Index of Projects by Laboratory

Aboriginal Health ................................................................. 3
Cardiac Hypertrophy ............................................................... 5
Cellular & Molecular Metabolism ............................................. 9
Diabetes & Dyslipidaemia ......................................................... 11
Diabetic Complications .......................................................... 14
Heart Failure Research ............................................................ 22
Heart Failure Pharmacology .................................................... 24
Lipoproteins & Atherosclerosis ................................................. 30
Metabolic & Vascular Physiology .............................................. 33
Neuropharmacology ............................................................... 35
Vascular Pharmacology .......................................................... 39
Muscle Biology & Therapeutics ............................................... 43
**Project title:** A comprehensive approach to Aboriginal and Torres Strait Islander Tobacco Control (CATS) & Reducing smoking among adolescents

**Laboratory:** Aboriginal Health

**Primary Supervisor (s)** Sandra Eades, Catherine Chamberlain

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**Research Focus:** Strategies to reduce smoking among Aboriginal and Torres Strait Islander peoples

**Keywords** tobacco, smoking, Aboriginal and Torres Strait Islander, adolescents

**Project description:**

Tobacco smoking among Aboriginal and Torres Strait Islander people is the leading cause of health inequities in this population, and its control is essential to “closing the gap” in health status between Aboriginal and other Australians. Australia, however, currently lacks a comprehensive framework that guides and monitors the effectiveness of tobacco control efforts among Aboriginal people at the local, state and national levels. (Eades and Chamberlain 2015).

This project, auspiced under the Australian Prevention Partnership Centre, aims to establish parameters for reducing smoking among Aboriginal and Torres Strait Islander peoples. A review of current framework is being conducted to establish parameters for assessing evidence and current activities for tobacco control in the medium to long term. There are a number of objectives which would be amenable to 1-2 student projects, including:

1. Conducting a an overview of reviews about ‘what works’ to reduce tobacco use among Aboriginal and Torres Strait islander Australians and map against the framework using an ‘evidence gap map’.
2. Assist with conducting an audit of current tobacco reduction programs across several jurisdictions and map against the ‘evidence gap map’
3. Explore the determinants of smoking uptake among Adolescents (using data generated from NHMRC-funded adolescent study in 3 jurisdictions).
4. Develop potential interventions focused on reducing smoking uptake among Aboriginal adolescents.

**Project related methods/skills/technologies:**

- Systematic review skills, including use of evidence mapping software, within an evidence-based framework
- Conducting a survey/interviews/audit of current tobacco reduction programs and using evidence mapping software
- Data planning, collection and analysis of factors influencing adolescent smoking uptake (suitable for PhD level)
- Developing research design and intervention development skills with a pilot intervention to reduce smoking uptake.

Aboriginal and/or Torres Strait Islander students are warmly encouraged to consider this project. Knowledge and/or experience working with Aboriginal and Torres Strait Islander communities is desirable.

**References:**


2. Evidence gap maps [http://www.3ieimpact.org/evaluation/evidence-gap-maps/] accessed 30/7/2015
**Project title:**  
'Generation Now': Exploring Health Trajectories in Aboriginal Adolescents and Youth

**Laboratory:** Aboriginal Health

**Primary Supervisor(s)**  
Sandra Eades; Lina Gubhaju; Catherine Chamberlain

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**Research Focus:** Health and wellbeing of Aboriginal adolescents

**Keywords**  
Aboriginal health; Adolescent health; Longitudinal cohort studies; Participant recruitment

**Project description:**

Despite the importance of transitions in adolescence to future health, there has been little attention given to adolescent health in recent efforts to 'close the gap' in Aboriginal health and disadvantage. Aboriginal Young people experience significantly poorer health and greater social and economic challenges to future health than other young Australians. Whilst cross-sectional data provide a snapshot of the current health and wellbeing of Aboriginal adolescents, there are major gaps in evidence and longitudinal studies highlighting health trajectories and opportunities for appropriate interventions are urgently needed.

The aim of this project is to establish and conduct the first wave of follow-up for a cohort of approximately 2,250 Aboriginal young people aged 10 to 24 years recruited from remote, rural and urban Aboriginal communities, in order to:

1. Quantify patterns of: physical and mental health risk and protective behaviours; and major physical and mental health conditions and disability
2. Describe the social and environmental context in which these young people are growing up including community, school, family and individual level factors;
3. Quantify changes in resilience and risk behaviours and health outcomes over time;
4. Identify factors relating to resilience and risk behaviours and physical and mental health outcomes at baseline and changes over time;
5. Establish partnerships with communities to better understand factors relating to positive adolescent and youth health and support them to take action to improve it.

Multiple research projects are expected to arise from this program of work. Studies will involve participant recruitment, questionnaire development/pilot testing and collection of qualitative and quantitative data. Students interested in this research area are encouraged to contact the supervisors listed above to develop a research proposal.

Aboriginal and/or Torres Strait Islander students are warmly encouraged to consider this project. Knowledge and/or experience working with Aboriginal and Torres Strait Islander communities is desirable.

**Project related methods/skills/technologies:**

- Epidemiology and biostatistics
- Participant recruitment for research studies
- Data collection and analyses
- Experience in Aboriginal health
**Project title:** Evaluating the off-label use of tilorone as a novel therapeutic for heart failure  

**Laboratory:** Cardiac Hypertrophy  

**Primary Supervisor (s)** Dr Bianca Bernardo and A/Prof Julie McMullen  

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**Research Focus:** Developing new therapies for the treatment of heart failure  

**Keywords:** heart failure, fibrosis, tilorone, novel therapies  

**Project description:**  

**Synopsis:** Heart failure is one of the leading clinical problems in Australia, and its significance is increasing as the population ages. Existing therapies typically slow, rather than prevent or reverse heart failure progression and often have undesirable side effects. Thus, innovative and efficacious therapies that can prevent heart failure are urgently needed. Scarring (also called fibrosis) of the heart is a key clinical correlate of declining heart function. Recently, tilorone, an FDA approved drug which is primarily prescribed for viral infections and diarrhoea was shown to inhibit scarring in a mouse model of lung disease. We have since generated exciting Preliminary Data that demonstrate that tilorone can regulate the expression of a key anti-scarring pathway in heart cells called the bone morphogenetic protein pathway, and that administration of tilorone in a mouse model of heart failure can attenuate cardiac fibrosis.  

**Hypothesis:** Tilorone may therefore act as a potential novel therapeutic to inhibit scarring and preserve heart function in a setting of heart failure.  

**Aim:** To determine the effect of tilorone on fibrosis and cardiac function in a mouse model of pathological cardiomyopathy with established adverse cardiac remodelling, fibrosis and dysfunction.  

