Heart Research Institute
Honours and Postgraduate Research Opportunities 2018–2019
# HEART RESEARCH INSTITUTE

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Summary

This project will systematically develop proactive biomimetic surfaces integrated onto metallic cardiovascular devices including coronary stents and arterial heart valves. It includes: 1) plasma physics and vascular bioengineering; 2) cellular and hemocompatibility studies and 3) in vivo pre-clinical testing.

Background

Metallic cardiovascular implants, such as stents, used in the treatment of heart disease are not compatible with blood. They cause inflammation at the site of implantation and increase the risk of blood clots forming. Smooth muscle cells/smooth muscle derive cells and macrophages in to the atherosclerotic plaque.

The project will closely integrate vascular biology and bioengineering and physics to develop enableable to design materials for treatment of cardiovascular diseases that feature proactive biocompatibility through biomimicry.

Project Overview

These studies will investigate a number of newly developed biomaterials for application in endovascular medical devices in a cutting edge translational research program. There may be unique opportunities to integrate basic science discoveries with clinical studies to gain novel insights into the nature of the project will provide exposure to physics, biochemistry and vascular biology, interacting with a diverse research team. In vitro assays established at the HRI will assess blood compatibility, endothelial and smooth muscle cell interactions in conjunction with the physical and chemical properties of our unique surfaces. Evaluation of our most promising devices is currently underway in established pre-clinical small and large animal models.

DEVELOPING NEXT-GENERATION VASCULAR BIOMATERIALS

APPLIED MATERIALS GROUP

For more information contact: Dr Steve Wise, Steve.Wise@hri.org.au

Key references


Aim

The overall aim of this project is to understand the functional role of notch signaling in recruitment of smooth muscle cells/smooth muscle derive cells and macrophages in to the atherosclerotic plaque.

Background

Atherosclerosis is the underlying cause of most cardiovascular diseases, including coronary artery disease (CAD), aortic aneurysms, and many instances of heart failure and stroke. Atherosclerosis involves multiple processes including endothelial dysfunction, inflammation, vascular proilation and matrix alteration. Recent studies have emphasized the involvement of inflammation and proliferation of vascular smooth muscle cells (VSMCs) in mediating other stages of atherosclerosis. Although much progress has been made in identifying the mechanisms that initiate the inflammatory cell recruitment and SMCs proliferation during atherosclerosis, less is known about the intrinsic pathways that counteract these events. Notch proteins are transmembrane receptors that drive signaling pathways required for vascular development and remodeling.

Project overview

Recent studies implicated Notch pathway genes in coronary artery disease; however, notch signaling in atherosclerosis is unexplored. Our initial studies with high fat fed ApoE(-/-) mice indicate that expression of Notch3 is upregulated in atherosclerotic lesions and our preliminary results indicate that deletion of Notch3 gene in the plaque and macrophage-SMCs interplay in atherosclerosis. We will also test the hypothesis that reduction of Notch3 in SMCs reduces transdifferentiation of SMCs to macrophage-like cells and its effect in athero progression.

This work involves techniques such as in vivo cell culture, gene expression (PCR, Western blotting), molecular biology (e.g. luciferase assays, chromatin immunoprecipitation,) creating transgenic, animals, histology, bone marrow transplant, in vivo fate mapping and clonal analysis.

NOTCH SIGNALING IN ATHEROSCLEROSIS: FRIEND OR FOE

ATHEROSCLEROSIS AND VASCULAR REMODELLING GROUP

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Project: Investigating abnormal brain dynamics related to cardiovascular risk factors

Multiple brain abnormalities are thought to be associated with cardiovascular risk factors and ageing. The brain is increasingly thought of as a constantly changing and complex system that is relevant for thought processes and other morphological changes, such as loss of grey matter. This project will explore the pathological changes in the brain’s white matter before and after weight loss using advanced imaging techniques. In addition, we are interested in weight loss as a long-acting glucagon-like peptide-1 receptor agonist in cognition. In addition, we are interested in whether the use of a low-calorie diet alone and whether it is combination with a low-calorie diet for weight loss produces a high false positive rate of cognition. This project will explore the consequences of hypertension on brain gray matter volume and white matter tracts.

Background: Hypertension is a known risk factor for heart disease and stroke, but may also induce more subtle changes in the brain. Recent evidence suggests that hypertension can cause long-term brain changes, resulting in decreased brain volume and decreased dwell time of intrinsic mental states. This project is part of the Chronic Diseases Connectome Project (CDCP), a long-term study designed to enable early diagnosis, prognosis and treatment of diseases which affect the brain. The changes present in chronic brain diseases are complex but often hard to detect with standard clinical imaging. Recent developments in imaging technology allow us to meaningfully measure the complex neural circuits that make up the brain for the first time.

Project overview: This project will explore whether hypertension results in changes in brain gray matter volume and white matter tracts. Using techniques of in vivo and ex vivo imaging, requiring advanced imaging techniques to detect. Multiple brain abnormalities are thought to be associated with cardiovascular risk factors and ageing. The brain is increasingly thought of as a constantly changing and complex system that is relevant for thought processes and other morphological changes, such as loss of grey matter. This project will explore the pathological changes in the brain’s white matter before and after weight loss using advanced imaging techniques. In addition, we are interested in weight loss as a long-acting glucagon-like peptide-1 receptor agonist in cognition. In addition, we are interested in whether the use of a low-calorie diet alone and whether it is combination with a low-calorie diet for weight loss produces a high false positive rate of cognition. This project will explore the consequences of hypertension on brain gray matter volume and white matter tracts.
CARDIOVASCULAR INFLAMMATION AND FIBROSIS GROUP
INVESTIGATING THE MOLECULAR PATHWAYS CONTRIBUTING TO CARDIAC TISSUE DAMAGE FOLLOWING ISCHAEMIA REPERFUSION (I/R) INJURY

Project Overview

Whilst improvements in intensive care have reduced the number of deaths attributable to heart attacks, the damage caused by an ischemic event within the heart muscle is poorly managed, resulting in ongoing morbidity. A heart attack causes scar formation in the heart muscle, which if poorly managed, results in complete heart failure in extreme cases.

Scar tissue is composed of the protein collagen, which is cross-linked to form a pronounced alignment in a single direction resulting in inferior functional quality to the affected heart muscle. Mechanisms leading to enhanced scar formation following heart attack include the action of the Lysyl oxidases and Lysyl oxidase-like (LOXL) enzymes, which are highly expressed in the heart and directly responsible for the cross-linking of collagen evident in scar formation following heart attack. Additionally, scar formation is enhanced by the production of oxidants with mammalian cells. Particular emphasis will be placed on the role MPO-derived oxidant generation has on the activation of cellular signaling pathways responsible for adverse tissue remodeling following heart attack. The ultimate goal of this proposal is to develop viable therapeutic options for the treatment of ischemia-induced heart disease.

Key references
Background
The diagnosis and treatment of many diseases involves the use of medical devices, e.g., vascular stents, heart valves, pacemakers, devices that imitate heart beating, and cardio-pulmonary bypass circuits. However, these are all made with artificial metals and plastics, which cause a number of potentially fatal side effects including thrombosis (blood clots) and pathogen adhesion (biofouling). These processes are difficult to study in the lab because the devices are large and complex.

Advances in micro and nanotechnology have revolutionised bioengineering, allowing high precision manipulation of materials for modelling medical devices in the lab.

Project Overview
In order to better understand thrombosis and biofouling and develop improved materials for medical devices, we are creating innovative micro-systems to study medical device materials in the laboratory. Using the new facilities at Australian Institute of Nanoscale Science and Technology (AINST) at the University of Sydney, this multidisciplinary project aims to create micro-systems that mimic aspects of medical device materials and geometries. Using these micro-systems, 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.

Key references
**HAEMATOLOGY RESEARCH GROUP**

**THIOL ISOMERASES AS NOVEL ANTITHROMBOTIC TARGETS**

**Aim**
To discover alternative pathways in the clotting system that can be targeted to develop efficient and safer antithrombotic drugs.

**Background**
It has recently been discovered that thiol isomerases constitute a new clotting pathway. Thiol isomerases are a group of enzymes that regulate the function of blood cell receptors and clotting proteins by reacting with their disulphide bonds. We have identified a thiol isomerase, named ERp5, which is released into the circulation from activated platelets and promotes clot formation in vivo.

