SAHMRI
South Australian Health & Medical Research Institute

HEART HEALTH

Heart Health Theme
Student Opportunities

Honours and PhD projects

Welcome to the Vascular Research Centre within the Heart Health theme at SAHMRI. Our mission is to understand the factors that influence the natural history of atherosclerosis, the leading cause of death in our community. Using a range of experimental approaches, our investigators undertake translational studies that aim to elucidate the molecular pathways that influence vascular risk, develop novel biomarkers for the assessment of cardiovascular risk and evaluate the impact of potentially protective therapies. Our studies span the spectrum from early laboratory discovery through to clinical trials and ultimately studies to determine how novel treatments are applied in clinical practice.

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Revisiting the origins of macrophages in atherosclerosis, through a new paradigm of adventitial macrophage progenitor cells

Principal Investigator: Dr Peter Psaltis
Available as: Honours or PhD project

Atherosclerosis is a chronic, inflammatory disease of blood vessels, characterised by the build up of cholesterol-rich, inflamed lesions, called plaque. As plaques build up, they cause narrowing to arteries and restrict blood flow to organs and tissues. Sometimes plaques become disturbed and form clot which can lead to complete obstruction of the artery. This in turn causes tissue infarction, with prominent examples being heart attack and stroke.
Traditional views of atherosclerosis and other diseases of blood vessels have focused on the recruitment of inflammatory cells from bone marrow and spleen to the vessel wall via circulating blood. However, recent discoveries have shown that blood vessels themselves contain resident populations of stem or progenitor cells within their layers and these are being increasingly linked to a causative role in atherosclerosis. These include stem cells for endothelial, smooth muscle, mesenchymal and haematopoietic lineage.
Our group has identified for the first time the existence of macrophage progenitor cells in the adventitia or outer lining of adult arteries. Current and future projects are focused on acquiring a better understanding of these adventitial macrophage progenitor cells (AMPCs), including (1) where they come from in embryonic development and how they arrive in blood vessels, (2) how they are regulated and (3) what roles they play in normal and diseased blood vessels. This work involves a broad range of in vitro experiments performed with cells isolated from mouse and human arterial specimens, as well as in vivo fate-mapping studies and mouse models of atherosclerosis. The results of this project have the potential to provide novel and highly impactful insights into how macrophages develop in blood vessels, and the extent to which they come from a local progenitor cell source.

Understanding the nature, regulation and importance of adventitial mesenchymal stem cells in healthy and diseased arteries.

Principal Investigator: Dr Peter Psaltis
Available as: Honours or PhD project

Blood vessels play an integral role in maintaining the health of normal tissues and in contributing to the development of common and important disease processes. Recent discoveries, including those made by our group, have revealed that adult blood vessels harbour different populations of stem and progenitor cells, which are diverse in origin, phenotypic properties and fate. Among these are mesenchymal stem/stromal cells (MSCs), which are distributed widely in different tissues of the body in close association with the vasculature. These cells serve a range of biological functions, including to provide paracrine support to other cell types. MSCs have also been identified to be a component of the stem cell niche found in the adventitia or outer lining of large arteries and veins. The precise nature of their regulation in these blood vessels remains unknown, as is the extent of their

involvement in maintaining normal vascular biology and influencing vascular disease processes, such as atherosclerosis.

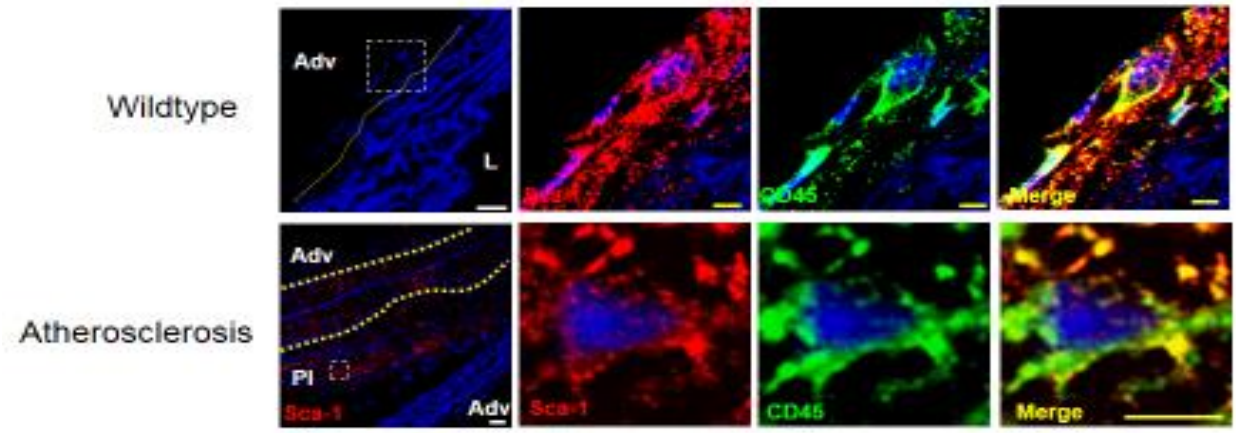
In this project, studies will be performed to characterise the adventitial MSC population in different mouse arteries, at different ages and different stages of atherosclerosis development. We will look specifically at the effect of well known vascular risk factors, such as cholesterol, diabetes and nicotine, on the biology and function of these cells, and the way they interact with other important cells in the blood vessel wall. We will also perform in vivo studies to track the fate of adventitial MSCs during the development of atherosclerosis to determine if they have a causative or protective role. The results of these experiments will shed light on how blood vessels are influenced by their outer adventitial layer and its content of MSCs, and whether this stem cell compartment can be manipulated for therapeutic anti-atherosclerotic purposes.