**Project related methods/skills/technologies:**  

- Experimental mouse procedures (echocardiography, dissection, i.p. injections)  
- qPCR  
- Western blotting  

**References:**  

1. Lepperantra et al., 2013 Am J Respir Cell Mol Biol 48:448-55  
5. Zeisberg et al., 2003 Nat Med 9:964-8
**Project title:** Atrial fibrillation and phosphoinositide 3-kinase signalling in the heart

**Laboratory:** Cardiac Hypertrophy

**Primary Supervisor (s) A/Prof Julie McMullen**

**Contact:** Julie.mcmullen@bakeridi.edu.au  8532 1194

**Research Focus:** Understanding mechanisms by which a decrease in PI3K makes the heart susceptible to AF

**Keywords:** heart, cardiac function & rhythm, PI3K signalling

**Project description:**

**Synopsis:** Atrial fibrillation (AF) is a cardiac disorder. It is the most common type of arrhythmia causing an irregular heart beat, weakness, fatigue and dizziness. AF is associated with increased risk of mortality, stroke and heart failure. Our laboratory has had a long term interest in the role of phosphoinositide 3-kinase (PI3K) in the heart. Utilising genetic mouse models, we have shown that increasing PI3K-Akt signalling in the heart provides protection against cardiac pathology, whereas decreasing PI3K can lead to cardiac dysfunction, heart failure, and increase the susceptibility to AF.

**Aim:** To understand how and why a reduction in PI3K increases the susceptibility to atrial fibrillation.

**Project related methods/skills/technologies:**

- Experimental mouse procedures (echocardiography, ecg, dissection)
- qPCR
- Western blotting
- Histological analyses

**References:**

Project title: Understanding and overcoming cardiotoxicity associated with new cancer therapies

Laboratory: Cardiac Hypertrophy

Primary Supervisor(s) A/Prof Julie McMullen and Dr Jenny Ooi

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Research Focus: Understanding cardiotoxicity of anti-cancer agents and identifying safer alternatives.

Keywords: heart, cardiac function & rhythm, anti-cancer agents

Project description:

Synopsis: Cancer therapeutics have evolved dramatically in the last five years with an explosion of potent small molecule inhibitors that target key survival pathways in the cancer cell. Many of these pathways are also crucial for cardioprotection. Hence, although the use of targeted agents in the clinic may ameliorate “traditional” side-effects such as myelosuppression and infections, they may paradoxically increase the risk of serious cardiac events. A thorough understanding of how these agents impact cardiac signalling is critical for their safe and widespread use in the community. Our laboratory has had a long term interest in the role of phosphoinositide 3-kinase (PI3K) in the heart. Utilising genetic mouse models, we have shown that increasing PI3K-Akt signalling in the heart provides protection against cardiac pathology, whereas decreasing PI3K can lead to cardiac dysfunction, heart failure, and increase the susceptibility to atrial fibrillation (AF). Despite the beneficial effect of PI3K in the heart, PI3K is amplified and mutated in a wide range of cancers. Thus, inhibiting components of the PI3K pathway is currently one of the most active drug developments in the cancer field.

Aim: To study the impact of anti-cancer agents on PI3K-Akt signalling in the heart and assess cardiac function.

Project related methods/skills/technologies:

- Experimental mouse procedures (echocardiography, dissection, i.p. injections)
- qPCR
- Western blotting
- Cell culture

References:

**Project title:** Identification of PI3K-regulated noncoding RNAs in cardiac diseases

**Laboratory:** Cardiac Hypertrophy

**Primary Supervisor(s)** Dr Jenny Ooi, A/Prof Julie McMullen

**Contact:** Julie.mcmullen@bakeridi.edu.au, 85321194  
jenny.ooi@bakeridi.edu.au, 85321712

**Research Focus:** Bioinformatics approaches for cardiac disease

**Keywords** Cardiac hypertrophy, bioinformatics, microRNAs, noncoding RNAs

**Project description:**
Heart failure is a major clinical problem affecting 1-3% Australians, therefore strategies to protect the heart against insults that lead to heart failure such as pathological cardiac hypertrophy (growth of the heart) is becoming more critical. Protein-coding genes are the most well studied sequences but only account for approximately <2% of the genome. Previously unknown non-coding RNA species (ncRNA, formerly known as ‘junk’) have been discovered, and add a new dimension and complexity to the regulation of DNA, RNA and protein. MicroRNAs (miRs) are a family of small RNAs that play important roles in the regulation of target genes. Our laboratory has successfully regulated one of these miRNAs with an RNA-based therapy in a mouse model with cardiac dysfunction, and demonstrated improved outcome and reduced pathology with this treatment strategy (1, 2).

Previously, we demonstrated that the gene phosphoinositide 3-kinase (PI3K) protects the heart in settings of cardiac stress (3). We identified miRNAs controlled by PI3K and reported that regulation of these PI3K-controlled miRNAs was beneficial in models of heart failure (3). The main aim of this project is to identify other non coding RNAs controlled by PI3K. We have collected tissues from these mice and with the development and improvement of deep sequencing technologies we now have the opportunity to identify and comprehensively assess the role of other small ncRNAs in addition to miRNAs simultaneously (3).

This project will use bioinformatics approaches to investigate changes in other small RNAs and build ncRNA-associated networks that will improve our understanding of the pathways that regulate complex diseases like heart failure. After identification of key miRNAs/ncRNAs, the student will use molecular and cell culture experimental techniques to perform validations.

**Project related methods_skills_technologies:**
- Bioinformatics
- Molecular techniques

**References:**

Project title: Protective effects of exercise on metabolism

Laboratory: Cellular and Molecular Metabolism Laboratory

Primary Supervisor(s): Darren Henstridge, Mark Febbraio

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Research Focus:
My research focus is on how metabolism is impacted in different disease settings such as obesity, insulin resistance, type 2 diabetes and Alzheimer’s disease. I have a special interest in the impact of exercise on metabolism and the role of a family of proteins known as heat shock proteins (HSPs) on metabolic function.

Keywords: Metabolism / exercise / mitochondria / Alzheimer’s disease / obesity / diabetes / liver / skeletal muscle / heat shock proteins

Project description:
Exercise is an effective therapy for many conditions where metabolism is impaired including obesity, insulin resistance and type 2 diabetes. However, many people especially those who are frail or elderly cannot exercise and of those that can exercise, rates of compliance are low. Therefore, finding therapeutics that target pathways regulated by exercise and/or finding the best modes of exercise training to give maximal metabolic effect are of interest. While many of the benefits of exercise in relation to metabolic disease such as increased energy expenditure leading to weight loss and improved cardiovascular function are well known, others such as exercise’s affect on the type of bacteria in the gut (gut microbiota) and the way in which exercise is protective against liver disease have been less studied.

We have ongoing research in our laboratory which is examining how exercise impacts the composition of the bacteria in the gut and whether this alteration leads to any changes in metabolism. We are also interested in how exercise improves fatty liver a condition that is associated with obesity and type 2 diabetes and a condition that can be a precursor to the development of liver cancer (hepatocellular carcinoma).

Other interests of the laboratory include the identification of the role of the gene ACAD10 in whole-body metabolic function. And the role of overexpression of heat shock protein 72 in the brain’s of mice with Alzheimer’s disease.

Project related methods/skills/technologies:
- Animal (mouse) work on metabolism measuring fat mass (echoMRI), exercise training mice, glucose tolerance etc.
- Laboratory analysis of tissue samples (protein levels, mRNA etc.)
- Data analysis and graphical presentation

References:
Project title: Does skeletal muscle mitochondrial dysfunction cause insulin resistance?

