL administration more beneficial in atherosclerotic patients with metabolic dysfunction. This work was in collaboration with researchers from the Kolling Institute and UNSW and published in the *Journal of Diabetes Research*.
- Additional publications for 2021 include a paper published in *Frontiers in Pharmacology* with colleagues from the Kolling Institute and the HRI Coronary Diseases Group. This study showed that activating the $\beta_3$ adrenergic receptor ($\beta_3$AR) could have therapeutic potential in patients with peripheral artery disease (PAD), since it can stimulate the development of new blood vessels and improve cardiovascular homeostasis. In a second collaborative study with the Coronary Diseases Group and researchers from UNSW, the Group showed that colchicine could inhibit inflammation, in part, by its ability to suppress neutrophil extracellular trap formation. This work was published in the *Journal of the American Heart Association*.
- Additional highlights include a successful Australian Cardiovascular Alliance bioplatforms grant to comprehend gene-to-gene, cell-to-cell, and gene-to-cell interactions in PAD pathophysiology using single cell RNA sequencing from patients and pre-clinical models.
- PhD student Ms Manisha Patil was awarded third place in the moderated flash talks at the Sydney Cardiovascular Symposium. She was also selected as a finalist for the Heart Pitch, NSW Cardiovascular Research Network. Dr Siân Cartland was invited to speak at the Australian Atherosclerosis Society Seminar Series on her study on the protective role of myeloid-derived suppressor cells in atherosclerosis.

## GLOBAL MEDIA INTEREST IN HRI'S WORLD-FIRST STROKE DRUG TRIAL

*Appeared in The Australian, 19 July 2021; 10News, 17 July 2021; and across 128 regional radio stations, resulting in over 250 media stories*

HRI researchers led by Prof Shaun Jackson have developed an anti-clotting drug that offers new hope to stroke sufferers. This drug, which has successfully completed two phase I clinical trials, has the potential to improve blood flow to the brain following stroke onset, reducing associated death and disability. With the award of a $2.7M Federal Government Medical Research Future Fund grant, this research can progress to phase II clinical trials in stroke patients. View the full media report and video here.

## PESKY BUSH TICKS COULD BE KEY TO SAVING LIVES IN WORLD-FIRST HRI RESEARCH

*Appeared in The Australian, 27 September 2021, and across 64 regional radio stations 28 September 2021*

HRI's Prof Shaun Jackson, Assoc Prof Simone Schoenwaelder, Dr Xuyu Liu and Dr Mike Wu, together with Prof Richard Payne of The University of Sydney, received a $750,000 grant from the Australian Government's Targeted Translation Research Accelerator (TTRA) program to continue their project investigating the potential use of bush tick saliva for developing anti blood-clotting drugs to treat stroke. The team is modifying the proteins found in the saliva of these ticks to discover what the modifications do to the activity of the protein – something never done before. These proteins are effective anticoagulants that stop blood from clotting.

The research was promoted across 83 pieces of media. View the full media report and video here.

# Notable Awards 2021


## Medical Research Future Fund grant awarded for stroke research

Prof Shaun Jackson was awarded a $2.7M Federal Government Medical Research Future Fund grant for a phase IIa clinical trial in humans of a new anti-clotting drug that has the potential to improve blood flow to the brain and prevent brain injury, reducing death and disability from stroke. This research will be carried out at leading stroke units at the Royal Prince Alfred and Prince of Wales Hospitals in Sydney, John Hunter Hospital in Newcastle, Royal Adelaide and Royal Melbourne Hospitals, and managed by the George Institute. Read more here.


Dr Ashish Misra

### DR ASHISH MISRA

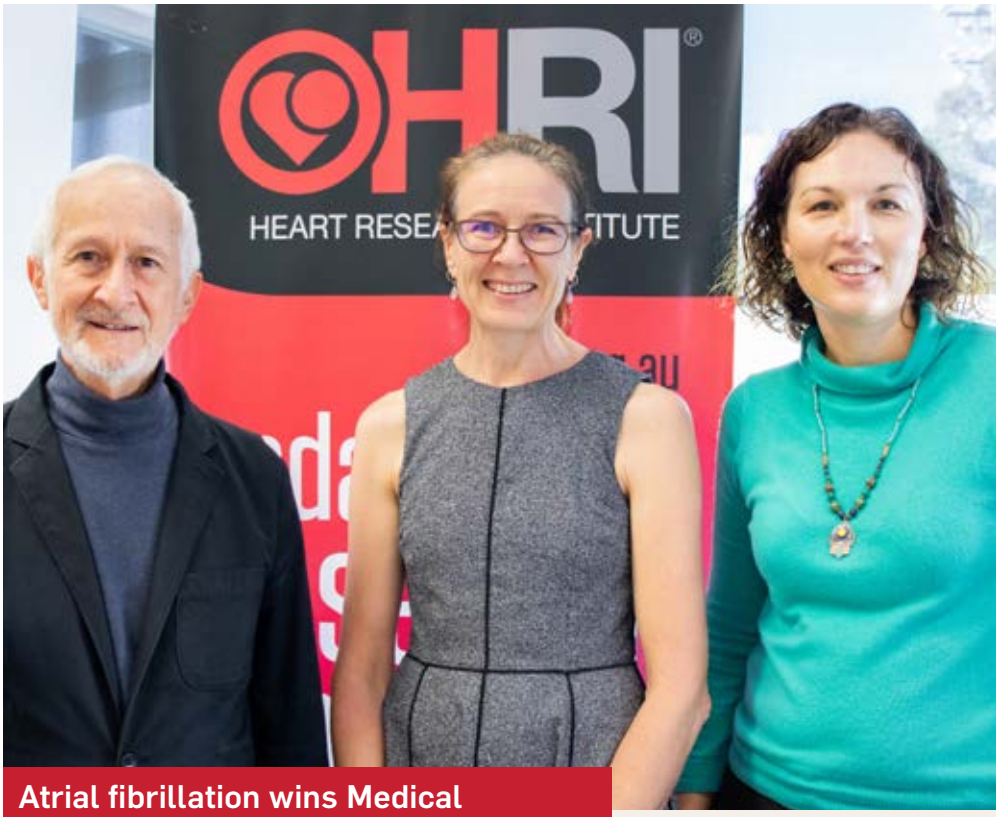
Dr Ashish Misra was awarded his second Perpetual IMPACT grant to investigate the anti-inflammatory effects of colchicine in reducing cardiovascular risk. Dr Misra found that colchicine stabilises the diseased arteries so that they have less risk of rupturing and causing heart attack. This new IMPACT grant will investigate mechanisms underlying the suppressive effects of colchicine and in combination therapies using colchicine. Read more here.

### HRI NZ DONORS FUND THREE GRANTS

Three grants funded by HRI NZ donors were awarded to support HRI's vital research into cardiovascular disease with collaborators in New Zealand. The Cardiovascular-protective Signalling and Drug Discovery Group led by Dr Xuyu Liu, was awarded a grant for "Photo-responsive anticoagulants enable precise control of localised clot lysis therapy". The Clinical Research Group, led by Prof David Celermajer, was awarded for "Congenital Heart Alliance of Australia and New Zealand (CHAANZ) Congenital Heart Disease Registry; Initiating the New Zealand CHD Registry". The Haematology Research Group, led by Dr Freda Passam, was awarded for "Defining the diabetic platelet proteome". Read more here.

## Quadruple success for HRI

HRI researchers were awarded four grants under the NSW Cardiovascular Research Capacity Program. Early-Mid Career Researcher (EMCR) Grants were awarded to Dr Anna Waterhouse and Assoc Profs Rachael Cordina and John O'Sullivan, and a Senior Researcher Grant was awarded to Prof Ben Freedman, for a total of over $2.3M to advance research in the fight against cardiovascular disease – the world's number one killer. Read more here.




## Atrial fibrillation wins Medical Research Future Fund grant

Prof Ben Freedman, Dr Nicole Lowres and Dr Katrina Giskes (pictured L–R) received a $1.7M Medical Research Future Fund grant poised to transform Australia's stroke-related healthcare. Atrial fibrillation (AF), the most common abnormal heart rhythm, causes one in three strokes that are often severe and largely preventable. AF affects about 10 per cent of people aged over 70 and increases stroke risk by five times. The grant will be used to screen those over 70 for AF, to provide definitive evidence on whether more intensive ECG screening prevents stroke, morbidity and death. Read more here.

### HRI UK AWARDS SIX SIGNIFICANT GRANTS

Six grants funded by HRI UK donors were awarded to ensure the advancement of critical heart research with collaborators based in the UK. The Arterial Inflammation and Redox Biology Group, led by Prof Roland Stocker, was awarded for "Developing a novel molecular probe to identify high-risk AMI patients". The Atherosclerosis and Vascular Remodelling Group, led by Dr Ashish Misra, was awarded for "Integrating transcriptomics with lineage tracing to identify novel candidates to stabilise atherosclerotic plaque". The Cardiometabolic Disease Group, led by Assoc Prof John O'Sullivan, was awarded for "Determining the interaction of ketone metabolism with mitochondrial respiration in heart failure with preserved ejection fraction and myocardial infarction". The Heart Rhythm and Stroke Prevention Group, led by Prof Ben Freedman, was awarded for "SAFER and SAFER-AUS: External stakeholder qualitative comparative analysis". The Microvascular Research Group, led by Dr Chris Stanley, was awarded for "A 'potential' to fix peripheral arterial tone in sepsis". The Vascular Complications Group, led by Assoc Prof Mary Kavurma, was awarded for "Novel mechanisms mediating SIPS in cardiovascular disease".

Read about other research highlights on pages 12–17, or download a full list of HRI awards here.

# Arterial Inflammation and Redox Biology Group

GROUP LEADER

**Prof Roland Stocker**

PhD, FAAHMS, FSAMS

## OUR MISSION

The mission of the Arterial Inflammation and Redox Biology Group is to understand the contribution of specific oxidative processes to the formation of unstable atherosclerotic plaque. We aim to understand the mechanisms and factors that distinguish formation of unstable versus stable plaque, and how this knowledge can be used to selectively identify and treat unstable plaque.

Our key research areas are: (i) high-risk atherosclerotic plaque, identification, and treatment; (ii) arterial inflammation; and (iii) arterial redox biology.

## OUR IMPACT

Atherosclerosis is the biggest cause of heart attack, stroke, and death in Australia.

It occurs when there is a build-up to fatty deposits and inflammatory cells in the wall of your arteries, which carry

oxygen to your heart and other tissues. Atherosclerotic lesions may be divided into two types: stable and unstable. Stable plaque builds up over years and causes arteries to become hardened, eventually restricting blood flow to the heart and other organs, which can be readily detected and treated with appropriate intervention. Unstable plaque is vulnerable to 'rupture' before it substantially restricts blood flow. These plaques are difficult to detect/identify yet can be fatal when they rupture and cause acute thrombosis and occlusion of the artery.