Exploring the therapeutic potential of bone marrow mesenchymal stem cells (BM-MSCs) in stable and unstable atherosclerosis.

Principal Investigator: Dr Peter Psaltis
Available as: Honours or PhD project

As the principle cause of myocardial infarction (MI) and stroke, atherosclerosis is a leading cause of mortality and morbidity worldwide. Atherosclerosis describes a chronic, systemic, inflammatory process, in which plaques develop in arteries and limit blood flow. Unstable plaques that are vulnerable to rupture and thrombotic occlusion have hallmark features, including high plaque volume, necrotic core, lipid and inflammatory cell content, thin fibrous cap, intraplaque neovascularisation and haemorrhage. Multiple unstable plaques often co-exist in the vasculature. Consequently, the risk of recurrent plaque ruptures after MI remains high, even with current revascularisation and secondary prevention treatments.
Stem cell therapy has been widely investigated to restore myocardial function after MI. Recent meta-analyses have reported that it may also reduce the risk of recurrent MIs and need for repeat coronary revascularisation. These findings suggest that stem cell therapy may have unanticipated benefits on the underlying process of coronary atherosclerosis. Our group has extensive experience in the use of bone marrow mesenchymal stromal/stem cells (BM-MSCs) in animal models of heart disease. BM-MSCs are immunoprivileged, enabling their safe, allogeneic use with minimal risk of immune rejection. They primarily exert their benefits on cardiac repair through paracrine stimulation of angiogenesis, cardiac cell support, modulation of fibrosis, and mitigation of oxidative stress and inflammation. These latter properties may also enable BM-MSCs to modify the inflammatory substrate of atherosclerosis, although very few studies have directly addressed this question.
The studies in this project will examine whether BM-MSCs can reduce atherosclerosis and prevent atherosclerotic plaque from becoming "unstable". In vitro experiments will examine the capacity of MSCs to down-regulate the pro-inflammatory functions of immune cells, such as macrophages and lymphocytes, and modify the deleterious effects that vascular risk factors (e.g. high sugar, nicotine, "bad" cholesterol) have on these cells. In vivo studies will

use mouse models of stable and unstable plaque to observe the anti-atherosclerotic effects of BM-MSCs and unravel their mechanisms. The findings from these studies will provide the basis for using stem cells to treat human atherosclerosis, with the ultimate goal being to reduce atherosclerosis-related illness and death and to reduce the high costs of heart attack and stroke to the healthcare system.



Investigating the link between PCSK9 and Vascular Disease.

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme involved in the metabolism of the low density lipoprotein receptor (LDLr) with the PCSK9 protein expression mainly occurring in the liver and intestines. PCSK9 is involved in the degradation of the LDLr in hepatocytes. High activity of PCSK9 results in elevated plasma LDL concentrations as LDL is not as cleared from the plasma as effectively. Genetic variation of PCSK9 activity have been shown to be associated with plasma LDL cholesterol concentration in humans and mice. Clinical studies have also shown that gain-of-function missense mutations of the PCSK9 gene is linked to familial hypercholesterolemia and coronary artery disease (CAD) while loss-of-function is associated with decreased CAD risk. PCSK9 is now recognised as a therapeutic target for cardiovascular disease and there are multiple ongoing clinical trials. However, there is still wide gaps in knowledge regarding the role of PCSK9 in other lipid systems. There have been suggestions that PCSK9 contribute to apoB plasma concentrations and it may play a role in triglyceride-rich lipoprotein metabolism. These interactions and relationships need to be determine particularly in view of the potential use of PCSK9 as a therapeutic target.

Investigating the Factors that drive Heart Disease in Inflammatory Arthritis.

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

Arthritis patients have a 1.5 to 2-fold increase risk of cardiovascular disease (CVD) compared to the general population. Rheumatoid arthritis (RA) is an autoimmune condition where the inflammatory system is hyperactive. Similarly, the underlying pathology of CVD is the dysregulation of the inflammatory response to insult, in the blood vessel wall. The systematic hyperinflammatory state found in RA most likely play a role in accelerating CVD development but the exact mechanisms involved has still to be systemically determined. These mechanisms include altered atherogenic lipid profiles, changes to the functionality of high density lipoproteins (the "good cholesterol"), the systemic release and circulation of pro-inflammatory cytokines and the polarity of macrophages to an inflammatory phenotype.

Novel approaches to imaging hot and cold atherosclerotic plaques.

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

Our group has a longstanding interest in imaging of atherosclerotic plaques in order to understand the factors that underlie the natural history of heart disease. In addition to detecting the presence of plaque and measuring its overall burden, we are now using molecular imaging approaches to directly target factors within plaques that underlie their progression to heart attacks and strokes. Given that most plaques remain clinically silent, the ability to detect the more clinically relevant plaques are important in terms of risk prediction and use of medical therapies. A number of translational projects are available in this area that employ molecular imaging of atherosclerosis spanning studies in the laboratory through to the bedside.

Investigating factors that link stress, depression and heart disease.

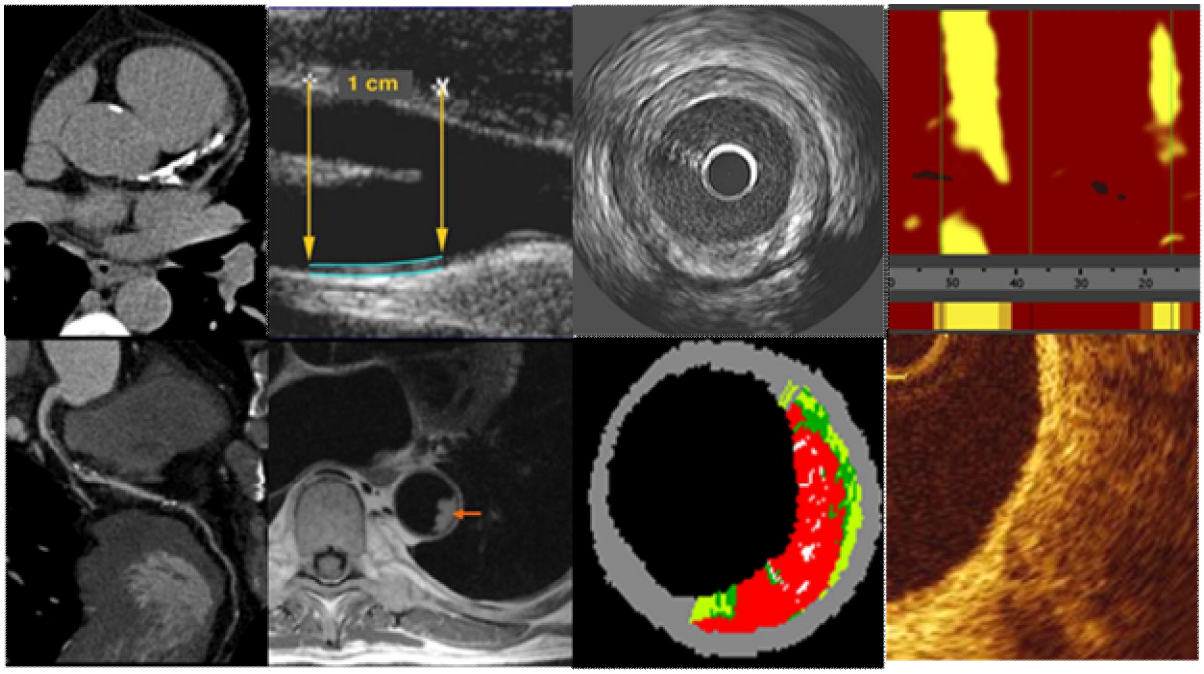
Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

Heart disease, stress and depression represent three of the largest burdens on our community in terms of their impact on health outcomes. Increasing evidence suggests that the presence of stress and depression can each have an impact on outcomes in patients with heart disease. The mechanisms responsible for this remain unclear. Furthermore, this has important implications for the management of patients with established heart disease. A number of projects spanning preclinical studies of mechanisms linking the heart and brain through to health intervention studies are available in this area.

Investigating the factors that promote heart disease and kidney failure.

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

Heart and kidney disease are common, often coexist and are associated with poor health outcomes. The mechanisms that link kidney disease to worse outcomes in patients with heart disease are poorly understood. This translational project will aim to investigate the inflammatory impact of kidney disease on atherosclerotic plaque spanning the continuum from its early formation through to the impact of vessel occlusion on heart muscle.



Investigating the factors that promote heart disease in patients with sleep disordered breathing.

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

Disorders of breathing during sleep are associated with a range of metabolic risk factors and heart disease. The mechanisms by which sleep disordered breathing impacts atherosclerotic plaque is poorly understood. This translational project will aim to study preclinical and clinical aspects of atherosclerotic disease in the setting of sleep disordered breathing.

Developing novel nanoscale biosensors of blood vessels.

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

The ARC Centre of Excellence in Nanoscale BioPhotonics aims to develop novel sensing approaches by developing unique collaborations between biology with physics and chemistry. We lead the Inside Blood Vessels challenge, whose mission is to develop novel biosensors of the vascular system spanning from a cellular level through to whole vessel imaging. This provides a unique opportunity to develop innovative approaches to studying the factors that regulate normal vascular function and diseases of blood vessels.

Investigating the role of lipoproteins and inflammation in the regulation of vascular calcification.

Principal Investigator: Dr Belinda Di Bartolo
Available as: Honours or PhD project

Vascular calcification is found in advanced atherosclerotic lesions and is an independent predictor of cardiovascular morbidity and mortality in patients with chronic kidney disease. Long considered a passive process, there is evidence to suggest that vascular calcification is a tightly regulated balance of promotion and inhibition of calcification in the artery wall. Dysregulation of this balance leads to chronic kidney disease, diabetes mellitus, and atherosclerosis. In vitro and in vivo studies have implicated numerous positive and negative regulatory factors in the pathogenesis of calcification.
High-density lipoproteins (HDL) have been well established to protect against the development of atherosclerosis. In addition to the promotion of reverse cholesterol transport, HDL possess a number of functional properties that contribute to their beneficial influence on the arterial wall. HDL has been shown to regulate calcification in vascular cells and is able to modify processes that occur in the formation of bone similar to what occurs in calcifying vascular cells. This project will investigate the effects of lipoproteins and inflammation on vascular calcification.

Investigating the role of osteoprotegerin, inflammation and calcification in peripheral artery disease.

Principal Investigator Dr Belinda Di Bartolo
Available as: Honours or PhD project

Peripheral artery disease (PAD) is a blocking or narrowing of the arteries and is one of the major macrovascular complications of type 2 diabetes. Inflammation and atherosclerosis is recognized as the most direct and important cause of PAD, but acute or chronic limb ischemia may be the result of various risk factors. The role of calcification in PAD is unclear but is related to the site and location of calcification within the arterial layers.

Osteoprotegerin (OPG) is a secretory glycoprotein that belongs to the tumour necrosis factor receptor family and plays a role in atherosclerosis and vascular calcification. Elevated OPG concentrations have been reported in microvascular complications of diabetes. Patients with diabetes are at increased risk of macrovascular complications, particularly PAD. This project will identify the role of calcification in the progression of PAD and the involvement of OPG as a potential biomarker of this disease.

What Makes Good Cholesterol Good (and not so good)?

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

A range of lipoproteins are found in the circulation which have different influences on the risk of heart disease. Translational studies leading from the laboratory to the clinic will characterise the effects of different lipoproteins on the artery wall and understand the impact of medical therapies on these activities.

How does inflammatory disease cause heart attacks?

Principal Investigator: Prof Stephen Nicholls
Available as: Honours or PhD project

Increasing evidence suggests that patients with chronic inflammatory disease are at a higher risk of developing heart disease. Using a range of preclinical studies we will investigate the mechanistic pathways that link systemic inflammation and heart disease.

Summer Scholarships – Heart Health theme

The Heart Health theme will be offering **Summer Scholarships:**

If you are interested in undertaking a summer scholarship, please contact one of our Post-Doctoral Researchers below to discuss:

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Dr MyNgan Duong: myngan.duong@sahmri.com

Dr Nisha Schwarz: Nisha.schwarz@sahmri.com