Laboratory: Cellular and Molecular Metabolism Laboratory / Diabetes & Dyslipidaemia

Primary Supervisor (s) Darren Henstridge (CMML), Brian Drew (Diabetes & Dyslipidaemia)

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brian.drew@bakeridi.edu.au 8532 1134

Research Focus:
This research focuses on whether insulin resistance (a state whereby the body no longer responds normally to the actions of the hormone insulin) can be caused by skeletal muscle mitochondrial dysfunction.

Keywords: Metabolism / mitochondria / obesity / diabetes / skeletal muscle / Parkin / PolG / insulin resistance

Project description:
Mitochondria are cellular organelles known as the “power plant” of the cell, due to their ability to convert fatty acids and glucose to energy. In recent years, it has become clear that mitochondrial dysfunction and defects in oxidative metabolism are characteristic features of many chronic illnesses including obesity, insulin resistance, type 2 diabetes and neurodegenerative diseases. However, the underlying reasons for this association are still poorly understood.

Mitochondrial activity is heavily contingent on the quality of mitochondria in the cell, which in turn is governed by a balance between the generation of new mitochondria (mitochondrial biogenesis), the removal of old or damaged mitochondria (mitophagy) and cellular processes including mitochondrial fission (separation and isolation) and fusion (joining together). Fusion helps mitigate cellular stress by sharing critical nutrients amongst mitochondria, whilst fission is a necessary pathway for the removal of damaged mitochondria via mitophagy. Mitochondrial dysfunction has been shown to be induced by various insults including, amongst others, mutation(s) in the mtDNA.

Over the years there have been various lines of evidence suggesting that mitochondrial dysfunction may cause skeletal muscle insulin resistance. To definitively determine whether this is indeed the case, we are creating two mouse lines that will have two genes involved in mitochondrial function (parkin and PolG) deleted specifically from the skeletal muscle. To establish this resource we are using a technique called CRISPR/Cas9 (Clustered Regularly Interspaced Short Palindromic Repeat system) in collaboration with the Australian Phenomics Network (APN). CRISPR is a novel gene editing tool that takes advantage of an adaptive immune defense system used by Archea and bacteria, which facilitates genomic engineering in mammalian organisms. Together, this will allow us to determine whether skeletal muscle specific mitochondrial dysfunction causes insulin resistance?

Project related methods/skills/technologies:
- Animal (mouse) work on metabolism measuring things such as body weight, fat and lean mass (echoMRI), glucose tolerance etc..
- Laboratory analysis of tissue samples (protein levels, mRNA, mitochondrial function etc.)
- Data analysis and graphical presentation

References:
Research Focus:
Animal studies to investigate the role of IDOL in the prevention of cardiovascular disease, diabetes and liver disease

Keywords
cholesterol, triglyceride, insulin resistance, diabetes, steatosis, myocardial infarction, mice

Project description:
More than one in five Australians has elevated levels of circulating triglycerides caused by excess dietary intake, genetics or diabetes. These excess triglycerides can accumulate in peripheral tissues where they can have pathological effects. In the heart this result in increased risk of cardiovascular disease (CVD); in skeletal muscle it can lead to insulin resistance and in the liver this can result in steatosis. Currently, there are few effective therapies for lowering triglyceride levels. Thus, there is a need to prevent the damage caused by excess triglycerides.

IDOL is an E3 ligase identified for its ability to degrade the LDL receptor (1). In addition, we have confirmed its importance in regulating the accumulation of triglycerides in the heart and skeletal muscle. We have various projects which will test the role of IDOL in protecting against the following,
- lipid-induced cardiac dysfunction
- lipid-mediated insulin resistance in skeletal muscle
- lipid-induced hepatic steatosis

These studies will involve the use of genetically modified mouse models as well as the use an adeno-associated virus (AAV) to turn on the IDOL pathway in mice. These studies will involve the assessment of metabolic parameters such as glucose tolerance, insulin sensitivity and the response to a myocardial infarction. Tissues will be assessed for metabolic signaling and substrate metabolism using a range of techniques including western blotting and qPCR as well as an Oroboros. Immunohistochemical, histological and lipidomic approaches will also be utilised.

Project related methods/skills/technologies:
- Western blotting – assessment of metabolic signaling pathways
- Quantitative PCR – assessment of regulators of lipid metabolism
- Immunohistochemistry/Histology – tissue morphology/protein expression
- Lipidomics – assessment of lipid species
- Oroboros – analysis of cellular respiration
- Animal studies – AAV transduction, cross-breeding, metabolic assessment

References:
**Project title:** Characterizing new genetic approaches to improve mitochondrial health and prevent disease

**Laboratory:** Diabetes & Dyslipidaemia Laboratory (DDL)

**Primary Supervisor(s):** Brian Drew, Anna Calkin

**Contact:**  
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Anna.calkin@bakeridi.edu.au, Ph: 8532 1140

**Research Focus:** This project focuses on increasing energy production in cells by improving the health of mitochondria in specific tissues including skeletal muscle, adipose and brain. We will test if this approach may have benefit in treating diseases including diabetes, obesity and neurodegeneration.

**Keywords:** energy metabolism, mitochondria, obesity, diabetes, neurodegeneration

**Project description:**

Numerous diseases including some cancers, diabetes, obesity and neurodegeneration are associated with a decline in the health and function of mitochondria – small structures within every mammalian cell responsible for generating energy. However, the cause of this mitochondrial dysfunction - or ways in which we can prevent or reverse it remain incompletely understood.

In a healthy cell, mitochondria are continuously degraded and regenerated in a tightly controlled cycle that results in a constant supply of fresh and efficient mitochondria. It is disruption of this tight cycle that leads to mitochondrial dysfunction. Very little is known about the cellular mechanisms that control this cycle, even though identification of these mechanisms could have significant therapeutic implications.

To this end, we have recently made some new and exciting findings that identify a number of important proteins which regulate mitochondrial flux, and also appear to be critical to maintaining mitochondrial health. Consequently, we have projects available that will test whether manipulation of these proteins in various tissues (skeletal muscle, adipose tissue, brain) can effect mitochondrial dysfunction in cells and mice, and therefore affect disease pathogenesis.

**Project related methods/skills/technologies:**

- Cell culture
- qPCR/Western blotting
- Genetic manipulation
- Mouse handling, phenotyping and characterization

**References:**

## Project title:
Identification of Novel Regulators of Cholesterol Metabolism

## Laboratory:
Diabetes & Dyslipidaemia

## Primary Supervisor(s):
Dr Anna Calkin, Dr Eser Zerenturk, Dr Brian Drew

## Contact:
anna.calkin@bakeridi.edu.au 8532 1140

## Research Focus:
Cell culture and animal studies to validate novel regulators of cholesterol metabolism identified through our proteomic/lipidomic discovery platform

## Keywords
Cholesterol, Atherosclerosis, Mice, Gene Discovery, Novel Therapies

## Project description:
One in three Australians has elevated levels of circulating cholesterol caused by excess dietary intake, genetics or diabetes. This can have pathological effects in peripheral tissues such as the heart, increasing the risk of cardiovascular disease (CVD). Currently, although statins have had a substantial impact on reducing plasma cholesterol and CVD risk, some individuals experience side effects such as muscle soreness and others respond poorly, highlighting an unmet need for new cholesterol lowering therapies. Thus, studies are required to identify novel regulators of cholesterol metabolism as potential targets for therapeutic intervention.

We provide a novel approach to identify new pathway(s) associated with cholesterol regulation. We have linked genetic differences in 100 strains of mice to changes in plasma cholesterol levels. Excitingly, this approach has identified many new targets, never before linked to cholesterol metabolism.

This project will involve validation of these identified targets in liver cells and translation of these findings to mouse models including a hypercholesterolaemic model developed by our group, L-sIDOL transgenic mice (1). *In vitro* studies will be performed in the human liver cell lines, HepG2 and Hep3B, overexpressing and inhibiting a given target and assessing outputs of cholesterol regulation such as induction of the LXR and SREBP2 pathways. Animal studies will involve administration of target AAVs and assessment of parameters including plasma and liver cholesterol levels, atherosclerotic lesion development and cholesterol signaling pathways.

## Project related methods/skills/technologies:
- Molecular biology – cloning, generation of adenovirus, expression constructs
- Cell culture – liver cell lines, primary liver cells, transfection, infection
- Assessment of cholesterol pathways - cholesterol uptake, western blotting, qPCR
- Animal studies – AAV transduction, metabolic assessment

## References:
**Project title:** The role of Nox5 in diabetes associated cardiovascular disease

**Laboratory:** Diabetic Complications

**Primary Supervisor (s)** Dr. Stephen Gray and Prof. Karin Jandeleit-Dahm

**Contact:** Stephen.gray@bakeridi.edu.au 8532 1198

**Research Focus:**
Oxidative Stress, Diabetic Complications, Vascular Disease

**Keywords**

**Project description:**
The development of diabetic complications including vascular and renal disease is enhanced in diabetic patients. However, the underlying mechanism as to why this disease process is accelerated is largely unknown.

Oxidative has been proposed to play a key role in the development of diabetic complications, particular the NADPH oxidase (Nox) family. There are primarily 4 Nox isoforms that have been shown to be important in the development of diabetic complications, Nox1, 2, 4 and 5. All of these isoforms have increased expression and activity in diabetic patients. Our group has established a role for the Nox1 isoform in the development of diabetic atherosclerosis, and the Nox4 isoform in diabetic kidney disease. However, to date a role for the Nox5 isoform in diabetic complications is unknown.

**Keywords**

**Project description:**
The development of diabetic complications including vascular and renal disease is enhanced in diabetic patients. However, the underlying mechanism as to why this disease process is accelerated is largely unknown.

Oxidative has been proposed to play a key role in the development of diabetic complications, particular the NADPH oxidase (Nox) family. There are primarily 4 Nox isoforms that have been shown to be important in the development of diabetic complications, Nox1, 2, 4 and 5. All of these isoforms have increased expression and activity in diabetic patients. Our group has established a role for the Nox1 isoform in the development of diabetic atherosclerosis, and the Nox4 isoform in diabetic kidney disease. However, to date a role for the Nox5 isoform in diabetic complications is unknown.

**We have multiple Honors and PhD projects involving the role of Nox5 in diabetes associated cardiovascular disease, which will focus on the following areas:**

1. Vascular Reactivity
2. Atherosclerosis development and remodeling
3. Cardiovascular function

The projects will utilize a highly novel humanised Nox5 knockin mouse, where Nox5 is expressed only in the vascular smooth muscle cells or the endothelial cells. The project will involve applying various experimental techniques that include immunohistochemistry, RT-PCR for gene expression analysis and cell culture analysis to delineate the role that Nox5 plays in the development of diabetic complications.

**Project related methods/skills/technologies:**
- Cell Culture
- RT-PCR
- Tissue morphology & histology

**References:**
### Project title:
The role of Linagliptin in diabetes associated kidney disease

### Laboratory:
Diabetic Complications

### Primary Supervisor (s) Dr. Stephen Gray and Prof. Karin Jandeleit-Dahm

### Contact:
Stephen.gray@bakeridi.edu.au 8532 1198

### Research Focus:
Diabetic complications, kidney disease,

### Keywords

### Project description:

Diabetic nephropathy is the leading cause of end stage renal disease in the Western World and is associated with enhanced morbidity and mortality. Linagliptin has been demonstrated to have potential as not only a glyceamic control agent, but also as a direct renoprotective agent in diabetes. However, the direct effect of linagliptin in the development of diabetic kidney disease has not yet been examined.

The current honors project aims to investigate the direct renoprotective effects of linagliptin in a rat model of STZ induced diabetic nephropathy and in a mouse model of spontaneous insulin deficiency, the Akita mouse which develops diabetic nephropathy.

The project will involve the utilization of diabetic mice and rats. The end points of the study will involve kidney tissue analysis for kidney structure and disease, ELISA and immunohistochemistry for analysis of kidney function as well as RT-PCR and Western Blot to determine the mechanism involved in disease development and progression.

### Project related methods/skills/technologies:
- RT-PCR
- Tissue morphology & histology
- Animal handling

### References:
### Project title:
The interaction between the Renin Angiotensin System (RAS) and Nox derived ROS in diabetes associated vascular and renal disease.

### Laboratory:
Diabetic Complications

### Primary Supervisor(s):
Dr. Stephen Gray and Prof. Karin Jandeleit-Dahm

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8532 1198

### Research Focus:
Oxidative Stress, Diabetic Complications, Vascular and Kidney Disease

### Keywords

### Project description:
The development of diabetic complications including vascular and renal disease is enhanced in diabetic patients. However, the underlying mechanism as to why this disease process is accelerated is largely unknown.

A number of mechanisms interact with each other to enhance the development of diabetic complications. However, the level of interaction is unexplored. One such interaction is oxidative stress and the rennin angiotensin system (RAS). Studies have shown that blocking the RAS system prevents the accelerated development of kidney and vascular disease. In addition, studies have shown that blocking Nox derived ROS also reduces the development of kidney and vascular disease development in diabetes. However, no study has explored how these two systems interact and if the combined inhibition enhances the attenuation of diabetes associated vascular and kidney disease development.

Our group has established animal models that have Nox isoforms genetically deleted in addition to pharmacological inhibition of the RAS system.

The project on offer will explore this interaction using tissue collected from these Nox deleted diabetic mice that have been administered RAS inhibitors. Furthermore, a novel aspect of these studies will be the co-administration of a Nox inhibitor and RAS blocker to identify if there are enhanced effects on diabetic complications development when two pathways are blocked at the same time.

### Project related methods/skills/technologies:
- Cell Culture
- RT-PCR
- Tissue morphology & histology

### References:
### Project title:
The role of let 7 micro-RNA in atherosclerosis: endothelial cells

### Laboratory:
Genes and Diabetes (Diabetic Complications Laboratory)

### Primary Supervisor(s):
Phillip Kantharidis

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8532 1462

### Research Focus:
Diabetes associated atherosclerosis

### Keywords
microRNA, atherosclerosis, endothelial cells, inflammation

### Project description:
Patients with diabetes have mortality from cardiovascular disease that is over twice that observed in the general population, resulting in atherosclerotic plaque formation. The diabetic plaque is characterized by macrophage accumulation and abnormalities in both aortic endothelial and vascular smooth muscle cell function. Within the atherosclerotic cytokine network, tumor necrosis factor-alpha (TNF-alpha) is implicated as a key molecular driver. Our data in vascular smooth muscle cells suggests that the let-7 micro-RNA family may have an important role in the pathogenesis of the diabetic plaque, with TNF-alpha down regulating the expression of this miRNA family. Restoring the expression of let-7 miRNAs in vascular smooth muscle cells can attenuate TNF-alpha-mediated signaling. However, the impact of restoring let-7 expression in aortic endothelial cells and macrophages is unclear. This project will investigate whether restoring let-7 miRNA levels in primary mouse aortic endothelial cells and macrophages can suppress inflammatory signals mediated by TNF-alpha. The project will involve the use of transfection techniques but also the use of novel therapeutic compounds to attenuate the effect of TNF and hence atherosclerosis.

### Project related methods/skills/technologies:
- Animal experiments
- Tissue culture
- Transfection with miRNA mimics
- rtQ-PCR analysis for gene and microRNA expression
- Western analysis
- NFκB reporter gene assays
- Monocyte adhesion assays
- Animal tissue handling, processing and analysis

### References:
**Project title:** RNA biomarkers predictive of patients at risk of developing diabetic nephropathy

**Laboratory:** Genes and Diabetes (Diabetic Complications Laboratory)

**Primary Supervisor (s):** Phillip Kantharidis

**Contact:** Phillip Kantharidis  
Phillip.kantharidis@bakeridi.edu.au

**Research Focus:**  
Biomarkers for diabetic nephropathy

**Keywords**  
microRNA, biomarkers, RNA-seq, bioinformatics

**Project description:**  
Not all patients with diabetes are at risk of also developing complications such as end stage kidney disease and diabetes associated atherosclerosis. Approximately 30% of patients develop these debilitating conditions. Despite the research to date we do not have any good means of identifying patients at risk of developing complications. In terms of the kidney, diabetic nephropathy is the most common cause of chronic kidney disease in people with diabetes. This condition is characterized by glomerular changes such as glomerular basement thickening, mesangial expansion, renal hypertrophy and the accumulation of extracellular matrix (ECM) proteins. These changes are largely driven by TGF-β which stimulates ECM production in many cell types.

The aim of this project is to use RNA-seq techniques to identify RNA biomarkers in urine from control and diabetic patients which not only are diagnostic of disease, but more importantly may be able to predict disease development. Archival and fresh samples will be used to identify RNA (mRNA and miRNA) biomarkers and these will be then be tested against a panel of samples from patients whose history is known. Potential biomarkers will be further assessed in terms of relevance to disease using in vitro assays and animal models of diabetic nephropathy.

**Project related methods/skills/technologies:**
- RNA isolation techniques
- RNA-seq and bioinformatics
- Tissue culture
- Transfection with miRs
- rtQ-PCR analysis
- western analysis

**References:**
**Project title:** Lipoxin A4 analogues as a treatment for diabetic nephropathy

**Laboratory:** Genes and Diabetes (Diabetic Complications Laboratory)

**Primary Supervisor(s):** Phillip Kantharidis

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8532 1462

**Research Focus:**  
Biomarkers for diabetic nephropathy

**Keywords**  
Inflammation, microRNA, diabetic nephropathy

**Project description:**  
Diabetic nephropathy (DN) is the most common cause of chronic kidney disease in people with diabetes. The major characteristics of DN include glomerular basement thickening, mesangial expansion, renal hypertrophy and the accumulation of extracellular matrix (ECM) proteins. TGF-β is the most potent inducer of renal fibrosis because it stimulates ECM production in many cell types, but because it also transformed cells to a profibrotic phenotype, inducing the expression of other fibrogenic molecules (e.g. CTGF), thus amplifying the effect of TGF-β. Many fibrogenic mechanisms appear to converge on TGF-β and its receptors to signal through the SMADs, MAPKs and other pathways. The role of altered expression of certain miRNAs in TGFβ treated proximal tubular cells appears to contribute to the increased expression of ECM proteins (collagens, fibronectin, αSMA, etc). Restoring the expression of some of these miRs can attenuate the effects of TGFβ in terms of ECM synthesis. However, the direct targeting of TGF-β as an anti-fibrotic treatment has been problematic because of the critical role this factor plays in immune surveillance. We have found that a family of naturally occurring molecules in the body (lipoxins) have the ability to modulate TGFβ signaling and restore the expression of certain miRNAs that contribute to renal disease, and hence are able to reduce the damage caused by diabetes in the kidney. Access to newly designed stable analogues of these compounds provides us with a unique opportunity to test new treatments against diabetic nephropathy.

**Project related methods/skills/technologies:**  
- Animal experiments  
- RNA isolation techniques  
- rtQ-PCR (gene expression) analyses  
- Tissue culture  
- Transfection with miRs  
- western analyses  
- mitochondrial and oxidative stress assays

**References:**
**Project title:** MicroRNAs and mitochondrial function in diabetic nephropathy

**Laboratory:** Genes and Diabetes (Diabetic Complications Laboratory)

**Primary Supervisor(s):** Phillip Kantharidis

**Contact:** Phillip Kantharidis
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**Research Focus:**
The impact of altered miRNA expression on mitochondria

**Keywords**
Oxidative stress, mitochondria, microRNA, diabetes, kidney

**Project description:**
Diabetic nephropathy (DN) is the most common cause of chronic kidney disease in people with diabetes. It is characterized by scarring of the kidney, with changes in both glomeruli and the tubulointerstitial areas of the kidney. The laying down of excess extracellular matrix (ECM) protein results in reduced kidney function and finally leads to end stage renal disease. TGF-β is the most potent inducer of renal scarring, stimulating ECM production in many cell types. More recently it has become evident that mitochondrial structure and function is also affected by TGF-β1, contributing to the overall disease phenotype.

Our work has demonstrated that microRNAs play an important role to the regulation of ECM in the kidney and more recently we have demonstrated the miR-21 in particular is important for mitochondrial biology and targets several genes that are relevant to mitochondrial structure and function.

This project will investigate the link between elevated miR-21 in diabetic nephropathy and the effect this has on mitochondria using renal proximal tubular cells as a model. Parallel studies will be conducted in kidney tissue from diabetic animals to confirm findings and develop new strategies for the treatment of diabetic nephropathy.

**Project related methods/skills/technologies:**
- Animal experiments
- RNA isolation techniques
- rtQ-PCR (gene expression) analyses
- Tissue culture
- Transfection with miRs
- western analyses
- mitochondrial assays
- oxidative stress assays

**References:**
**Project title:** Targeting the AT2R as a novel therapeutic approach for diabetes-associated atherosclerosis

**Laboratory:** Diabetes & Atherosclerosis

**Primary Supervisor(s):** A/Prof Terri Allen, Dr Bryna Chow

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<tr>
<th>Contact:</th>
<th><a href="mailto:terri.allen@bakeridi.edu.au">terri.allen@bakeridi.edu.au</a></th>
<th>8532 1453</th>
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<tr>
<td></td>
<td><a href="mailto:bryna.chow@bakeridi.edu.au">bryna.chow@bakeridi.edu.au</a></td>
<td>8532 1311</td>
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**Research Focus:**
Diabetes is a major risk for the development of cardiovascular disease leading to the clinical consequences of heart attacks, stroke and amputations and contributing to increased morbidity and mortality observed in diabetes patients. Current treatment options fail to fully protect patients from macrovascular complications of diabetes and thus new treatments are urgently needed. Our laboratory aims to address key clinical questions centering on the prevention and treatment of diabetes-associated macrovascular complications.

**Keywords:** Atherosclerosis, diabetes, cardiovascular disease, inflammation

**Project description:**
Background: Atherosclerosis is well-implicated to be the main contributor to the mortality and morbidity in diabetes patients (1). Hyperglycaemia often accelerates the progression and development of atherosclerosis and cardiovascular disease. Following the rupture of an atherosclerotic lesion, diabetic patients are at high risk of suffering from heart attacks and strokes. Angiotensin (Ang) II, the main effector hormone of the renin-angiotensin system, is regarded as the key factor that drives the destabilisation of atherosclerotic lesions on blood vessel walls. Its ability to stimulate the production and secretion inflammatory, oxidative stress and fibrotic molecules during pathological conditions is well-considered to be mediated primarily through its type 1 receptors (AT1Rs) subtype (2).

Interestingly, accumulating evidence has postulated that Ang II negatively regulates AT1R-mediated actions and attenuates fibrosis by signalling through its type 2 receptors (AT2R). Although activation of the AT2R has been shown to be protective in numerous diseased models (3-6), such an approach in type 1 diabetes has yet to be fully characterised.

Project aim: Therefore, the current project aims to specifically explore the role of the AT2R using the novel selective non-peptide AT2R agonist, Compound 21 (C21) in a mouse model of atherosclerosis which closely mimic the pathology of human plaque, and elucidate the signaling transduction pathways associated with C21’s ability to regulate its activity. These studies are novel and crucial to an overall program of research devoted to developing the clinical potential of C21 as a therapeutic intervention for diabetic associated atherosclerosis. *Honours, Masters and PhD projects are available.

**Project related methods/skills/technologies:**
- Animal procedure
- Cell culture
- Protein biochemistry and molecular biology (i.e. Western blotting, ELISA)
- Gene analysis (i.e. Quantitative real time PCR)
- Histology

**References:**
**Project title:** Dietary role in the prevention of heart failure – an intergenerational study

**Laboratory:** Heart Failure research Group

**Primary Supervisor(s)** Dr Francine Marques and Prof David Kaye

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**Research Focus:** epigenetic mechanisms to prevent cardiac fibrosis

**Keywords:** heart failure, fibrosis, diet, epigenetics

**Project description:**

Heart failure is the leading cause of death in developed countries. Patients with heart failure have marked cardiac fibrosis, the scarring of the heart with the accumulation of fibroblasts and extracellular matrix, leading to stiffness and, thus, a decrease in myocardial function. While the role of a high fat diet has been well studied in the development of cardiovascular disease, the effect of a high fibre diet in the prevention or attenuation of heart failure is less known. We have recently found that dietary manipulation in mice for 3 weeks prior to deoxycorticosterone acetate (DOCA) challenge (which causes hypertension and cardiac fibrosis) has beneficial effects on cardiac structure. Recent studies performed in the context of other inflammatory disease suggest that epigenetic modifications could also be passed on across generations. The overall aim of this project will be to determine the effect of the maternal diet in the prevention of myocardial fibrosis in the progeny. This will be achieved by treating pregnant mice with different diets, DOCA surgery, *in vivo* echocardiography, immunohistochemistry to determine cardiac fibrosis, and validation of DNA methylation and target messenger RNA (mRNA) sites in the progeny.

**Project related methods/skills/technologies:**

Mouse surgery, mouse echocardiography, immunohistochemistry (Masson’s trichrome), RNA and DNA extraction, next-generation sequencing (bisulfite sequencing), real-time PCR.
**Project title**: Targets of microRNA miR-181a regulating blood pressure

**Laboratory**: Heart Failure research Group

**Primary Supervisor(s)**: Dr Francine Marques, Prof Geoff Head, Prof Gavin Lambert

**Contact**: francine.marques@bakeridi.edu.au 8532 1916

**Research Focus**: mechanisms that regulate high blood pressure

**Keywords**: microRNAs, kidney, biomarker

**Project description:**

High blood pressure (BP), also known as essential hypertension, is responsible for more than 50% of cardiovascular deaths worldwide, being the principal risk factor for global burden of disease. Hypertension is a multifactorial condition with a substantial contribution from heritable genetic factors. Unravelling the molecular predisposition to high blood pressure (BP) has, however, proven challenging. MicroRNAs are small non-coding RNAs which bind to untranslated regions of many genes including those responsible for cardiovascular disease. We found previously that the microRNA miR-181a binds to and regulates the levels of renin mRNA in cells in culture and is inversely associated with the level of expression of renin in the kidney (Marques et al., Hypertension 2011; Jackson, Marques et al., Hypertension 2013). This microRNA was also detected in the circulation and was associated with the BP level. Other genes besides renin seem, however, to be involved (Marques et al., submitted). The aim of this project will be to determine if miR-181a is associated with early markers of high BP and cardiovascular disease using 200 human plasma samples obtained from young adults, and also whether miRNA levels change with exercise and/or diet. We will also determine what other messenger RNAs are targeted by miR-181a, especially ones in pathways that affect BP and cardiovascular disease. This will be achieved by performing bioinformatics analyses, then validating the levels of these genes in tissues of models of hypertension (treated with a microRNA mimic, renal denervation, etc), followed by cloning and in vitro transfection experiments.

This project will involve collaborations with the Menzies Institute for Medical Research, Tasmania.

**Project related methods/skills/technologies**: Bioinformatics, RNA extraction, real-time PCR, cloning and microbiology, cell culture, transfections, luciferase assays, and statistical analyses

**References**:


Project title: Circumventing Impaired Nitric Oxide Function in the Cardiovascular Complications of Diabetes

Laboratory: Heart Failure Pharmacology

Primary Supervisor: Assoc Prof Rebecca Ritchie

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Research Focus:
Our laboratory seeks to improve the understanding of the causes of heart failure, identify new targets for its precursors and develop new pharmacotherapies for delaying their progression.

Keywords: Cardiac function; Coronary vasculature; Diabetes; Nitric Oxide; Nitroxyl; Oxidative stress; Platelets.

Project description:
BACKGROUND: The global epidemic of diabetes mellitus is imposing an exponential burden on society – not only because of the substantial associated healthcare costs, but also because of the poor health outcomes for those with the condition, particularly as a result of diabetic cardiovascular complications-induced morbidity and mortality. Impaired nitric oxide (NO) signalling is an independent marker of poor prognosis. Defined as a diminution or absence of the protective cardiovascular actions downstream of NO, the phenomenon is particularly manifest in diseased human vasculature, likely as a consequence of elevated oxidative stress (see diagram). Loss of NO responsiveness is particularly debilitating in diabetes, where cardiovascular emergencies (acute myocardial infarction, transient ischaemia, cardiogenic shock) occur more frequently, yet the ability of NO-based pharmacotherapies to target platelet aggregation and vasoconstriction is deficient. We have identified nitroxyl (HNO) as a putative strategy for enhancing NO signalling in the heart and vasculature over the short- and longer-term, which we believe can potentially address this clear area of clinical need.

GENERAL HYPOTHESIS: Diabetes-induced NO resistance in the heart and vasculature is exacerbated by poor glycaemic control, and can be circumvented by HNO

AIMS: To determine whether diabetes induces NO resistance in the myocardium (not previously known), to investigate the relationship between hyperglycaemia and NO responsiveness in the diabetic heart and vasculature, and to demonstrate that HNO circumvents this impaired NO signalling induced by diabetes.

SIGNIFICANCE: Strategies that circumvent (for management of cardiovascular emergencies) and/or ameliorate (targeting the incidence of these emergencies) impaired NO signalling in the diabetic heart and vasculature will improve prognosis in affected patients, of substantial clinical importance.
### Project related methods/skills/technologies:

- *in vivo* models of diabetic cardiac disease
- isolated rodent hearts *ex vivo*
- assessment of cardiac and vascular function
- biochemical techniques: Westerns, ROS detection, ELISA, real-time PCR, histology

### References:

Project title: Annexin-A1 Mimetics: a Novel Therapeutic Approach for Targeting the Cardiac Complications of Diabetes

Laboratory: Heart Failure Pharmacology

Primary Supervisor: Assoc Prof Rebecca Ritchie

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Research Focus:
Our laboratory seeks to improve the understanding of the causes of heart failure, identify new targets for its precursors and develop new pharmacotherapies for delaying their progression.

Keywords: Annexin-A1; Cardiac function; Diabetes; Heart failure; Inflammation.

Project description:
BACKGROUND: Diabetes is Australia’s fastest growing chronic disease. The disease affects almost 2 million Australians; diabetes increases heart failure risk 2.5-fold and accelerates its onset. Our laboratory has an established track record for identifying new pharmacotherapies for diabetic cardiomyopathy. Building on this experience, we have obtained recent evidence that cardiac inflammation is a key contributor to myocardial damage in the diabetic heart. We have previously shown that the glucocorticoid-regulated anti-inflammatory mediator annexin-A1 is a key regulator of cardiac viability and function. Annexin-A1 thus offers an attractive approach to minimise the detrimental consequences of diabetes on the heart.

GENERAL HYPOTHESIS: Annexin-A1-based therapies limit diabetic cardiomyopathy by reducing cardiac inflammation and protecting cardiac contractile function.

AIMS: To compare the time-course of cardiac inflammation and impaired cardiac function, in both type 1 and type 2 diabetes, and to investigate annexin-A1 cardioprotection for the cardiac complications of the disease in vivo.

SIGNIFICANCE: The alarming global epidemic of diabetes gives rise to an ever-increasing heart failure burden. We propose that annexin-A1 addresses the unmet clinical need of the extra burden posed by concomitant diabetes, inflammation and cardiomyopathy. The potential cardioprotective annexin-A1 mechanisms represent a strategic new therapeutic intervention for diabetic cardiomyopathy. These interventions may ultimately limit progression to heart failure and death in diabetes-affected patients.
Project related methods/skills/technologies:

- *in vivo* models of diabetic cardiac disease
- assessment of cardiac function
- biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence

References:

**Project title:** Therapeutic targeting of the cardiac hexosamine biosynthesis - ROS axis to protect the diabetic heart  
**Laboratory:** Heart Failure Pharmacology  
**Primary Supervisor:** Assoc Prof Rebecca Ritchie  
**Contact:** rebecca.ritchie@bakeridi.edu.au 8532 1392

**Research Focus:**  
Our laboratory seeks to improve the understanding of the causes of heart failure, identify new targets for its precursors and develop new pharmacotherapies for delaying their progression.

**Keywords:** Cardiac function; Diabetes; Glucose metabolism; Heart failure; Oxidative stress; Mitochondria.

**Project description:**

**BACKGROUND:** Diabetes is Australia’s fastest growing chronic disease. The disease affects almost 2 million Australians; diabetes increases heart failure risk 2.5-fold and accelerates its onset. Our laboratory has an established track record for identifying new pharmacotherapies for diabetic cardiomyopathy, many of which target reactive oxygen species (ROS). Building on this experience, we have obtained recent evidence that the hexosamine biosynthesis pathway (HBP), an alternative fate of glucose, has now emerged as a contributing factor to the cardiac complications of diabetes.

**GENERAL HYPOTHESIS:** that the concomitant impairments in both glucose handling and ROS that are hallmarks of diabetes together provide an additional drive towards unchecked HBP dysregulation, such that this post-translational modification switches from serving an adaptive, to a maladaptive, role, affecting both cardiac function in vivo and mitochondrial integrity.

**AIMS:** The major goal of this study is to demonstrate that cardiac-directed therapeutic targeting of the ROS-HBP axis will delay or even overcome diabetes-induced cardiac dysfunction in the intact heart in vivo.

**SIGNIFICANCE:** The lack of existing management of heart failure in the context of the poorer prognosis of concomitant diabetes highlights a clear, unmet clinical need. By specifically regulating cardiac HBP signalling in either the early or later stages of diabetes-induced heart failure, our approach is therapeutic rather than prophylactic, in addition to permitting tissue-selective regulation of this important, otherwise cytoprotective, post-translational modification.
Project related methods/skills/technologies:

- *in vivo* models of diabetic cardiac disease
- assessment of cardiac function
- assessment of mitochondrial function
- biochemical techniques: Westerns, ELISA, real-time PCR, histology, immunofluorescence

References:


# New Cellular Cholesterol Transporter

## Project title:
New Cellular Cholesterol Transporter

## Laboratory:
Lipoproteins and Atherosclerosis

## Primary Supervisor(s):
Prof. Dmitri Sviridov, Dr. Ying Fu

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8532 1363

## Research Focus:
Treatment for atherosclerosis and diabetes

## Keywords:
Atherosclerosis, lipids, diabetes, heart disease, vascular biology

## Project description:

Atherosclerosis is the cause of majority of cardiovascular diseases, a major cause of death in Western societies. Atherosclerosis is essentially accumulation of excessive cholesterol in the walls of arteries with the formation of atherosclerotic plaque blocking the blood flow and causing thrombosis. Accumulation of cholesterol may be caused by excessive delivery of cholesterol from blood or by damaged pathways responsible for eliminating excess of intracellular cholesterol. Disturbances in intracellular cholesterol metabolism are the primary cause of impairment of cholesterol release and are on the full front of rapidly emerging anti-atherosclerotic therapies. Cholesterol homeostasis also plays a key role in diabetes: accumulation of cholesterol in β cells severely disrupts insulin secretion.

A key element of intracellular cholesterol metabolism is a group of proteins moving cholesterol around the cell called ABC transporters. ABC transporters regulate release of cholesterol from cells to plasma and maintain correct intracellular cholesterol content. Surprisingly, very little is known about how these transporters work.

We have recently discovered that one of the transporters, ABCA12, which was known to play an important role in skin, also plays an important role in macrophages, cell central for development of atherosclerosis and inflammation and in β cells. It appears that ABCA12 is responsible for “regulating the regulator” — modulating a major pathway responsible for coordinate action of other ABC transporters. The same pathway is also involved in regulation of inflammation. The study is a combination of sophisticated *in vitro* study aimed at discovering the molecular and cellular mechanisms of how ABCA12 regulates this pathway, and *in vivo* study aimed at testing the effects of ABCA12 deficiency on development of atherosclerosis and diabetes in mouse model of these diseases. The project is conducted in collaboration with Monash University.

## Project related methods/skills/technologies:
- Cell biology
- Animal models

## References:

**Project title:** Cholesterol metabolism and complications of HIV disease

**Laboratory:** Lipoproteins and Atherosclerosis

**Primary Supervisor(s):** Prof. Dmitri Sviridov, Dr. Nigora Mukhamedova

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8532 1363

**Research Focus:** Pathogenesis of complications of HIV disease

**Keywords:** HIV, atherosclerosis, lipids, diabetes, heart disease, vascular biology

**Project description:**

Current treatment for HIV infection has dramatically reduced mortality, however, co-morbidities that are not directly related to immunodeficiency are now increasingly recognized as a consequence of HIV infection. One such co-morbidity is an increased risk of cardiovascular and metabolic disease. The current view is that HIV infection and/or its treatment are associated with elevated risk of development of atherosclerosis and consequently with increased prevalence of acute and chronic cardiovascular events. HIV also causes disturbances of lipoprotein metabolism, metabolic syndrome, lipodystrophy, dementia.

We currently investigate how HIV is causing co-morbidities in the organs not infected with the virus. Our hypothesis is that HIV-infected cells release viral proteins and MiRs in the bloodstream that affect uninfected cells causing pathology in these cells without infection. Our study is focused on establishing how factors released by HIV-infected cells affect uninfected cells. Our hypothesis, supported by large volume of data, is a key affected pathway is the pathway related to cholesterol metabolism. The project is a combination of in vitro work in cell culture, animal studies and some clinical work. It is on the crossroads of virology and cardiology and gives an opportunity to learn a wide range of techniques, from cell biology to biochemistry as well as clinical studies. The project is conducted in collaboration with a number of Australian and overseas laboratories and gives the participants an exposure to research in various disciplines.

**Project related methods/skills/technologies:**

- Cell biology
- Animal models

**References:**

**Project title:** Apolipoprotein A-I mimetic peptides and Treatment for Heart Disease

**Laboratory:** Lipoproteins and Atherosclerosis

**Primary Supervisor(s):** Prof. Dmitri Sviridov, Dr. Michael Ditiatkovsky

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8532 1363

**Research Focus:** Treatment for atherosclerosis

**Keywords:** Atherosclerosis, lipids, heart disease, vascular biology, animal models

**Project description:**

Drugs affecting lipid metabolism have revolutionized treatment of atherosclerosis reducing the risk of cardiovascular diseases by 30-40%. There is, however, an urgent need for further reduction of the unacceptably high remaining risk of CVD. A most promising direction is complementing decreasing levels of the pro-atherogenic lipoproteins (“bad cholesterol”) with increasing levels of the anti-atherogenic lipoprotein, high density lipoprotein (HDL, “good cholesterol”), i.e. “HDL Therapy”. The efficiency of HDL therapy critically depends on the method used to for elevate HDL levels. A promising type of HDL therapy is the use of peptides mimicking the structure of the main protein of HDL, apolipoprotein A-I (apoA-I). One advantage of these peptides is that their structure can be easily changed to fine-tune their properties.

In the lead up to this project we developed a series of peptides that mimic various anti-atherogenic properties of HDL. The project has two aims. One is to use various peptides that have one, but not other anti-atherogenic properties of HDL to determine which properties are most important for the protection against atherosclerosis. The second aim is to develop a peptide, or a combination of peptides which manifest most significant anti-atherogenic properties of HDL and can be further developed into a drug.

The project is substantially animal based, involving the infusion of peptides into a mouse model of atherosclerosis to examine their effect on atherosclerotic plaques. In addition this study will include a sizable *in vitro* component; where the effect of peptides on plasma lipoproteins is investigated. The study is conducted in close collaboration with National Institutes of Health, USA.

**Project related methods/skills/technologies:**

- Cell biology
- Animal models

**References:**


Project title: High-density lipoprotein (HDL) effects on cardiac metabolism, inflammation and function

Laboratory: Metabolic & Vascular Physiology

Primary Supervisor(s): Andrew Siebel, Adele Richart, Bronwyn Kingwell

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Research Focus:
Study of the effects of HDL on cardiac glucose metabolism in the setting of type 2 diabetes

Keywords:
heart disease, glucose metabolism, inflammation, cardiac function, type 2 diabetes

Project description:
High-density lipoprotein (HDL) is best known for its anti-atherosclerotic and anti-inflammatory actions, which have prompted development of HDL-raising strategies to combat cardiovascular disease. We have characterized previously unrecognized mechanisms by which HDL modulates glucose metabolism in both skeletal muscle and the pancreas. This project extends our discoveries to examine the effects of HDL on glucose metabolism, inflammatory responses and cardiac function following myocardial ischaemia/reperfusion injury using in vivo mouse models. Mechanisms will be further interrogated using cardiac muscle cells. We are also interested in determining whether HDL is cardioprotective in the context of obesity and type 2 diabetes. Given the escalating prevalence of obesity and type 2 diabetes, and the associated increase in cardiovascular complications, understanding mechanisms which may lead to new therapeutic approaches targeting myocardial metabolism, inflammation and function has potential for significant impact.

Opportunities exist for Honours, Masters and PhD students.

Project related methods/skills/technologies:
- Cell culture
- Western blotting, qPCR, radiolabelled assays
- In vivo animal handling, surgery, functional analyses and tissue collection

References:
**Project title:** Development of brown adipose tissue for treatment of obesity

**Laboratory:** Metabolic & Vascular Physiology

**Primary Supervisor(s):** Andrew Carey & Bronwyn Kingwell

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**Research Focus:**
Study of brown adipose (fat) in humans as a potential treatment for obesity

**Keywords:**
Obesity, diabetes, fat, brown fat, brown adipose tissue, energy expenditure

**Project description:**
Fundamentally, obesity results from an imbalance between energy intake and expenditure. Current preventative and therapeutic approaches have been either unsustainable or result in significant negative side effects. Brown adipose tissue (BAT) is unique with respect to its sole function of burning potentially great quantities of energy, therefore increasing BAT content and activity is currently considered one of the most promising strategies to increase energy expenditure to combat obesity. BAT function in small animals is well described, however in humans knowledge is limited due to only recently being conclusively identified in adults and the identification of novel techniques to measure its activity.

Our ongoing studies therefore provide opportunities to explore the possibility of combating obesity related disease while gaining broad research experience and skills ranging from clinical research to numerous wet lab techniques.

**Project related methods/skills/technologies:**
Numerous aspects of human clinical research, including
- Volunteer recruitment
- Tissue collection
- Body composition analysis
- Measurement of whole body energy expenditure
- Examination of nuclear medicine scans for BAT activity
- Basic Science/wet laboratory analytical techniques
- Opportunity to discuss your work regularly to both lay people and those involved in research

**References:**
**Project title:**
Role of the brain in a mouse model of neurogenic hypertension

**Laboratory:**
Neuropharmacology laboratory

**Primary Supervisor(s)**
Prof Geoff Head, