Experimental Cardiology

Lab Head name:  A/Prof Xiao-Jun Du
Email:          xiao-jun.du@bakeridi.edu.au
Phone:          8532 1267

Research Focus
Our research has focused on mechanisms and novel therapies of pathological components of a failing heart

- Cardiac inflammation and remodeling following acute myocardial-infarct;
- Cardiovascular fibrosis (accumulation of excessive amount of scar tissue) and its reversal
- Autonomic nervous control and β-adrenergic signaling in heart disease

Experimental Cardiology Laboratory, Baker IDI Institute
Project 1

Title: Reversal of arterial remodeling and stiffening by relaxin therapy

Hypertension and/or ageing result in structural changes (remodeling) of conduit arteries and vessel stiffening, which is an independent risk factor for cardiovascular morbidity and mortality. Thus, reversal of large artery remodeling/stiffening is regarded as an important therapeutic goal. However, current anti-hypertensive therapies are in general unsatisfactory and slow in achieving this and there has been no report of a drug that can reverse arterial remodeling within a short-term. Our recent studies have demonstrated that the reproductive peptide hormone relaxin is potent and specific in the reversal of established fibrosis in the heart and large arteries. This project will further these findings and seek for pre-clinical evaluation of relaxin on its specific ability to reverse large arterial remodeling/stiffening seen in hypertension and ageing. The plan is based on the well-documented therapeutic actions of relaxin and on our recent findings in senescent spontaneously hypertensive rats (SHR) showing that short-term relaxin therapy reversed large arterial remodeling and improved arterial compliance. This project would be expected to generate proof-of-concept data critical for the design of clinical trials using relaxin either as monotherapy or in combination with other drugs to reverse arterial remodeling/stiffening in ageing and hypertensive patients.

The study will be conducted on aged SHR and normotensive control rats (WKY). Detailed assessment of blood pressure, large artery stiffness and histological changes in the large artery will be performed in rats without and with relaxin therapy for a period of four weeks. The persistence of the efficacy of relaxin will also be examined. In vitro study will examine the action of relaxin on cultured human vascular smooth muscle cells and adventitial fibroblasts focusing on collagen and elastin turnover.

This project is suitable for honours students as well as students wishing to continue for PhD degree.

Supervisors: A/Prof Xiao-Jun Du, Dr Qi Xu, Dr Helen Kiriazis
Project 2

Title: Cardiac phenotype in a transgenic model of Huntington’s disease

Huntington’s disease (HD) is one of the neurodegenerative diseases due to intracellular accumulation of poly-glutamine (Poly-Q) aggregates with profound interference in gene expression in the brain tissue. HD represents a single gene mediated neuronal disorder with poor quality of life and shortened life-span. Although heart disorder is believed to be the second leading cause of death in HD patients accounting for >30% mortality, the nature of the cardiac abnormalities in HD patients remain largely unexplored either clinically or experimentally.

This project will be conducted using a transgenic mouse model of HD, R6/1, due to expression of a human Huntington gene derived from a HD patient. Our recent experiments on this strain of mice have revealed significant abnormalities in the cardiac regulation by the autonomic nervous system. As a consequence, HD mice showed aberrant levels and irregularity in heart rate at baseline and during ß-adrenergic activation. Interestingly, these abnormalities occur at the pre-motor syndrome phase. We will examine the autonomic nervous function by telemetry method in conscious animals and test the cardiac responses to stressors including pressure overload and ischemic insult to fully explore the cardiac phenotype in the HD mice. We will also test effects of beta-adrenergic antagonists and muscarinic antagonists on neurocardiac phenotype in HD mice.

This study represents the first to thoroughly investigate the cardiac phenotype in a clinically relevant mouse model of HD, an area that has rarely been explored. Whereas HD is not a common disease in Australia, its genetic mechanism is representative of a class of neurodegenerative diseases (e.g. Alzheimer’s, Parkinson’s, familial amyotrophic lateral sclerosis FALS), recently defined as Poly-Q diseases.

Supervisors: A/Prof Xiao-Jun Du, Dr Helen Kiriazis, Dr Parmela Davern (Neuropharmacology Lab)
Project 3 (can be extend to 3 years for PhD study)

Title: Novel inflammation-independent action of MIF in hypertrophic heart

Hypertension is a leading cause of heart failure and a major risk factor for cardiovascular diseases. Cardiac hypertrophy is an adaptive response to increased work-load. However, if hemodynamic stress persists, maladaptive hypertrophy ensues and eventually leads to heart failure through mechanisms that remain poorly understood. Macrophage migration inhibitory factor (MIF) is a pleiotropic cytokine that regulates inflammatory response and energy metabolism. MIF acts as a proinflammatory cytokine in a variety of inflammatory disorders, including ischemic heart disease. Cardioprotective effects have been reported by inhibition of MIF. However, our recent pilot studies have found that deletion of MIF gene leads to an exacerbated cardiac hypertrophy and dysfunction in response to long-term pressure overload. This finding raises an interesting question: why MIF has such distinct actions under different disease stress? We propose that a novel and inflammatory-independent action of MIF contributes to such benefit in the hypertrophic heart. We will use in vivo and in vitro models to investigate the potential mechanism. Results from this project will shed a light on the novel role of MIF in energy balance and angiogenesis in hypertrophic progression and provide important experimental evidence for developing a new anti-hypertrophy strategy.

Research approach

1. In vivo animal model of pressure overload induced by microsurgery in genetic-modified mice. Echocardiography and micromanometry will be performed to monitor the structural and functional changes. Molecular studies to examine alterations of key genes and proteins during the hypertrophy development.

2. In vitro model: Cell culture work to further dissecting the key molecular mechanism.

Supervisors: Dr Xiao-Ming Gao, A/Prof Xiao-Jun Du
Project 4 **(can be extend to 3 years for PhD study)**

**Title:** Targeting ventricular remodeling and fibrosis of infarcted heart by anti-platelet therapy

Inflammation following acute myocardial infarction (MI) contributes to geometry change of the ventricle (ventricular remodeling) and fibrosis of non-infarcted regions, increasing the risk of heart failure. Recent studies, including ours, have shown that platelets contribute significantly to the inflammatory responses of infracted hearts and that anti-platelet therapy is effective in suppressing acute inflammation and related complications. However, it remains to be studied whether anti-platelet therapy given during the acute phase of MI exerts longer term benefits in terms of ventricular remodeling and fibrosis.

This project will be conducted on mice with surgically induced MI. Animals will then be assigned to either no treatment control or anti-platelet drug treatment. Animals will be examined by serial echocardiography to estimate ventricular remodeling and function over a period of 4 weeks post surgery. Detailed histopathological, molecular and biochemical analyses will be performed on hearts to evaluate the extent of ventricular remodeling, fibrotic healing of infarcted region and interstitial fibrosis of non-infarcted myocardium.

This project is expected to generate novel information on the efficacy of anti-platelet drugs in the setting of ischemic heart disease. This project is suitable for honours student with strong interest in cardiology.

**Supervisors:** A/Prof Xiao-Jun Du, Dr Helen Kiriazis, Prof Anthony Dart (Alfred Heart Centre)
Project 5

Title: Novel biomarkers for confirmation and assessment of acute myocardial infarction

Acute myocardial infarction (MI) is an urgent clinical condition where successful restoration of myocardial blood flow would be critical to control for the extent of myocardial ischemic injury and the size of infarction. To achieve this, early confirmation of acute MI is important for appropriate clinical therapy. A biomarker that changes early after the onset of acute MI with good sensitivity and reliability is of great clinical value. The commonly used biomarkers include troponin I (TnI) and creatine kinase (CK). However, their plasma levels remain low at the time of admission and peak levels appear around 15-18 hours after onset of MI. We have documented a novel biomarker that increase early after MI and correlated well with myocardial infarct size. This project will examine the potential clinical use of this novel biomarker in patients at the emergency department (ED) suffering from chest pain. Specifically we will study the capability of using MIF to differentiate MI and non-MI patients. Patients who arrive at ED and suffer from chest pain will be recruited. Blood samples will be collected at the time of arrival and 6, 18, 24 hrs afterwards for assays of the selected biomarkers. Patients will be followed up for the final diagnosis for MI or non-MI. The sensitivity and accuracy of the newly identified biomarker versus hsTnI and CK will be analysed.

Supervisors: Prof Anthony Dart (Alfred Heart Centre), Dr Xiao-Ming Gao
Recent publications from Experimental Cardiology Laboratory


5. Xu Q, ChakravortyA, Bathgate RA, Dart AM, Du XJ. Relaxin therapy reverses stiffened large arteries and improves arterial compliance in senescent spontaneously hypertensive rats. *Hypertension* 2010;55:1260-1266