The Group is trying to understand what changes in the arteries, how they become diseased and how atherosclerosis can be prevented. More specifically, they examine the contribution of arterial inflammation and oxidative processes to the formation of unstable plaque, and how we can use this information to detect high-risk plaque and interfere with the formation and rupture of these plaques.

## RESEARCH PROJECTS

### Treatment of high-risk atherosclerotic plaque

This project tests the hypothesis that pharmacological inhibition of the pro-inflammatory and oxidant-producing enzyme myeloperoxidase (MPO) stabilises 'vulnerable' lesions and hence may prevent a heart attack or stroke. MPO is expressed in certain white blood cells where it plays an important role in the innate immune system by producing hypochlorite (bleach) to kill bacteria and other pathogens. However, there is also evidence for MPO contributing to vascular disease by inducing endothelial dysfunction (*Arterioscl Thromb Vasc Biol* 2019;39:1448) and destabilising atherosclerotic plaque (*Eur Heart J* 2018;39:3301). The project is a collaboration with Dr Alkystis Phinikaridou and Prof René Botnar (King's College, London) and AstraZeneca (Sweden). It makes use of a new class of molecules, ie, 2-thioxanthines, that effectively inhibit MPO. Using pre-clinical models, we are currently investigating how MPO inhibition stabilises existing unstable plaque, how this relates to intra- vs extra-cellular MPO in plaque, and for how long MPO needs to be inhibited for a lasting beneficial effect. Together with our collaborators at King's College, we are also investigating whether MPO inhibition prevents plaque rupture and thrombosis in a model system.

### Non-invasive identification of high-risk atherosclerotic plaque

Acute myocardial infarction ('heart attack') remains the most common cause of death in Australia, and atherosclerotic plaque rupture with blood clotting and artery blockage accounts for most myocardial infarctions. Despite this, assessment of specific characteristics that predispose plaques to rupture is not currently incorporated into standard diagnostic or treatment regimes. Non-invasive, molecular imaging of biological processes known to contribute to plaque rupture is an exciting new way to potentially identify patients at risk of heart attack. We recently discovered that the pro-inflammatory enzyme myeloperoxidase (MPO) contributes to the formation of plaque with features of plaque vulnerable to rupture (*Eur Heart J* 2018;39:3301). Therefore, it is a potential target for molecular imaging of high-risk plaque. Our laboratory is assessing the utility of molecular imaging of myeloperoxidase activity using molecular magnetic resonance imaging (MRI) and positron emission tomography (PET) to specifically identify vulnerable plaque by their increased MPO activity. In addition to using pre-clinical models of plaque instability and rupture, we are increasingly focusing our attention on human carotid and coronary arteries. This work is a collaboration with Dr Alkystis Phinikaridou and Prof René Botnar (King's College, London) and Dr Imran Rashid (University Hospitals Cleveland) and Assoc Prof Andrew Jabbour (St Vincent's Hospital, Sydney). The validation of such diagnostic tools could have significant impact for the assessment management of heart disease.

### Biomarkers of unstable, high-risk atherosclerotic plaque

In addition to non-invasive imaging, we also aim to identify biomarkers of high-risk atherosclerotic plaque. Using state-of-the-art proteomics, metabolomics and lipidomics, this project characterises the molecular changes that distinguish stable from unstable atherosclerotic plaque in pre-clinical models, whether some of these characteristic molecular changes can be detected in blood of animals and, if so, how these findings extend to humans suffering from acute coronary syndrome or stroke. If successful, these studies may open the way for the development of novel biomarkers for and treatments of patients at elevated risk of a heart attack or stroke.

Find out more: www.hri.org.au/AIRB


Arterial Inflammation and Redox Biology Group

# Atherosclerosis and Vascular Remodelling Unit


UNIT LEADER

**Dr Ashish Misra**

PhD, MTech, BSc

## OUR MISSION

The mission of the Atherosclerosis and Vascular Remodelling Unit is to identify and gain insights from the genetic and molecular pathways involved in atherosclerotic disease in which the build-up of plaque in blood vessels causes thrombotic events including heart attacks. We aim to exploit these pathways to improve therapies with the aim of eradicating atherosclerotic diseases.

Our main objective is to broaden understanding of the cellular and molecular mechanisms involved in blood vessel wall patterning and define the role of these pathways in vascular abnormalities and complications. We continue to link these insights into translational research to prevent and treat atherosclerosis in humans.

To this end, we employ a unique blending of exclusive pre-clinical models and cultured cells, as well as human samples, with the aim of unveiling the pathogenesis of atherosclerosis.

Our ultimate goal is to prevent and reverse certain vascular diseases to prevent heart attacks and strokes.

## OUR IMPACT

Atherosclerotic cardiovascular disease is the leading cause of death globally, accounting for approximately one third of all deaths. Currently available therapies are not universally effective and do not reverse vascular disease completely, resulting in premature deaths and reduced quality of life for disease sufferers. With the need for continued treatment, there is a large burden on the health care system. Our work to identify the factors and signalling mechanisms involved in cardiovascular disorders has the potential to improve treatment options and eradicate atherosclerotic disease, thus increasing life spans and decreasing its burden on society.

## RESEARCH PROJECTS

### The role of Notch signalling in cardiovascular disease and related pathologies

Notch has been comprehensively studied as a conciliator of cell-to-cell communication that mediates cell fate decisions of progenitors. While Notch signalling has been extensively studied in cell fate determination at distinct development stages of mammalian cells and cancer stem cell progenitor maintenance and renewal, the functional role in vascular wall patterning and cardiovascular disease is not well understood. By using advanced microscopic techniques, fate mapping approaches and single cell clonal analysis, we aim to study the role of Notch signalling in blood vessel wall patterning and maintenance of smooth muscle cell progenitors in developing walls as well as disease of the vasculatures. Thus, we believe that the investigation of Notch signalling in vascular biology promises to be a fruitful way forward to designing new therapeutics.

### Factors and regulators of smooth muscle cells and macrophages in progression of atherosclerosis

Atherosclerotic plaque consists of smooth muscle cells (SMCs) and macrophages in the malefactor lesion and are comprised of a lipid-laden core covered by a fibrous cap. Plaque rapture, due to weak caps, leads to thrombosis with dire consequences such as myocardial infarction and stroke. SMCs and macrophages are key players in this process. Although extensive research has been done in the past on atherosclerosis, exactly how cells from normal blood vessel walls contribute to atherosclerotic plaques is still far from clear. Our studies aim to discover the origin of the cells that form healthy blood vessels, how these cells contribute to plaque formation, and how these plaque cells can be manipulated to advantageously stabilise plaques to prevent rupture.

Atherosclerosis and Vascular Remodelling Unit

## Social impact

Atherosclerosis is considered the underlying cause of most cardiovascular diseases. Our research aims to understand the complex processes involved in the development of atherosclerosis and to identify interventions that may be able to reverse or stop atherosclerosis. Through gaining insights into the fundamental cellular workings that contribute to inflammation and plaque development, our research will identify key markers and pathways that should be targeted therapeutically to halt or prevent plaque formation in blood vessels.

Many current medications used for atherosclerotic management have extensive side effects limiting their use. Hence, we also investigate how such medications provide beneficial effect in atherosclerotic disease. The findings from these projects can guide new therapeutic discoveries that have fewer side effects and greater effectivity.

### Modulating coronary atherosclerosis through perivascular fat

Organ-to-organ communications are vital for living systems and play critical roles in cellular homeostasis. Perivascular adipose tissue (PVAT) anatomically proximal to vasculature has a distinctive cellular composition that modulates a range of cardiovascular disease processes. We have previously shown that low dose colchicine therapy in patients with coronary disease significantly reduced inflammatory trans-coronary cytokine levels. As such, we hypothesise that colchicine pre-treatment prior to cardiac surgery will reduce diffusion of inflammatory cytokines from the vessel wall, thereby inhibiting differentiation of pre-adipocytes into mature adipocytes. Ultimately, this novel project will uncover how biological processes observed in one tissue (eg, PVAT) may influence key processes observed in a different tissue (eg, blood vessel). In turn, understanding these inter-organ communications will increase our understanding of pathways in cardiovascular disease, and hence provide new avenues to explore with existing and new therapeutics. Read more about this project here.

Find out more: www.hri.org.au/AVRU

# Cardiometabolic Disease Group

GROUP LEADER

**Associate Professor John O'Sullivan**

MD, PhD, MSc, Cert Biostatistics (Harvard), FRACP, FAHA, FRCPI

## OUR MISSION

The mission of the Cardiometabolic Disease Group is to transform the management of heart failure, especially "stiff" heart failure, or heart failure with preserved ejection fraction (HFpEF).

We aim to make fundamental advances in understanding how the heart uses fuel to generate energy.

We employ clinical and preclinical research programs to address our aims. We combine a specialist HFpEF clinic, the Sydney Heart Bank (Director, Dr Sean Lal), the world's largest cryorepository of human heart tissue, a novel cardiac biopsy program with Prof Paul Bannon, cardiac MRI, a human ex vivo myocardial tissue slice model, murine heart failure models, ex vivo beating hearts, and stable isotope tracing.

We also examine the relationship of diet, microbiome, and cardiac development from in utero to adulthood.

## OUR IMPACT

We are performing two clinical trials that will replenish a vital molecule in the hearts of patients with HFpEF. These trials will be performed at the Royal Prince Alfred Hospital in Sydney and The Alfred Hospital in Melbourne (with collaborator Prof David Kaye), and Assoc Prof John O'Sullivan as the Chief Investigator of the trials.

We have recently discovered a new fuel pathway in the heart, which serves as a rescue fuel in HFpEF. Remarkably, this pathway can be activated by replenishment of the above molecule. We were recently awarded grants from the National Heart Foundation (Level 2 FLF; Vanguard), NSW OHMR (Capacity Building Grant; EMCR Fellowship), and HRI UK to perform these clinical trials.

## RESEARCH PROJECTS

### Transforming diagnosis and treatment of stiff heart failure

Our unique collection of technologies/capabilities places us at the forefront of HFpEF research. Using these strategies, our aims are as follows:

1. Determine key mechanistic underpinnings in each subclass of HFpEF
2. Develop novel management strategies and treatment guidelines to treat each HFpEF subclass (with Dr Sean Lal, co-Director of HFpEF clinic and Director of Sydney Heart Bank)
3. Develop novel therapeutics to improve HFpEF outcome (with Dr Xuyu Liu, HRI)
4. Employ novel techniques in human heart tissue to uncover novel mechanisms and test new treatments (with Prof Paul Bannon, RPAH and The Baird Institute).

Outcomes: New management guidelines and therapeutic agents for HFpEF, the most common form of heart failure globally that currently has no approved pharmacotherapies.

### Leveraging cardiac substrates to improve cardiac energetics and outcomes in diabetic cardiomyopathy and HFpEF

The "stiff" type of heart failure, where the heart cannot relax properly, has become the most common type of heart failure. While a range of therapies has been developed for the better-understood impaired-squeeze type of heart failure, shockingly there are no therapies for the stiff, impaired-relaxation type of heart failure, which is called heart failure preserved ejection fraction (HFpEF).

We have recently identified key pathogenic changes in human and model system HFpEF left ventricular myocardium and have also identified therapeutic strategies based on each of these discoveries.

We perform investigation of human heart tissue in conjunction with Dr Sean Lal from Sydney Heart Bank (over 17,000 samples, one of the largest in the world). We run a dedicated HFpEF clinic in our hospital, in which we use cardiac MRI to carefully characterise key features of HFpEF including extracellular volume, microvascular disease and fibrosis.

We have extensive tools to probe mechanisms including, in conjunction with HRI's Dr Xuyu Liu, drug modification technology to enhance therapeutic effectiveness. We also perform primary cardiomyocyte culture isolation from our human HFpEF myocardial tissue and our murine HFpEF myocardium to further probe mechanism. Read more about this project here.

**Dietary-microbiome-metabolic interactions in cardiovascular disease**

We are studying the interaction of dietary macronutrients with the microbiome, gut and plasma metabolome on cardiac phenotypic expression. Recently, we discovered a profound effect of high dietary fibre (resistant starch) diets on microbial profile and the plasma redox system, energetics, gut-derived vitamins, citric acid cycle metabolites, and a potent effect on tryptophan metabolism that confers anti-inflammatory effects. We are investigating further a tryptophan derivative that is produced exclusively in the gut and seems to have important roles in inflammatory-driven diseases like atherosclerosis and insulin resistance. This work is being performed with Prof Stephen Simpson and Assoc Prof Andrew Holmes at the Charles Perkins Centre, The University of Sydney.

**A key metabolic switch in cardiometabolic disease**

Non-alcoholic fatty liver disease (NAFLD) is now the most common form of liver disease in the Western world. We recently discovered a new plasma biomarker (dimethylguanidino valeric acid [DMGV]) of liver fat that independently predicted diabetes up to 12.8 years before diagnosis in three distinct human cohorts of different ethnicity (O'Sullivan et al., *J Clin Invest*, 2017). We have

Assoc Prof John O'Sullivan

subsequently shown that DMGV is a "lifestyle" molecule, and predicts who will and will not respond to exercise intervention to modify their cardiovascular risk. We have delineated the dietary factors that alter its blood levels. It is also a marker of future coronary artery disease in patients independent of other risk factors. Future work will determine if modulating the generative pathway can modulate metabolic and cardiovascular risk. Read more about this project here.

**Uncovering the interaction of obstructive sleep apnoea with cardiac metabolism, function, and disease**

Working with HRI's Dr Melissa Farnham and Dr Kristina Cook, we have recently uncovered that intermittent hypoxia (as seen in obstructive sleep apnoea) causes hallmarks of cardiac insulin resistance and changes in cardiac substrate utilisation such as upregulation of cardiac ketone bodies. We have developed a program that includes home sleep studies in all our heart failure patients (with Prof Peter Cistulli, ResMed Chair in Sleep Medicine), a lab model of intermittent hypoxia (Dr Melissa Farnham, HRI), with expertise in the master regulator of hypoxia transcriptional change, HIF-1$\alpha$ (Dr Kristina Cook, Charles Perkins Centre). Read more about this project here.

**Developmental and dietary origins of myocardial disease**

We examine the effects of maternal diet on cardiac development in utero, and thereupon its effects on adult cardiac development and disease. The insights gained from our studies thus far have reframed understanding of dietary regulation of cardiac development in utero; for example, we have found that the type of monosaccharide ingested is a major determinant of foetal cardiac size. We will now explore the long-term effects of in utero cardiac thickening secondary to ingestion of fructose or sucrose-enriched diets.

With Assoc Prof Kim Bell-Anderson (Charles Perkins Centre), we have uncovered striking cardiac enlargement in in vivo models of pregnancy during ingestion of diets enriched with sucrose or fructose (compared to glucose and normal chow). To further explore this, we are performing RNA seq in these in vivo models. Read more about this project here.

Find out more: www.hri.org.au/CAMDG

## Social impact

Our group is providing hope for patients with HFpEF. This most common form of heart failure has almost no treatments. We will soon be performing the first clinical trials in HFpEF to directly target mechanisms in HFpEF, led by Assoc Prof John O'Sullivan.

We have established a "Stiff Heart Failure Alliance" across Sydney Local Health District (SLHD) that aims to improve recognition of HFpEF, and to harmonise investigation and management. Part of this Alliance is recognition of patients as key stakeholders and formalising this recognition with Patient Advocacy Groups, and forming an enabling "Community of Practice" across SLHD.

# Cardiovascular Medical Devices Group

## OUR MISSION

The mission of the Cardiovascular Medical Devices Group is to develop new medical devices for cardiovascular research and medicine to improve patient outcomes.

We focus on creating new medical devices for two major goals: 1) to design new biomimetic model systems that replicate clinically relevant environments to improve research and development of new therapies and devices, and 2) to develop new materials to make medical devices to reduce their complications.

The team uses cutting-edge bioengineering tools to develop new models and materials. We use the models to evaluate materials and understand the interplay of events in disease progression and at the biomaterial interface. Using this strategy, we aim to improve medical device function as well as create novel devices, diagnostics and drug and non-drug-based avenues for therapies.

## OUR IMPACT

Cardiovascular disease remains the leading cause of death worldwide despite tremendous success in new therapeutics and technologies in recent decades.

One reason for this is because we do not fully understand disease progression and side effects of interventions. Many drugs and medical devices that look promising during development, however, do not show efficacy in the clinic.

GROUP LEADER

**Dr Anna Waterhouse**

PhD, BSc (Hons I)

Drugs fail to reduce disease burden. Medical devices cause complications such as blood clotting (thrombosis) and require patients to receive blood thinning drugs as mitigation. This failure is largely to do with the fact that many model systems we use to evaluate drugs and devices in the laboratory do not adequately replicate clinical conditions.

We use engineering principles to replicate clinical conditions, such as blood flow, in the laboratory on a small scale. We also take inspiration from nature to design new materials to be used in medical devices to reduce their side effects.


Cardiovascular Medical Devices Group

## RESEARCH PROJECTS

### Biointerfaces

Understanding the interactions of medical devices with patients' blood, proteins and cells will allow the development of more sophisticated and compatible materials for medical devices for the diagnosis and treatment of cardiovascular disease. We investigate how material surface properties dictate blood clot structure and mechanical properties. This has implications for the stability of blood clots, their mechanical properties, and if they can be broken down or break off under blood flow.

### Biomimetic model systems

Advances in material fabrication techniques and 3D printing in micro and nanotechnology have revolutionised bioengineering, allowing high precision manipulation of materials for modelling medical systems and devices in the lab. Using these strategies, biomimetic in vitro model systems can be generated to recreate physiological conditions to evaluate medical device materials, geometries and drugs. Device failure mechanisms and how different disease states progress can be investigated with the aim of developing new treatments or preventative therapies.

*Creating micro-systems to study medical devices and their failure mechanisms*

Utilising the new facilities at The University of Sydney Nano Institute, this multidisciplinary project aims to create microsystems that mimic aspects of medical device materials and geometries. Using these microsystems, we will study how variations in material properties and blood flow dynamics govern the initiation of biomaterial-induced thrombosis. This knowledge can ultimately be used to improve or generate new materials for use in medical devices to improve their function and patient outcomes. Read more about this project here.

*Microsystem to replicate blood vessel dynamics*

We are developing microsystems that replicate aspects of blood vessel function to understand cell dysfunction and ultimately study disease initiation and cell interactions with varying materials. This will allow us to evaluate new drugs and novel therapies. These systems use human-derived cells and therefore could potentially reduce the use of animals in pre-clinical testing of new therapies.

## Social impact

We are working towards the development of technologies that would enable patient-specific care through new diagnostics, therapies and materials for medical devices.

### Bioengineering smart materials

Using bioengineering strategies, increasingly sophisticated materials can be constructed, and we have the capacity to modify or build materials on the nano scale. By combining physical, chemical and biological methods, medical devices can be manipulated to interact with, repel or adhere proteins or cells to improve medical device function, create novel diagnostics and medical devices, and both drug and non-drug-based avenues for therapies.

*Slippery surface coatings to prevent thrombosis and pathogenic biofouling of medical devices*

Newly developed, super slippery, liquid-repellent surface coatings have great potential to revolutionise medical devices, imparting anti-adhesive properties to materials.

Surface adhesion of proteins and cells is the driving factor in medical device fouling in processes such as thrombosis and pathogen adhesion in biofilm formation. We aim to clarify the mechanism by which the liquid-surface, Tethered-Liquid Perfluorocarbon (TLP), is anti-adhesive to proteins, mammalian cells and bacteria, with the goal of translating this to medical devices in the clinic to prevent their failure. Read more about this project here.

*Nanorobotics*

Molecular-level changes in early heart disease occur on the nanoscale, and current diagnostic methods are inadequate for early detection. Bio-inspired by immune cells, we have established a multidisciplinary team from HRI, science, medicine and engineering to build synthetic nanorobots that move around the body to find and identify early-stage diseased blood vessels.

In this project, we are focusing on designing and developing haematological and immunological compatible biomolecular devices by integrating molecular, protein and materials engineering. Read more about this project here.

Find out more: www.hri.org.au/CVDG

# Cardiovascular Neuroscience Unit

UNIT LEADER

**Dr Melissa Farnham**

PhD, BSc (Hons I)

## OUR MISSION

The focus of the Cardiovascular Neuroscience Unit is on how the brain controls breathing and blood pressure. We are interested in what goes wrong in the brain to result in the development of cardiovascular disease. We study peptides and their receptors in cardiovascular, autonomic, centres of the brain. Our current research aims to understand the central mechanisms driving the sympathetically mediated increases in blood glucose and blood pressure in models of sleep apnoea. By understanding the mechanisms driving the cardiovascular consequences of sleep apnoea, we aim to identify new therapeutic targets to treat sufferers and reduce disease burden.

## OUR IMPACT

Cardiovascular disease (CVD) remains the leading cause of death in Australia and worldwide. It is often present with other confounding conditions such as obesity or obstructive sleep apnoea (OSA), both of which are independent risk factors for CVD.

The global burden of OSA is recently estimated as approximately 1 billion people and is comorbid in 30–80 per cent of cardiovascular (particularly hypertension) conditions and in approximately 70 per cent of diabetics. The associated Australian healthcare and economic costs due to comorbid disease and lost productivity are over $19B per year and are largely attributed to undiagnosed OSA. In conditions such as OSA, excess sympathetic activity may trigger development of cardiometabolic diseases, but research and concrete evidence is lacking.

We aim to significantly advance this research area. Our unique models and techniques are designed to uncover a previously unexplored mechanism that suggests OSA induces autonomic plasticity, which is important in the pathogenesis of CVD.

Results have the potential to dramatically expand our knowledge into the effects of intermittent stimulation and the capacity for plasticity to occur in primitive, life-sustaining areas of the brain.

## RESEARCH PROJECTS

### The autonomic consequences of sleep apnoea: a critical role for neuropeptides

OSA is characterised by repetitive pharyngeal collapse during sleep, with resultant oxygen desaturation (intermittent hypoxia) and sleep fragmentation. Metabolic effects of intermittent hypoxia occur rapidly. These early changes could initiate triggers that promote insulin resistance and development of type 2 diabetes in human OSA conditions.

Importantly, an excitatory neuropeptide and its receptors are present in areas of the brain activated by hypoxia; these areas control both blood pressure and blood glucose. In humans, genetic variations in this neuropeptide or its receptors are linked to sleep and metabolic disorders. Our focus is on how intermittent stimulation of brain circuits regulate blood glucose and blood pressure.

We recently showed that a neuropeptide is necessary in the brainstem for the sympathetic response to acute intermittent hypoxia. Our exciting new data indicates that the characteristic sympathoexcitation of OSA, that is likely to cause most of the subsequent pathological metabolic changes, is mediated by intermittent release of small amounts of this neuropeptide that act on receptors located on sympathetic neurons in the spinal cord.

### Low carbohydrate (ketogenic) diet in type 1 diabetes: do ketones protect the brain from adverse effects of hypoglycaemia?

Type 1 diabetes accounts for 10–15 per cent of Australian diabetic patients. Type 1 diabetic patients are prone to repeatedly experiencing low blood sugar levels (hypoglycaemia), which results in a condition called hypoglycaemia unawareness. This condition, termed 'hypoglycaemia-associated autonomic failure' (HAAF), is life-threatening for type 1 diabetic patients.

Glucose is the major energy source for the brain under normal physiological conditions. However, during extended fasting, following exercise, or while on a high fat/low carbohydrate (ketogenic) diet, an alternative source of energy becomes available – ketone bodies. Although ketones are effective in the preservation of brain cognitive functions under hypoglycaemic conditions in type 1 diabetic patients, the effects of ketones on brain reflex response to recurrent hypoglycaemia and the development of HAAF in this patient population are unknown.

The aim of this project is to investigate the low carbohydrate ketogenic diet as a potential strategy in preventing the detrimental consequences of insulin-induced hypoglycaemia and the development of HAAF in type 1 diabetes.

Find out more: www.hri.org.au/CVNU

Cardiovascular Neuroscience Unit

## Social impact

Our work on ketogenic diets and diabetes management is providing much needed mechanistic insights into the effects of this diet outside of weight loss. The ketogenic diet is a popular diet for weight loss and for improving glycaemic control in patients with diabetes but there is virtually no safety data available, particularly with respect to effects at the liver and on blood pressure. Our work provides valuable information into the safety and whole organism effects of the ketogenic diet in preclinical models, which works towards informing future clinical studies.

Our work investigating the autonomic drivers of cardiometabolic disease in people with sleep apnoea is beginning to generate greater interest from the sleep field. As studying the disease progression of sleep apnoea is challenging in people, Dr Melissa Farnham has developed a preclinical model to mimic, and hence investigate, the changes that occur in the brain, and the downstream implication of those changes. This work led to assessing the blood of sleep apnoea patients and the subsequent filing of a provisional patent for a novel biomarker of sleep apnoea in patients. Our work has the potential to result in a more accessible and simple blood test for the diagnosis of sleep apnoea, and potentially even a novel therapeutic target. This would lead to earlier diagnosis and more effective treatment with a resultant decrease in disease burden.

# Cardiovascular-protective Signalling and Drug Discovery Unit

UNIT LEADER

**Dr Xuyu Liu**

PhD, MSc, BSc

## OUR MISSION

The mission of the Cardiovascular-protective Signalling and Drug Discovery Unit is to better understand the therapeutic mechanisms of cardiovascular-protective natural supplements in platelets and the heart, and use this knowledge to develop next-generation precision medicine for the prevention and treatment of life-threatening thrombosis and ischaemic stroke.

Recently, there has been considerable interest in the development of natural supplements for cardiovascular-protective therapeutics, due to their inherent safety profiles and the clinical evidence for ameliorating chemotherapy-induced cardiovascular complications. However, it remains a huge challenge to understand the cardiovascular-protective mechanisms at the molecular level, which impedes pharmacological optimisation of these bioactive agents for therapeutic use.

Our research aims to determine the protective mechanisms underlying heart-healthy diets and herbs, and apply this knowledge to design and develop safer and more effective cardiovascular therapeutics.

To this end, we focus on the development of new proteomic platforms to enable genome-wide understanding of how natural supplements and drugs perform in the context of cardiovascular complications, and on constructing a comprehensive chemical-proteomics database to reveal the therapeutic impacts on thrombosis at the cellular and molecular level.

We also focus on adopting new drug discovery technologies – PROTAC and ABPP that have led to a tremendous achievement in anti-cancer drug discovery – to accelerate the development of precision medicine to tackle thrombosis and ischaemic stroke. In particular, leukocytes, ie, neutrophil and macrophage, have been strongly implicated in the pathogenesis of thrombosis. We aim to develop new PROTAC molecules to tackle the challenge of severe thromboinflammation that leads to the poor prognosis of cardiovascular disease and COVID-19.

## OUR IMPACT

Thrombotic complication is the leading cause of mortality and accounts for one in four deaths worldwide. Despite intense investigation over the past decades, the discovery of novel cardiovascular drugs has remained disappointingly low. Novel antithrombotic drugs entering clinical testing has stalled due to the large attrition in investment and increasing demand in risk assessment. However, the existing antithrombotic drugs such as aspirin and clopidogrel are ineffective, with less than 15 per cent of diabetic patients taking these medicines avoiding a fatal thrombotic event. This situation is likely to worsen in the near future due to the rapidly growing incidence of obesity and diabetes.

The chemical biology research approach adopted by this Unit is designed to identify effective and durable antithrombotic therapy inspired by natural supplements, and to repurpose anti-cancer and anti-inflammatory drugs for thrombotic conditions.

## RESEARCH PROJECTS

### Understanding heart-healthy diets at the molecular level

Sulforaphane and alliin are known to be the cardioprotective "ingredients" in broccoli and onion diets. They have been shown to promote cardiomyocyte survival against ischaemic injury and exhibit potent anti-cancer activity by potentiating apoptosis. However, the protein target spectra of these small molecules in cells remain unclear. There is no unified model to explain the cell-type-dependent phenotypes observed in the treatment. This research is partially conducted in collaboration with the Payne research group (School of Chemistry, The University of Sydney).

### Chemical synthesis and phenotypic validation of precision proteolysis targeted chimeras (PROTACs) for cancer and cardiovascular disease

Akt kinases have been associated with the development of thrombosis, cancer and other major killer diseases. This kinase family is composed of three highly homologous isoforms: Akt1, Akt2 and Akt3. Recently, the revolutionary approaches in drug development termed PROTAC (PROteolysis-TArgeting Chimera) have attracted considerable attention in repurposing broad-spectrum therapeutics to be target-selective degraders. This project aims to develop Akt-isoform-specific PROTACs and to investigate their therapeutic potential in thrombosis. We have recently established two Akt2-isoform-selective degraders and are in the process of optimisation and biological validation. Read more about this project here.

### Towards the development of more effective and safer high-affinity ACE2 variants for the treatment of COVID-19

Infection by SARS-CoV-2 – the etiological virus underpinning the current COVID-19 pandemic – has been shown to lead to a substantial decrease in surface expression of the ACE2 receptor. Ultimately, this leads to a high tendency to trigger acute respiratory distress syndrome. To address these ongoing issues, we aim to develop high-affinity ACE2 variants that are capable of scavenging SARS-CoV-2 virus effectively in vivo while offering lung- and cardiovascular-protective effects to equivalent levels with respect to current recombinant ACE2 therapeutics. Read more about this project here.

### Chemical knock-out of proteins in primary leukocytes using PROTAC-based modulators

In this project, we will design and create a conditional knock-out system that leverages the potency of PROTACs and photosensitive molecular probes, which will enable the investigation of transient protein functions in leukocytes and platelets responding to thrombotic cues. Read more about this project here.

Find out more: www.hri.org.au/CSDDU

## Social impact

While anticoagulant and antiplatelet medicines are used extensively in the treatment of thrombosis and stroke, they have a narrow therapeutic window, and accidental overdose of the medicines can result in severe haemorrhage, which often nullifies their clinical benefit. The importance of developing innovative new treatments for stroke has been highlighted by the National Institute of Neurological Disorders and Stroke (NINDS), which has called for the "urgent development of innovative new treatments that achieve rapid, complete and sustained cerebral reperfusion whilst minimizing the risk of hemorrhagic transformation".

Our recent studies on natural anticoagulants derived from the saliva of Australian bush ticks have led to the discovery of a novel natural product (AIS-109) that manifests a superior anticoagulant activity, while minimising the risk of haemorrhagic transformation in animal models. Our next step is to develop a high-capacity manufacturing platform to produce a sufficient quantity of this natural product for clinical translation studies.

The Unit has also pioneered a number of cutting-edge drug discovery technologies to enhance our understanding of the molecular mechanism underlying healthy diets. Outcomes of the research have significant contribution to the health and wellbeing of Australians through generating abundant knowledge on how natural products in our diets influence cardiovascular health and the ability of platelets to aggregate and clot under normal and diseased conditions.

Cardiovascular-protective Signalling and Drug Discovery Unit

# Clinical Research Group

## OUR MISSION

The primary missions of the Clinical Research Group are: (i) to study the impacts of and best treatments for congenital heart diseases (CHDs) and (ii) to detect cardiac and vascular disease promptly in order for treatments to be administered at an early, optimal stage to prevent serious late consequences of disease.

Our goals are to detect and prevent complications from three primary types of serious heart disease:

(i) atherosclerosis – the narrowing of the main blood vessels in the body, and the main cause of heart attack and stroke;

(ii) congenital heart disease – as an increasing number of adults surviving with inborn heart problems still require extensive care and treatment; and

(iii) pulmonary vascular disease – the narrowing of the main blood vessels to the lungs, which can lead to overload of the right side of the heart.

## OUR IMPACT

Our work on CHD has the potential to revolutionise care for the "whole of life" for CHD patients. Funded by the Medical Research Future Fund (MRFF), we will create one of the world's best registries for children and adults with CHD across Australia and New Zealand, documenting the burden and outcomes of CHDs, and define the best exercise strategies for CHD patients. Our work on early detection and prevention of advanced heart disease may save hundreds of thousands of lives each year.

We aim to detect heart and blood vessel abnormalities at an early stage, before the condition becomes irreversible. We design interventions to treat a wide range of abnormalities, with a particular focus on the prevention of atherosclerosis in children and young adults who have risk factors for early heart disease, obesity, exposure to passive smoke in the home, those who smoke themselves, or those with high levels of cholesterol. We also concentrate on all subject ages with pre-diabetes or diabetes, and babies who are born small at full term.

GROUP LEADER

**Professor David Celermajer AO**

MBBS, MSc, PhD, DSc, FAHA, FRACP, FAA, FAAHMS

## RESEARCH PROJECTS

We have a series of projects to detect early blood vessel damage in children and young adults, as well as programs to intervene to prevent late serious complications. We also study heart disease in those with congenital cardiac abnormalities with a view to minimising complications and maximising quality of life.

### Detecting heart attacks

In collaboration with Prof Sanjay Patel and the Coronary Diseases Group at HRI, we have discovered that the heart releases certain proteins and cell remnants during a disruption of plaques (during heart attacks) and we can now detect these in the laboratory. Dr Gonzalo Martinez, a cardiologist from Chile, helped perform this work, collaborating with our Group for 18 months. Read more about this project here.

### Early detection of pulmonary vascular disease

Pulmonary vascular disease, or high blood pressure in the lungs, is a very severe condition affecting young adult Australians and (as we are increasingly finding out) older Australians. We conducted two projects to outline novel techniques for detecting this complication before it caused more serious health problems. Read more about this project here.

### Young adults with congenital heart disease

At the Royal Prince Alfred Hospital (RPAH), we run one of the largest Adult Congenital Heart Disease Clinics in the country. Our work with these young adults has focused on rarely studied conditions such as Ebstein's anomaly of the heart, congenitally corrected transposition of the great arteries and dextrocardia (the unusual situation where the heart lies on the right side of the chest rather than the left). We have also collaborated with the Department of Radiology at RPAH to make important discoveries about a condition called noncompaction of the heart. Read more about this project here.

Prof David Celermajer AO

## Social impact

Our pioneering work on "passive smoking" has helped change smoke exposure practices worldwide, while our work on rheumatic heart disease and malaria has helped early diagnosis of cardiovascular damage and pointed the way to new treatment strategies. Our work on congenital heart disease has improved care of vulnerable children and young adults, and our drug development work in pulmonary vascular disease has the potential to improve treatment options for this devastating health problem.

### Improving health outcomes in congenital heart disease for young adults, their families and the health system

Ninety per cent of children born with CHD are surviving to adult life. Recently, the characteristics of this population have been changing, as advances in medical practice are allowing people with CHD to live longer. This project aims to acquire missing "life experience" and "health systems" knowledge, enabling further research that will drive new care strategies that will improve patient wellbeing and ease the burden on the health system. This type of project has not been done elsewhere, so has the potential to be a world first. Read more about this project here.

### Optimising exercise prescription and delivery in congenital heart disease – The Congenital Heart Fitness Intervention Trial: CH-FIT

This project is designed to improve quality of life and exercise capacity for people living with CHD. HRI will undertake the first multi-centre randomised controlled exercise intervention in children and adults living with CHD employing a scalable model of care, integrating physical activity and behaviour change techniques. Read more about this project here.

### Australian-wide study of the outcomes and burden of congenital heart disease across the life-course

This project is working to establish a unique National CHD Registry for 25,000 CHD Australians and develop it into a world-class resource with profound translational impact. Read more about this project here.

Find out more: www.hri.org.au/CLRG

# Coronary Diseases Group

GROUP LEADER

**Professor Sanjay Patel**

MBBS (Hons 1, Sydney), PhD, FRACP, FCSANZ

## OUR MISSION

The mission of the Coronary Diseases Group is to reduce death and disability associated with heart disease by reducing atherosclerotic plaque build-up.

Our research aims to develop novel therapies to target atherosclerosis (arterial blockages) and its consequences (heart attack). Our treatment mission is to develop dedicated agents that specifically target the inflammation that drives coronary plaque instability. Our work is performed in collaboration with the Clinical Research, Vascular Complications and Atherosclerosis and Vascular Remodelling Groups within HRI, drawing upon their expertise in each area of research.

## OUR IMPACT

One Australian dies from an acute coronary syndrome (ACS) every 51 minutes. Failure to specifically target persistent coronary inflammation, which drives high rates of recurrent events, is likely a major factor. To address this problem, our program's overarching aim is to: (i) elucidate new inflammatory pathways in ACS patients and (ii) re-purpose established anti-inflammatory drugs that target these pathways. We have focused on colchicine, a safe, cheap and effective anti-inflammatory agent.

Our program was the first to show that colchicine has striking athero-protective effects. Our findings are recognised internationally, with 20 papers and 25 presentations (at national and international scientific symposia) in the last five years. Notably, this program's work has been cited 202 times by groups in 16 countries (Google Scholar), demonstrating its reach.

## Social impact

ACS affects 75,000 Australians annually, and is a major cause of death, with health costs exceeding $8B per annum. Stroke affects 50,000 Australians annually, is the second leading cause of global death, the most common cause of adult disability, and with health costs at $5B per annum. This number of strokes will double by 2050. Further, in many more people the accumulation of 'silent' cerebrovascular lesions manifests as irreversible cognitive impairment. Highlighting this, the Coronary Diseases Group's consumer consultation determined that understanding drivers of recurrent cardiovascular events and thereby preventing events was a key priority for patients and their families.

## RESEARCH PROJECTS

**Determining the effects of colchicine on smooth muscle cell plasticity in advanced atheroma**

This collaborative study (with the Atherosclerosis and Vascular Remodelling Unit at HRI) uses novel murine models of atherosclerosis to understand molecular athero-protective properties of colchicine.

**Effects of colchicine on miRNA levels in coronary disease patients**

We continue to collaborate with Assoc Prof Hardiker's groups at the NHMRC Clinical Trial Centre to determine effects of colchicine on miRNA signatures in ACS patients.

**Effects of colchicine on metabolomic profiles in coronary disease patients**

Via collaboration with HRI's Cardiometabolic Disease Group, we continue to investigate new mechanisms of action of colchicine in ACS patients.

**Determining the anti-atherosclerotic properties of TRAIL**

Through collaboration with HRI's Vascular Complications Group, we continue to study potential therapies to boost TRAIL, a novel mediator with marked anti-inflammatory and anti-atherosclerotic properties, in patients with coronary disease.

**Effects of colchicine on prognostically significant vascular endpoints in patients post-ACS**

We recently showed that oral colchicine has striking anti-inflammatory and plaque-stabilising properties in ACS patients already on optimal medical therapy (OMT), including high dose statin. In particular, we found that in ACS patients, "single shot" colchicine markedly suppresses monocyte inflammasome activation and trans-coronary inflammatory cytokine levels (PMID: 26304941). Also, long-term oral colchicine therapy in patients post-ACS resulted in coronary plaque stabilisation and a concomitant reduction in plasma CRP concentrations (PMID: 29055633). We recently were awarded funding (from NHMRC, MRFF) to conduct multi-centre randomised control trials of colchicine in ACS (COLCARDIO-ACS) and stroke (CASPER) survivors, who have elevated biochemical markers suggestive of persistent coronary inflammation (hsCRP ≥3 mg/L). Importantly, these patients have the highest risk of recurrent MACE and are expected to derive most benefit from suppression of coronary inflammation. We will embed imaging endpoints into these studies, including coronary inflammation imaging to identify colchicine's effects on ruptured and high-risk coronary plaque and carotid plaque. Read more about the project here.

**Effects of colchicine on neutrophil function in ACS patients**

We have previously shown the presence of activated neutrophils and downstream mediators in vulnerable plaque from ACS patients (PMID: 27913753). Here we will investigate the ability of colchicine to stabilise vulnerable coronary plaque via suppression of neutrophil function in ACS patients undergoing percutaneous coronary intervention.

**Salutary effects of colchicine in a murine model of type 2 diabetes**

We previously showed that colchicine has potent suppressive effects on the NLRP3 inflammasome (PMID: 27129183), a multiprotein complex, which plays a key role in athero-inflammation.

The NLRP3 inflammasome has also been implicated in modulation of insulin signalling and resistance, via caspase-1 mediated IL-1β and IL-18 secretion, and two studies have proposed that inflammasome inhibition may improve insulin sensitivity and glucose tolerance.

Therefore, in this study, we will examine the effects of colchicine on pancreatic beta islet cells function, glycaemic profile and organ inflammatory infiltrate in diabetic mice.

**The effects of colchicine on the development and regression of atherosclerosis**

This study aims to investigate colchicine's effects on both plaque development and regression.

In this study we are utilising a well-established lab model of atherosclerosis. By employing this model, we are able to determine whether colchicine treatment can affect the contents of atherosclerotic plaque by modulating its cellular components and subsequently reducing overall plaque burden.

This study consists of two models: a treatment regression model, in which we will assess whether colchicine can reverse pre-formed plaque build-up, and a prevention model, in which we will assess whether colchicine can prevent plaque development.

**The effects of colchicine on immune cell migration in acute coronary syndrome (ACS) patients**

We have previously shown that colchicine reduces the local cardiac production of cytokines in ACS patients (PMID: 26304941). To expand on this, we are investigating the effects of colchicine on chemokine production and the resulting immune cell migration.

The infiltration of immune cells, specifically monocytes, is a hallmark feature of atherosclerosis and is necessary for its progression. Our preliminary data suggests that colchicine suppresses monocyte migration via a reduction in chemokine and chemokine receptor expression.

Therefore, this study aims to confirm our findings in humans and potentially provide a novel therapy to reduce plaque burden.

Find out more: www.hri.org.au/CDG

# Haematology Research Group

GROUP LEADER

**Dr Freda Passam**

MD, PhD, FRACP, FRCPA

## OUR MISSION

The mission of the Haematology Research Group is to discover new mechanisms of clot formation that can lead to the development of efficient and safer antithrombotic drugs.

We have a special interest in the development of biochips for the detection and monitoring of thrombotic tendency. We are currently investigating the application of our biochips for the detection of COVID-19 vaccine associated thrombosis thrombocytopenia, which emerged as a major concern for public safety during the rollout of COVID-19 vaccination.

In fundamental research, we are studying the role of enzymes, named thiol isomerases, in the development of thrombosis, and their potential as novel antithrombotic targets. An exciting new project of our group is to define the proteomic signature of the diabetic platelet to identify causes for increased thrombotic risk in patients with diabetes. In the clinical space, we are interested in the management of venous thrombosis in the community and high-risk thrombosis.

Our research goals are to: (i) discover new targets to prevent thrombotic complications in patients with diabetes; (ii) characterise thiol isomerase inhibitors as new antithrombotics; and (iii) develop new methods to detect prothrombotic tendency in patients with cardiovascular risk factors.


Haematology Research Group

## OUR IMPACT

Current antithrombotic treatment is not effective or has bleeding side effects, eg, one in six patients who have had a heart attack will have another attack despite optimal treatment. We aim to find answers to fundamental biological problems that will enable the development of new diagnostics and treatments for patients with blood clots.

We are committed to discovering targets for new and safe antithrombotics and to develop new assays for the diagnosis and management of thrombotic disease.

## RESEARCH PROJECTS

### Link between AstraZeneca COVID-19 vaccine and blood clots

This pilot study will seek to find biomarkers for blood clot risks in patients who have been given the AstraZeneca COVID-19 vaccine. Patients will be screened 10 days after their first injection to determine their risk of developing a rare blood clot from the vaccine. This study will help increase understanding of why some people are more susceptible to blood clotting, which could allow them to take a preventative treatment to protect them from blood clots.

### Thiol isomerases as novel antithrombotic targets

Thiol isomerases are enzymes in the circulation that control the function of clotting receptors and proteins by reacting with their disulphide bonds. We have identified a novel clotting pathway that involves enzymes, named thiol isomerases. Inhibitors of these enzymes can be developed into drugs that treat thrombotic disease. The aim of this project is to dissect the role of thiol isomerases in thrombus formation using genetically modified lab models, in vivo thrombosis models and thiol isomerase inhibitors. Read more about this project here.

## Social impact

Dr Freda Passam was involved in the rapid response to the COVID-19 vaccine thrombosis thrombocytopenia syndrome with the development and optimisation of diagnostic assays used for patients all over Australia, as part of the Thrombosis and Haemostasis Society of Australia and New Zealand.

### Developing biochips for the evaluation of haemostasis and thrombosis

Many patients with bleeding and clotting disorders go undetected by routine laboratory tests because these do not reflect the conditions in the body's circulation. Our group uses biochips in a microfluidic system that simulates human circulation. These biochips can be used to detect a thrombotic or bleeding tendency in patient samples. Read more about this project here.

### Defining the diabetic platelet proteome

Patients with diabetes have increased platelet activity, which increases their risk for heart attacks and strokes. Differences in platelet function are predominantly due to changes in protein expression and post-translational modifications, given their anucleate nature. Despite recent advances in proteomics, information on the "diabetic" platelet proteome is limited. In this project, we will compare the proteomic phenotype of platelets with platelet function assays and cardiovascular risk factors in patients with diabetes. This study aims to identify biomarkers of thrombotic risk in diabetes and new therapeutic targets.

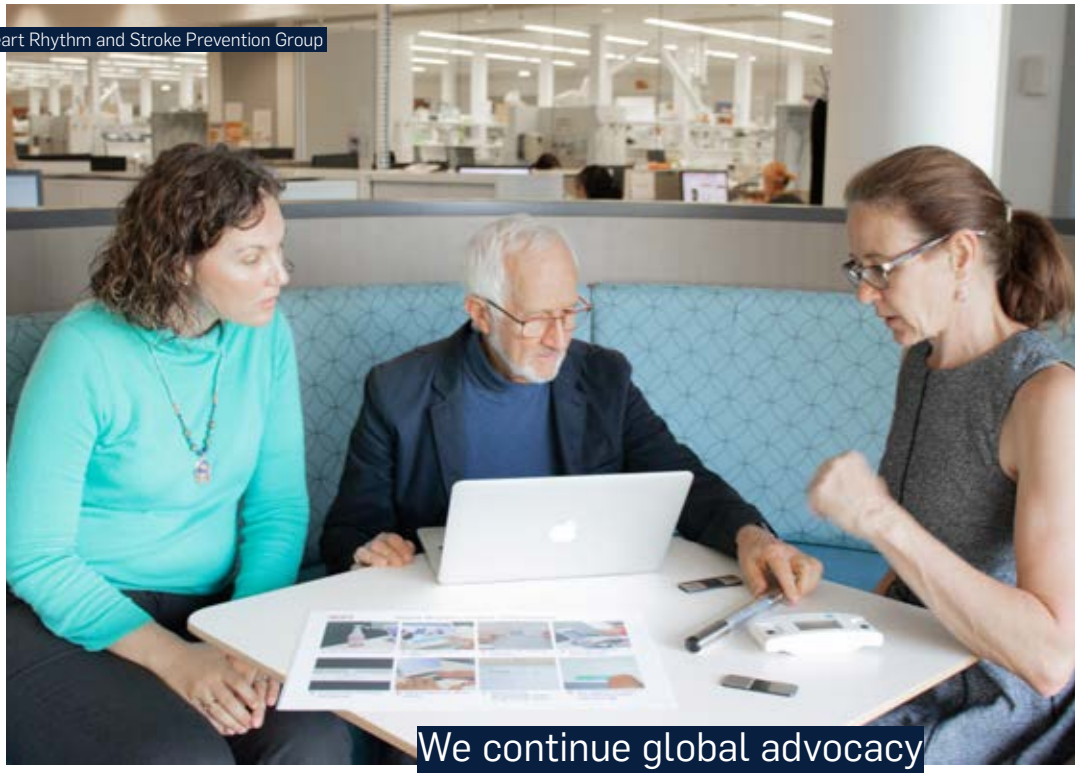
Find out more: www.hri.org.au/HMRG

# Heart Rhythm and Stroke Prevention Group

GROUP LEADER

**Professor Ben Freedman OAM**

PhD, MBBS, FRACP, FCSANZ, FACC, FESC, FAHA


Heart Rhythm and Stroke Prevention Group

We continue global advocacy for screening for atrial fibrillation through the AF-SCREEN International Collaboration and the World Heart Federation (WHF).

## OUR MISSION

Our mission is to prevent strokes through early detection of silent atrial fibrillation (AF) and implement appropriate guideline-based management.

With a clinical implementation focus, we are exploring novel strategies using eHealth tools and patient self-screening to detect unknown silent AF. AF is the most common abnormal heart rhythm – it is estimated that individuals over the age of 40 have a one in three lifetime risk of developing AF. AF is associated with one third of all strokes, which are largely preventable by anticoagulant medications that stop clots from forming inside the heart. Unfortunately, AF is frequently silent, especially in older people who are at greater risk of stroke, with the first sign of AF being a severe stroke.

Our AF screening research extends through collaborations with primary care and specialist clinics in Australia, the USA, Shanghai, Hong Kong, Japan, Vietnam, Germany and the UK.

Another major interest of our Group is to determine whether our Indigenous population has a higher burden of AF by screening in remote and rural Australia, in collaboration with the Poche Centre and the University of Auckland, NZ.

## OUR IMPACT

Our main activities are to determine how best to screen for AF at scale, and to prevent as many strokes as possible. The more people screened and treated, the more strokes we can prevent. We continue global advocacy for screening for AF through the AF-SCREEN International Collaboration and the World Heart Federation (WHF). This is likely to change guidelines and influence future government policy, and have a global impact on stroke reduction through the Leadership of the WHF Roadmap update on AF by Prof Freedman.

In fact, the Australian Heart Foundation and Cardiac Society of Australia and New Zealand 2018 guideline on the management of AF had opportunistic screening for unknown AF as its first recommendation, with a practice point being about use of a handheld ECG pioneered by our Group, quoting our Group's work in its recommendation. Many of our papers on screening were also cited in the 2020 European Society of Cardiology AF guidelines.

If screening for AF could be implemented widely in those aged 65 or older, and this could be coupled with greater prescription of anticoagulant therapy as advised in guidelines, then thousands of strokes could be avoided, not only in Australia but globally.

## RESEARCH PROJECTS

- Patient self-screening for AF in general practice using screening stations
- Analysis of time-trends of anticoagulant prescription for AF in general practice
- Assessment of general practitioner practices regarding AF management
- Collaboration with the Poche Centre to screen for AF in Indigenous Australians in remote and rural NSW, NT and WA, and to combine this with screening for hypertension
- Collaboration with researchers in Malaysia in screening as part of an aging cohort study

Find out more: www.hri.org.au/HRSPG

# Microvascular Research Unit

UNIT LEADER

**Dr Christopher Stanley**

PhD

## OUR MISSION

The mission of the Microvascular Research Unit is to determine the impact of inflammation on the structure and function of microvascular arteries, and to apply this knowledge to better understand how diseases affect blood flow, tissue, and organ perfusion. Ultimately, we aim to develop novel therapeutic strategies to treat patients with blood pressure disorders such as hypo- and hypertension.

## OUR IMPACT

Our research aims to understand disorders of blood pressure regulation specifically in conditions associated with systemic inflammation, such as low blood pressure seen in sepsis and high blood pressure seen in hypertension.

Hypotension (low blood pressure) in sepsis is an unmet clinical need and causes increased mortality through inadequate tissue and organ perfusion.

Hypertension (high blood pressure) is a major risk factor for cardiovascular disease. It can damage the arteries over the long-term and increase the risk of cardiovascular diseases, such as heart attack, stroke, diabetes and heart failure.

Our current research program aims to develop novel therapeutics in these two areas.

Each year, 18,000 Australians suffer from sepsis or septic shock, with an associated mortality rate of >25 per cent. Specific treatments to restore blood pressure in septic patients are unavailable.

Microvascular Research Unit

## RESEARCH PROJECTS

### Getting to the heart of sepsis – a novel approach to restore patient blood pressure

*The devastating effects of low blood pressure in septic patients*

Sepsis is a life-threatening syndrome caused by a dysregulated response to infection and characterised by cardiovascular and organ dysfunction. Conservative estimates indicate sepsis to be the leading cause of mortality in critically ill patients worldwide. Mortality rates dramatically increase in patients suffering from septic shock, a severe form of sepsis characterised by low blood pressure. Each year, 18,000 Australians suffer from sepsis or septic shock, with an associated mortality rate of >25 per cent. In-hospital costs of treating patients with sepsis amount to AUD$84M, with the annual all cost economic burden estimated at $1.5B. Due to the heavy financial burden and high fatality rate, sepsis has been given the highest severity assessment code 1 (SAC 1), and therefore represents an area of high national and state priority.

*Specific treatments to restore blood pressure in septic patients are unavailable*

The clinical management of sepsis relies on treatment of the underlying infection (via intravenous administration of antibiotics), resuscitation (administration of oxygen and fluid), and supportive care (lung ventilation, sedatives, nutrition, and glucose management). Alarmingly, however, there is still no specific treatment available for the clinical management of septic shock targeting the cause of loss of blood pressure control. The current treatment (administration of vasopressors) improves blood pressure, but it does not improve the ability of the small blood vessels to sufficiently perfuse important organs, such as the brain, heart and kidneys. Moreover, the current treatment has potentially serious side effects in that it perpetuates damage to the heart, skeletal muscle and kidney, and it interferes with the body's immune system and metabolism.

*A novel treatment target to restore blood pressure in septic patients*

Working with HRI's Prof Roland Stocker, we have recently discovered a completely novel way by which blood pressure is controlled in an experimental model of sepsis. Preliminary studies suggest that this pathway may also be operative in humans suffering from sepsis. The newly discovered pathway is predominantly active in the small blood vessels that regulate blood pressure, and it depends on both the formation of a novel molecule and a novel mode of action. We now aim to obtain proof-of-principle that the novel pathway is also relevant in human sepsis. In doing so, novel treatment options will be defined for the restoration of normal blood pressure in experimental sepsis as a lead towards its translation to human sepsis.

Find out more: www.hri.org.au/MVRU

## Social impact

The Microvascular Research Unit has had an exciting breakthrough during pre-clinical research that has significant relevance in human patients with sepsis. This is an initial key step in translating basic research into a clinical outcome. The team, in conjunction with intensivists at St Vincent's Hospital, are currently seeking ethics aproval from the St Vincent's Hospital Human Research Ethics committee to progress the research.

# Thrombosis Group

GROUP LEADER

## Professor Shaun Jackson

MBBS (Hons), BMedSci (Hons), PhD

### OUR MISSION

The mission of the Thrombosis Group is to establish new and innovative approaches to the prevention and treatment of heart disease and stroke, positioning Australia as a leader in the discovery and development of innovative therapies for the treatment of atherothrombotic diseases.

Our research is focused on the haemostatic and innate immune systems and their dysregulation in cardiovascular disease. Our main focus is on blood cells (platelets, leukocytes), blood coagulation proteases and endothelial cells.

Our studies are primarily aimed at defining new mechanisms underlying clot formation in healthy individuals, applying this knowledge to better understand mechanisms leading to platelet hyperactivity (thrombosis) and inflammation (termed thromboinflammation). Our ultimate aim lies in the translation of our research discoveries into new therapeutic approaches to treat cardiovascular diseases, including heart attack, stroke, diabetes and the metabolic syndrome.

### OUR IMPACT

Atherothrombosis is arguably Australia's greatest healthcare problem, affecting over 50 per cent of the adult population. Despite intense investigation over the last 40 years into the discovery and development of more effective antithrombotic drugs, the impact of these therapies on mortality rates has remained disappointingly low. This situation is likely to worsen in the future due to the rapidly growing incidence of obesity, diabetes and the metabolic syndrome – diseases that are typically more resistant to the benefits of "classical" antithrombotic therapy. The comprehensive research approach adopted by our Group is designed to identify and target thrombosis risk in such diseases.

### RESEARCH PROJECTS

**Understanding the mechanisms leading to microvascular dysfunction and poor cerebral perfusion in stroke**

For patients presenting with acute myocardial infarction or stroke, the primary goal of therapy is to promptly re-open blocked arteries (recanalization) to salvage the dying ischaemic tissue. A common complication of treatment is microvascular obstruction. Using cutting-edge techniques, we have observed previously unappreciated in vivo changes within the microvasculature during ischaemia reperfusion. Our findings not only demonstrate an intimate spatiotemporal relationship between endothelial injury and vaso-occlusive mechanisms, they also help explain why existing therapies remain ineffective. Read more about this project here.


Prof Shaun Jackson

**Biomechanical sensing and blood clot formation: Solving a sticky clotting problem in diabetes**

The leading cause of death in diabetes is cardiovascular disease, with up to 70 per cent of deaths relating to the development of blood clots supplying the heart (heart attack) or brain (ischaemic stroke). We have discovered a new biomechanical clotting mechanism severely affected by diabetes that is resistant to the beneficial effects of commonly used antithrombotic agents. Studies are also examining the role chronic oxidative stress plays in amplifying blood clotting in diabetes, and the mechanisms by which oxidative stress may modify platelet receptors to enhance adhesion. Read more about this project here.

**Developing novel approaches to the treatment of ischaemic stroke**

The central goal of stroke therapy is the prompt reperfusion of occluded blood vessels to minimise tissue death, with administration of "thrombolysis" (intravenous recombinant tissue-type plasminogen activator, rtPA) – the only clinically approved drug available to stroke patients. Despite this, the use of rtPA is associated with significant side effects, limiting its widespread use. We are designing new scientific models (i) and working on several novel approaches (ii, iii) to improve upon existing stroke therapies, making them safer and more effective.

(i) Development of a novel preclinical ischaemic stroke model: Our studies have successfully developed a novel pre-clinical model of thrombolysis (iCAT) that for the first time allows us the ability to examine the efficacy of novel drugs including novel thrombin inhibitors to facilitate clot lysis (recanalization), restore perfusion in the brain, as well as determine whether cerebral damage and cognitive impairment associated with stroke are reduced. We are using this model to assess the efficacy of currently approved and novel anticlotting agents to facilitate stroke treatment.

We have recently applied several novel imaging techniques to the iCAT stroke model in an effort to gain deeper insight into clot formation and lysis during stroke injury and treatment. These imaging modalities include light transillumination of the culprit lesion, as well as fluorescence macroscopy, and continue to provide detailed novel insight into the temporal and spatial dynamics of cellular changes following injury and treatment administration. These insights will be critical to informing safer and more effective treatment regimens.

(ii) Developing safer anti-clotting agents derived from "Mother Nature": In collaboration with Professor Richard Payne at The University of Sydney's School of Chemistry, we are characterising novel anticlotting agents that have been based around naturally occurring proteins found in saliva of blood-feeding insects, such as the bush tick. Our studies have demonstrated these bug-derived proteins are able to dissolve blood clots in disease models of thrombosis with fewer bleeding complications, laying the foundation for the development of safe anticoagulants for the treatment of thromboembolic diseases such as stroke in the future. Read more about this project here.

(iii) Safety and Tolerability of a novel antiplatelet in patients with Acute Ischaemic Stroke (STARS): We have established a key group of collaborators comprised of Australian stroke clinicians and clinical trialists in the area of ischaemic stroke: Chris Levi (UNSW, Newcastle), Craig Anderson (UNSW, The George Institute [TGI]), Candice Delcourt (UNSW, RPA, TGI), Bruce Campbell (RMH, University of Melbourne), Ken Butcher (Prince of Wales Hospital), Tim Ang (RPA), Mark Parsons (UNSW, Liverpool Hospital), Chris Blair (NSW/Victorian Telestroke Services, Senior Research Fellow – Ingham Institute; Translational Research Fellow in Stroke Medicine, Liverpool and Gosford Hospital). Together we are in the process of planning the following studies:

a. STARS: A phase IIa multicentre, multinational, dose escalation study. The primary aim of this study is to evaluate the safety and tolerability of our novel antiplatelet as an adjunct therapy in patients with acute ischaemic stroke, when given in combination with current standard of care. Patient recruitment will commence late 2022.

b. Data collected from this first safety and tolerability study will form the basis for phase IIb (and eventually III) efficacy studies, currently being planned.

**Platelet death as an important regulator of blood clot formation**

Our studies have demonstrated that procoagulant platelets are dying cells, undergoing a cell death process akin to necrosis, leading to PS exposure and thrombin generation. Our recent studies continue to characterise these pathways to determine their role in clot formation in health and disease, and have focused on the role of different cell death pathways in the development of platelet procoagulant function during ischaemic injury. Read more about this project here.

Find out more: www.hri.org.au/THRG

# Vascular Complications Group

GROUP LEADER

**Associate Professor Mary Kavurma**

PhD, BSc (Hons)

## OUR MISSION

Our mission is to understand the pathogenesis of blood vessel disease and its complications, and using this knowledge, identify new strategies to improve the burden of cardiovascular disease (CVD) in people.

Our research uses various models, genetic manipulation, and biochemical and molecular biology tools to dissect how blood vessels become dysregulated, with an emphasis on changes to gene expression, vascular cell adaptation and function in both normal and abnormal settings in the blood vessel wall.

## OUR IMPACT

Our research aims to understand the molecular, biochemical and cellular mechanisms underlying blood vessel diseases, focusing on atherosclerosis and its complications, including peripheral artery disease and diabetes. By providing new knowledge as to how blood vessels become dysregulated in CVD and related pathologies, our work will help uncover new strategies and therapeutics to combat disease, ultimately improving quality of life and life expectancy.

## RESEARCH PROJECTS

**Sex-dependent endothelial function: peripheral artery disease (PAD) in women**

PAD is the third most common form of atherosclerotic disease resulting in gangrene and requiring amputation of limbs. There is no cure, with treatment focusing on lifestyle changes and managing of risk factors. Importantly, females have worse outcomes than men. The reasons for this are unclear. The endothelium is a critical organ for cardiovascular homeostasis, controlling vessel tone and constriction, inflammation, platelet adhesion and thrombosis, and generating new blood vessels for repair after injury (angiogenesis). Endothelial dysfunction may contribute to sex-dependent changes in PAD. This project seeks to examine the sex-dependent changes in

By providing new knowledge as to how blood vessels become dysregulated in CVD and related pathologies, our work will help uncover new strategies and therapeutics to combat disease, ultimately improving quality of life and life expectancy.


PAD pathophysiology using vivo models and assess the behaviour of endothelial cells under low oxygen and diabetic conditions in vitro.

**Resolving atherosclerosis by targeting inflammation**

Atherosclerosis is an inflammatory condition and the main cause of CVD, initiated by retention of cholesterol in the vessel wall. Cells of the myeloid lineage, eg, monocytes, macrophages and myeloid-derived suppressor cells, play a pivotal role, either promoting or suppressing atherogenesis, depending on their functional state. The plasticity of these cells creates an opportunity for intervention that may retard or reverse disease progression and prevent acute events. To develop therapeutic strategies, the molecular switches that control myeloid cell function must be identified and characterised. This project seeks to explore functional consequences of several identified proteins that we have shown to control myeloid cell function(s) in atherosclerosis. Using in vivo, ex vivo and in vitro models, we will examine the therapeutic potential of these proteins on atherosclerosis and identify whether manipulating levels will attenuate disease.

**Novel mechanisms regulating angiogenesis in disease**

Diabetics are three to four times more likely to develop atherosclerotic coronary and PAD, conditions where narrowed arteries reduce blood flow to the heart and limbs. This is a major risk factor for lower-limb amputation and increased risk of myocardial infarction. Current interventions are insufficient in many patients because extensive disease precludes effective revascularisation. One option is to stimulate blood vessel growth to restore blood flow, preserve tissue survival and maintain optimal organ function. This ongoing project seeks to identify novel molecules that stimulate stable blood vessel networks in atherosclerosis and diabetes-accelerated atherosclerosis in the limb during ischaemia. Read more about this project here.

Find out more: www.hri.org.au/VAG

# Vascular Immunology Group

GROUP LEADER

## Distinguished Professor Annemarie Hennessy AM

PhD, MBBS, FRACP, FRANZCOG (Honorary)

### OUR MISSION

Our mission is to better understand the causes of preeclampsia (high blood pressure in pregnancy), the condition's impact on women during pregnancy, and the impact on long-term cardiovascular health. We seek to develop new drug treatments for preeclampsia.

Our research focuses on how placentas work and the benefits of placental treatment to women that we look after in clinical practice. Profs Annemarie Hennessy and Angela Makris, and Drs Shikha Aggarwal, Katrina Chau and Renuka Shanmugalingam are active physicians caring for hundreds of women annually with preeclampsia, hypertension, vascular and kidney diseases. Our research scientists, Drs

## The placenta and women's health research adds important and novel dimensions to the overall research plan at HRI.

Chia-chi (Jat) Liu, Suzanne Pears and Mikala Welsh are experts in pre-clinical studies and in growing placentas, and thus support the projects of the Group. Dr Liu will lead the new Molecular and Cell Biology Unit with the Vascular Immunology Group. The Group is supported by the Sydney Local Health District (SLHD) and significant National Health and Medical Research Council (NHMRC) project grant funding administered by Western Sydney University (WSU) and HRI. The placenta and women's health research adds important and novel dimensions to the overall research plan at HRI.

Our work is strongly driven by a women's action group, The PEARLS Group, who provide community engagement and review of research plans, as well as funding to support the Vascular Immunology Group's work. In 2021, The PEARLS Group raised over $20,000 for the Vascular Immunology Group for a PhD Scholarship and to continue to support our early career researchers to focus on improving outcomes for women with preeclampsia and to understand its causes. The clinical translation work of the Group is supported by a grant from the South Western Sydney Local Health District (SWSLHD) as the Women's Health Innovation and Translation Unit (WHITU).

The conduct of a clinical trial of aspirin in Africa (Malawi) by Public Health-trained midwife Memory Ngwira, has supported further aspirin work arising from Dr Shanmugalingam's doctoral thesis. This work is supported by the Vascular Immunology clinicians and scientists and is funded by The PEARLS Group. Prevention of preeclampsia is likely to have a positive impact on pregnancy outcome, but also favours preventing future cardiovascular disease. The south-western Sydney clinical trial of technology-enhanced home monitoring is being conducted in affiliation with WSU by Dr Theepika Rajkumar.

### OUR IMPACT

Our research goals are to better understand the causes of preeclampsia. By measuring the functions of the placenta and predicting preeclampsia, we seek to provide new, safe treatment that would allow the pregnancy to progress to full term, thus reducing the burden of premature delivery and also, long term, the risk to women's heart health. Our work is directly translatable to women in pregnancy, resulting in an immediate impact through translational research efforts. Our Group has a strong international and national reputation for the quality and effect of our research plans. If preeclampsia could be prevented, then one of the strongest risk factors for women's heart disease could also be prevented or reduced. This is an important long-term goal for women's heart health.

Prof Makris is the recent past president of the Australia and New Zealand Preeclampsia Collective through SOMANZ (the Society of Obstetric Medicine of Australia and New Zealand), and Distinguished Prof Hennessy AM is the President of the international equivalent, the International Society for the Study of Hypertension in Pregnancy. Prof Makris will lead the Clinical Trials Unit with the Vascular Immunology Group.

### RESEARCH PROJECTS

**The role of placenta antibodies in causing blood vessel damage and hypertension**

A study of 351 women enrolled in a past preeclampsia study, this work also involves growing placentas in the laboratory and looking at the impact of specific antibodies on placental growth.

**The potential for placental growth to prevent and reverse preeclampsia**

Placental growth factor is a recently discovered protein originating in the placenta, which is responsible for blood supply and oxygen to the placenta and baby.

**Safer prolongation of pregnancy**

A study of placenta growth and treatments that provide for a safer prolongation of pregnancy without premature delivery.

**The pharmacology of aspirin in preeclampsia**

Aspirin as a useful drug to prevent preeclampsia is being examined in terms of patient acceptability, drug dosing and its effect in preeclampsia prevention in a wide population across Sydney and south-western Sydney.

**Novel drug treatment for early severe preeclampsia**

In partnership with major researchers in the USA, the Group is investigating the effect and safety of new treatments targeting the placenta, for use in early severe preeclampsia. This is an NHMRC-funded project.

Find out more: www.hri.org.au/VIG

### Social impact

The care of hypertension in pregnancy as a common complication is being facilitated by the clinicians in this Group across Sydney. The Group also actively promotes education about complications in pregnancy to medical and nursing peers and to the broader community.

# Operations Report

CHIEF EXECUTIVE OFFICER

**Dr Stephen Hollings**

BA (Hons), PhD, FAICD

After a tough 2020, 2021 was much anticipated, but little did we know that it would prove to be even tougher, with strict lockdowns and high COVID-19 case numbers. Due to health regulations, many of our staff worked from home during 2021. However, thanks to the measures put in place, we were able to maintain all our core research and critical operations onsite throughout the entire lockdown period.

Despite a difficult year, and thanks to your generous and unwavering support, we had a number of good news stories, including the launch of the New Zealand Pathways program. This program was designed to bring students who have completed Honours in New Zealand to work as a research assistant with HRI in Sydney for a period of 12 months. Following the 12 months of employment, it is hoped the research assistants will go on to complete a PhD with HRI before returning to New Zealand. HRI has six New Zealand Pathways research assistants commencing with us in Sydney in early 2022, and we hope to add even more throughout 2022 with your ongoing support.

Following generous donations from our New Zealand and UK donors, HRI also launched its first Internal Grants program. This program was designed to provide seed funding to research collaborations in the UK and New Zealand and to build the research skills of their citizens. HRI ran an internal grants application process to review and award the funding. Six new collaborations with the UK are being funded over the next two years through this generous program, and three new collaborations with New Zealand.

As we adjusted to the 'new normal', we were continually inspired by the support of our donors and their passion for helping us to better understand the causes and complications associated with cardiovascular disease. From donors who continued to make their regular monthly contribution, to extraordinary gifts left to HRI as legacies, our ability to advance our science and support the next generation of cardiovascular researchers will be ever-dependent upon community support. For this, we remain incredibly humbled by and thankful for your generosity.

To capitalise on the great work you have helped us initiate and the discoveries that we're making to better inform treatment and care for those impacted by cardiovascular disease, your support remains as vital today and into the future as it has in the past. Thank you.

## FINANCE

### Income

HRI's main sources of revenue are fundraising, bequests and government grants received in Australia and overseas. Revenue for the year to December 2021 was $21.81M (FYR20: $20.11M). The Institute is reporting in FYR 2021, $5.774M in government grants revenue. This result is a 47 per cent increase on last year's position.

Bequest revenue when compared to what was reported in FYR 2020 was better by $1.305M, at $1.554M. This increase in revenue is a direct result of a stronger bequest program being initiated in 2021.

Fundraising is reporting a 9 per cent decline in revenue for FYR 2021 at $14.483M. The effects of COVID-19 lockdowns in Sydney and Melbourne during the year have directly contributed to the drop-off in the Institute's donor base and has also restricted the signing up of new financial contributors.

Other income of $0.827M in FYR 2021 is $1.14M lower when compared to FYR 2020. This decline in income relates directly to the amounts received from the Federal Government in JobKeeper and cash boost subsidies. In FYR 2021, the institute received $0.42M in government financial support. Last year at the height of COVID-19, the financial support to HRI was $1.59M.

### Expenditure

Operating expenditure of $21.27M during the year was 9.7 per cent higher when compared to the costs incurred in FYR 2020. Personnel expenses of $9.89M this year were $1.15M, or 13.2 per cent higher than in FYR 2020. This increase in personnel expenses is due to the appointment of additional scientific staff members in FYR 2021.

### Operating result

The Institute's results from operating activities plus net investment income less lease interest and foreign currency translation differences was $3.052M in total comprehensive income. This result was slightly better than last year's financial position of $3.033M.

### Financial position

The net asset position of HRI at 31 December 2021 was $48.30M. This consisted of $25.11M in current assets, $17.18M in investments, $14.4M in net fixed assets, $1.21M in right of use asset and $9.57M in total liabilities.

Cash and short-term investments of $23.44M, together with managed investments of $17.18M, places the Institute in an extremely strong position to continue its campaign of research against cardiovascular disease in FYR 2022 and beyond.

A copy of HRI's full annual financial report is available from our website at www.hri.org.au/reports or by contacting support@hri.org.au.

## SUSTAINABILITY

The 2021 utilities budget was adjusted down after achieving significant savings in 2020 from improvements made to HVAC controls, rainwater harvesting and the rooftop solar system at HRI's Eliza Street facility.

Thanks to a further reduction in electricity, gas and water usage in 2021, a saving of $27,000 was achieved against the adjusted utilities budget.

The Eliza Street kitchen also underwent a major upgrade to create an open plan space for staff to access appliances in a more efficient way while maintaining social distancing requirements.

## TECHNOLOGY

The past year was another in which HRI's cloud-first strategy enabled a fast and flexible transition to working from home for scientific and operations staff. While lockdowns can be challenging, our technology was able to provide the option to continue working and communicating from home, and quickly return to on-site work and research when allowed.

In the second half of 2021, HRI decided on a product and partner for a new Supporter Relationship Management system. This technology will allow HRI to strengthen its relationships with those who support us financially as well as in various other important ways. HRI is indebted to those who contribute to our mission, and the Supporter Relationship Management system will equip us to better engage with our supporters. The system will be built and put into operation in 2022.

In December, the Information Technology team enabled the technical production of the 2021 Sydney Cardiovascular Symposium using a virtual conference platform. Over 200 attendees and over 45 speakers participated virtually from nine countries, including international keynote speakers from the United States and Germany. The Symposium overall was a huge success, and we are very pleased to have been able to facilitate this important event in unpredictable times and maintain the focus on cardiovascular research.

## Donations in 2021

**72,062**
generous donors from Australia, NZ and the UK supported HRI

**18**
Gifts in Wills received

**27**
gifts from major individual donors, organisations and trusts and foundations

# Board of Governors

The Board of Governors is chaired by Professor Len Kritharides and comprises a representative of the Deans of the Medical Schools of Australia, two nominees from each of the Sydney Local Health District and The University of Sydney, and leaders from the corporate sector. The Board is responsible for the governance of the Heart Research Institute. It approves and monitors governance, strategy, budgets and scientific progress. Members are balanced to represent the corporate and scientific community. The majority of the Board positions are available to be filled via election by the members of the incorporated company, the Heart Research Institute Ltd.

Read the bios of our Board Members here.

CHAIR

**Professor Len Kritharides**

MBBS, PhD, FRACP, FCSANZ, FAHA, FESC, FACC

**Dr Teresa Anderson AM, FIPAA**
B App Science (Speech Pathology), PhD

**The Hon Bruce Baird AM**
BA (Syd), MBA (Melb)

**Mr John Batistich**
BBus, MMGT, GAICD
*Nine-year term completed May 2021*

**Professor Andrew Boyle**
MBBS (Hons), FRACP, PhD

**Mr Rod Halstead**
LLB (Syd), LLM (Lon), FAICD

**Mr Merrick Howes**
BA, LLB
*Joined December 2021*

**The Hon Peter McGauran**
BA, LLB
*Joined December 2021*

**Professor Shaun Jackson**
MBBS (Hons), BMedSci (Hons), PhD
*Stepped down June 2021*

**Mr Tony Pollitt**
BEc, MBA, FCA, GAICD
*Joined July 2021*

**Mr Richard Rassi**
BCom, FCA, GAICD

**Emeritus Professor Merilyn Sleigh**
BSc (Hons), PhD, FTSE, FAICD
*Joined October 2021*

**Professor Stephen Simpson**
AC, FAA, FRS

**Honorary Solicitor**
**Ms Trish Paton**
BA, LLB

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**Mr Alan Caton OBE**

**Mrs Kerry Cunningham**

**Dr Stephen Hollings**
BA (Hons), PhD, FAICD

**Mr Stephen Moodey**
BBus, MBA, CPA

**Mr Adrian Phillips**
BA (Hons)

**Mrs Elena Pintado**
BCom

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BBus, MBA, CPA

**Mrs Elena Pintado**
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