**Project overview**
In this project we will dissect the role of ERp5 in platelet function and clot formation by using mice with genetic deletion of ERp5 in their platelets. We will investigate how this thiol isomerase regulates the interaction of platelets with clotting proteins (fibronectin, von Willebrand factor) and vascular cells (endothelial cells and neutrophils). We will explore the potential of ERp5 inhibitors to prevent thrombus formation and become candidate antithrombotic drugs.

**Techniques:** These studies will employ platelet function tests, cell perfusion assays, flow cytometry and confocal microscopy. This project will provide the opportunity to learn the method of intravital microscopy for the study of clot formation in vivo.

**Key references**
3. Jasuja R, Passam FH, Kennedy DR, Kim SH, van Hessem L, Bowley SR, Joshi SS, Dilks JR, Furie B, Furie BC, Flaumenhaft R. Protein disulfide isomerase regulates the interaction of platelets with clotting proteins (fibrinogen, von Willebrand factor) and vascular cells (endothelial cells and neutrophils). We will explore the potential of ERp5 inhibitors to prevent thrombus formation and become candidate antithrombotic drugs.

**In vivo thrombus formation in the cremaster artery of (A) a mouse injected with inactive control compound and (B) a mouse injected with an ERp5 inhibitor. Platelets are labelled in red and fibrin in green.**

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**HAEMATOLOGY RESEARCH GROUP**

**REDOX BIOMARKERS IN THROMBOTIC DISEASE**

**Aim**
To identify new biological markers that can be used in the monitoring and treatment of patients with thrombotic disease.

**Background**
The redox balance (balance of reduction and oxidation reactions in our blood) is essential for a healthy circulation. Redox imbalance causes alterations of protein function contributing to the development of thrombosis. The Haematology Research group is focused on redox modification of disulphide bonds in two proteins critical for thrombus formation: the platelet receptor integrin α2β3 and the plasma protein von Willebrand factor. We have found that reduced forms of α2β3 and vWF have decreased thrombotic activity and may therefore protect from thrombotic disease, such as venous clots.

**Project overview**
We have developed assays which measure the redox balance in blood including tests which measure the disulphide reducing activity of plasma and the production of reactive oxygen species by platelets. We will study the redox modifications of platelet α2β3 and plasma vWF which occur in patients at high risk for thrombosis to identify those most likely to benefit from drugs which restore the normal redox balance.

**Techniques**
This project employs mass spectrometry to study the posttranslational modifications of clotting proteins using disulphide labels specifically developed for this purpose. It also involves plasma and platelet functional assays.

**Key references**

**Alterations of disulphide bonds in clotting proteins which cause decreased clotting activity in (A) the platelet receptor α2β3 and in (B) von Willebrand factor, bond Cys1669-Cys1670.**

For more information contact: Dr Freda Passam, Freda.Passam@hri.org.au
Project Overview

Blood pressure, the pressure applied by circulating blood on the walls of your arteries as it is pumped around the body, plays a vital role in the proper functioning of the heart and circulation. Blood pressure constantly changes in response to the activity requirements of the body. However, high blood pressure (or hypertension) is a pathological condition where blood pressure remains persistently higher than normal. Hypertension is a major cause of cardiovascular disease, and occurs in progressive disorders such as sleep apnoea and epilepsy. If left untreated, worsening hypertension can lead to kidney failure, heart attack or stroke.

Hypertension is almost always preceded by increased excitatory nerve signals from the brain. How does increased sympathoexcitation cause hypertension? Persistent activation of the sympathetic nervous system – especially when intermittent – causes a vicious spiral of narrowing of arteries, hypertension, organ damage and further increases in sympathoexcitation. The focus of our research is to tease apart the mechanisms responsible for excessive sympathoexcitation that results in cardiovascular disease.

Our most recent findings have implicated two factors in the dangerous elevation of blood pressure: the brain chemical, pituitary adenylate cyclase activating polypeptide (PACAP), and the activity of microglia – the immune cells of the brain, which express receptors for nearly every brain chemical known. Specific studies will focus on PACAP signalling and the interaction between microglia and central cardiovascular neurons in hypertension, sleep apnoea and diabetes.

Key references

Aim

To develop microfluidic devices which can detect the thrombotic or bleeding tendency in patients with clotting disorders.

Background

Many patients with bleeding and clotting disorders go undetected by rodent laboratory tests in part because the available assays do not reflect the conditions in the circulation. The Haematology Research Group uses biochips in a microfluidic system that allows blood to flow through passages under controlled conditions. The passages are designed to mimic blood vessels and include features such as stenoses, that simulate the circulation in stenosed vessels. The flow of blood through these biochips generates thrombus that can be visualized by real-time microscopy and quantified.

Techniques

This project involves the preparation of the microfluidics chips, perfusion assay and microscopy.

Haematology Research Group

DEVELOPING BIOCHIPS FOR THE MEASUREMENT OF HAEMOSTASIS AND THROMBOSIS

For more information contact: Dr Freda Passam, Freda.Passam@hri.org.au

Aim

To develop microfluidic devices which can detect the thrombotic or bleeding tendency in patients with clotting disorders.

Background

Many patients with bleeding and clotting disorders go undetected by rodent laboratory tests in part because the available assays do not reflect the conditions in the circulation. The Haematology Research Group uses biochips in a microfluidic system that allows blood to flow through passages under controlled conditions. The passages are designed to mimic blood vessels and include features such as stenoses, that simulate the circulation in stenosed vessels. The flow of blood through these biochips generates thrombus that can be visualized by real-time microscopy and quantified.

Techniques

This project involves the preparation of the microfluidics chips, perfusion assay and microscopy.

Microfluidic devices for measuring thrombotic and bleeding tendency. (A) Commercial biochip used to measure platelet adhesion in (B) patient 1 showing increased platelet adhesion to fibrinogen and in (C) patient 2 showing decreased platelet adhesion.

For more information contact: Dr Melissa Farnham, Melissa.Farnham@hri.org.au

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Techniques

This project involves the preparation of the microfluidics chips, perfusion assay and microscopy.

Microfluidic devices for measuring thrombotic and bleeding tendency. (A) Commercial biochip used to measure platelet adhesion in (B) patient 1 showing increased platelet adhesion to fibrinogen and in (C) patient 2 showing decreased platelet adhesion.

For more information contact: Dr Melissa Farnham, Melissa.Farnham@hri.org.au
THROMBOSIS GROUP
UNDERSTANDING CLOT FORMATION IN HEALTH AND DISEASE

Project Overview: "Bad Blood": Unravelling the Link between Gut Ischaemia and Remote Organ Injury

Ischaemic injury to vital organs is common in critically ill patients, producing deleterious effects on other organ systems. This is particularly common in the gut, with intestinal hypoperfusion inducing systemic inflammation and multiorgan dysfunction syndrome. In addition to promoting inflammation, prolonged ischaemic injury to the intestine can also lead to the development of a systemic inflammatory response. The biological formation of blood clots, which is particularly common in the lung, and leads to a very poor prognosis (>90% mortality). We have identified a new mechanism of pathological blood clotting (thrombosis) and vascular occlusion that is triggered by dying platelets in the intestinal microvasculature. Our ultimate aim is to identify new therapeutic targets to improve microvascular perfusion and reduce inflammation and organ injury, which may represent an innovative approach to reduce remote organ injury in critically ill patients. This project will involve the use of animal models, cell biology and biochemical approaches.

Co-supervisors – Dr Mike Wu and Dr Yuping Yuan

THROMBOSIS GROUP
UNDERSTANDING CLOT FORMATION IN HEALTH AND DISEASE

Project Overview: Solving a Sticky Clotting Problem in Diabetes

The leading cause of death in diabetes is cardiovascular disease, with up to 70% of deaths relating to the development of blood clots supplying the heart (heart attack) or brain (ischaemic stroke). Diabetic individuals are more prone to develop blood clots, and these clots are more resistant to standard antithrombing therapies. Our laboratory has discovered a new biophysical clotting mechanism severely affected by diabetes that is resistant to the beneficial effects of commonly used antithrombotic agents. Studies ongoing in our laboratory aim to identify how high blood sugar levels (hyperglycaemia) can enhance this new clotting mechanism. To achieve this, we are using BFP technology, which allows us to study how a single platelet senses mechanical cues at the molecular scale. We will also examine the role oxidative stress plays in amplifying blood clotting in diabetes, and the mechanisms by which oxidative stress can alter platelet shape changes to enhance adhesion. These studies may identify novel targets with which to treat thrombosis associated with diabetes. This project will involve the use of in vivo animal models, BFP technology, biochemistry and mass spectroscopy.

Co-supervisors – Dr Sophie Maiocchi and Dr Arnold Ju

THROMBOSIS GROUP
UNDERSTANDING CLOT FORMATION IN HEALTH AND DISEASE

Project Overview: New Approaches to the Treatment of Ischaemic Stroke

The development of a blood clot in the cerebral circulation (ischaemic stroke) is the third most common cause of death and the most common cause of adult disability globally. The central goal of stroke therapy is the prompt reperfusion of occluded blood vessels to minimise tissue death. The delivery of plasminogen activator (t-PA) is the only clinically approved means available to stroke patients. Despite this, the use of t-PA is associated with significant side effects, limiting its widespread use. We are working on a novel approach to improve upon existing stroke therapies, making them safer and more effective. Ongoing studies using a novel mouse model of thrombosis (IAT) developed in our lab will provide targets for potential new stroke therapies. This project will involve the use of animal models of stroke, histological analysis, laser speckle contrast and Laser Doppler Flow imaging, histology, and cell biology approaches.

Co-supervisors – A/Prof Simone Schoenwaelder and Prof Shaun Jackson

Project Overview: Investigating Blood Flow Reductions in the Brain after Stroke

Acute ischaemic stroke is a leading cause of death and disability worldwide. It is caused by the blockage of a major artery that supplies the brain. Injury occurs as a consequence of the reductions in blood flow and the longer the brain stays hypoperfused, the greater the damage inflicted. It has long been known that quickly restoring blood flow to the brain will limit the progression of cell death and improve patient outcome after stroke. However, there is evidence indicating that reopening the blocked artery does not always restore blood flow in the small vessels of the brain and correlates with worse prognosis for stroke patients. The causes of the continued hypoperfusion are poorly understood. Identifying the causes of these blood flow reductions despite large vessel re-opening will provide targets for potential new stroke therapies. This project will involve the use of animal models of stroke, behavioural analysis, laser speckle contrast and Laser Doppler Flow imaging, histology, and cell biology approaches.

Co-supervisors – A/Prof Simone Schoenwaelder and Imala Alwis

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For more information contact: Associate Professor Simone Schoenwaelder, Simones.Schoenwaelder@hri.org.au
Project Overview

Medial vascular calcification is increasingly recognised as a problem with aging, in patients with cardiovascular diseases such as atherosclerosis, as well as in diabetes mellitus and chronic kidney diseases. Importantly, medial calcification is associated with the morbidity and mortality of these patients. Medial calcification can take several forms including calcified deposits, mineralised cartilage and bone-like tissue. The pathobiology of medial calcification is not fully established, and current therapy is linked to preventing disordered bone and mineral metabolism by lowering the circulating levels of both phosphate and calcium. In order to lead to the development of new and better therapeutics, comprehension of the regulation of vascular calcification needs to be further investigated.

This project seeks to investigate the potential of targeting the Wnt signalling pathway in medial vascular calcification. In particular, we aim to test whether Wnt signalling contributes to vascular calcification by regulating the expression of osteoprotegerin (OPG, an inhibitor of vascular calcification), receptor activator of nuclear factor-κB ligand (RANKL, an activator of osteoclastogenesis and vascular calcification) and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL, modulator of RANKL expression) in vascular smooth muscle cells (VSMCs) in vitro, ex vivo and in vivo.

A range of techniques can be used in this study, including cell culture, molecular biology (e.g., luciferase assays, chromatin immunoprecipitation, electrophoretic mobility shift assay), PCR and Western blotting. Further interrogation will involve ex vivo aortic calcification experiments and in vivo models of vascular calcification.

Key references

VASCULAR COMPLICATIONS GROUP
INVESTIGATING THE ROLE OF WNT SIGNALLING IN VASCULAR CALCIFICATION AND AGING

For more information contact: Dr Mary Kavurma, Mary.Kavurma@hri.org.au or Dr Siân Cartland, Sian.Cartland@hri.org.au

Project Overview

Atherosclerosis, a chronic arterial disease that can lead to myocardial infarction, stroke and gangrene, is the most common cause of mortality in the world and a financial burden on healthcare. It is a condition where vascular cells, lipids, cholesterol and cellular waste accumulate, producing a thickened neointima in the arterial wall. Proliferation and apoptosis are intimately coupled processes in the development of atherosclerosis and cardiovascular pathologies. For example, proliferation of vascular cells can contribute to the development of atherosclerosis early in lesion development, whereas apoptosis of vascular cells can weaken the vulnerable regions of the plaque, leading to plaque instability and potential rupture.

Fas ligand (FasL) is a member of the tumour necrosis factor (TNF) ligand superfamily, known to induce apoptosis in cells expressing its receptor, Fas. The FasL has been implicated in atherosclerosis since it is expressed in vascular smooth muscle cells (VSMCs) and endothelial cells (ECs) in lesions of atherosclerosis. However, comprehension of FasL signalling pathway(s) in the vasculature is currently lacking and controversial. For example, under certain conditions FasL can induce apoptosis of vascular cells and contribute to cell death and plaque instability, whereas FasL overexpression in ECs has been shown to protect against atherosclerosis.

In this study, we will interrogate the role of the FasL/Fas pathway in atherosclerosis-prone mice, as well as investigate circulating levels in patients with coronary artery disease. This proposal has significant implications for understanding FasL signalling in the vasculature in vivo, but also in people with cardiovascular disease. Comprehension of these signalling pathways may lead to novel approaches in the prevention and/or treatment of the significant morbidity and mortality associated with atherosclerosis.

A range of techniques can be used in this study, including cell culture and molecular biology techniques (e.g., luciferase assays, chromatin immunoprecipitation, electrophoretic mobility shift assay), gene expression (PCR), Western blotting, ELISA, and in vivo models of atherosclerosis.

Key references

VASCULAR COMPLICATIONS GROUP
IS ACTIVATION OF THE FASL/FAS PATHWAY HARMFUL OR ADVANTAGEOUS IN ATHEROSCLEROSIS?

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VASCULAR COMPLICATIONS GROUP
IDENTIFY THE ROLE OF ENDOTHELIAL AND VASCULAR SMOOTH MUSCLE CELL CROSS-TALK IN BLOOD VESSEL DEVELOPMENT

Project Overview
Cardiovascular disease is a long-term complication of diabetes and aging, with atherosclerosis – or the abnormal thickening of the blood vessel wall – the main cause. Current interventions are insufficient in many patients because extensive disease precludes effective revascularisation. Additional treatments are urgently needed. One option is to stimulate blood vessel growth, to restore blood flow, preserve tissue survival and maintain optimal organ function. However, comprehension of mechanisms stimulating blood vessel development is fully established and requires further elucidation.

Angiogenesis is the growth of capillary networks consisting of endothelial cell (EC) tubes, driven by hypoxia-induced mediators, the most characterised being vascular endothelial growth factor (VEGF). Remodelling, maturation and stabilisation of existing vessels by perivascular cells (pericytes in capillaries, or vascular smooth muscle cells (VSMCs) in larger vessels) are essential for generating functional collateral vessel networks in ischaemia. This proposal extends on our published findings showing TNF-related apoptosis-inducing ligand (TRAIL) as a new molecule critical in generating stable blood vessels by simultaneously stimulating angiogenesis, vessel stability and remodelling. How TRAIL does this is not fully established, and the cross-talk between EC and VSMCs in TRAIL-dependent blood vessel generation is unknown.

Using world-first EC and VSMC-specific Trail-/- mice, we will identify the contribution of TRAIL coming from each cell type to blood vessel development in vivo using cutting edge technology and imaging. This work will determine how crucial TRAIL-dependent EC and VSMC cell-cell contact is crucial for vessel formation.

A range of techniques can be used in this study, including the in vivo Matrigel plug assay, histology, CT scanning, gene expression (PCR, Western blotting) and ELISA.

Key references
1 Di Bartolo et al. J Am Heart Assoc (2015); 4(11). pii: e002527
2 Di Bartolo et al. Diabetologia (2011); 54(12):3133-40

Atherosclerotic plaque in brachiocephalic artery sections, stained with Mac3 (left) for macrophages (brown) and Masson’s trichrome (right), demonstrating muscle fibres (red), collagen (blue) and cell nuclei (black). Image courtesy of Dr Siân Cartland, Vascular Complications Group.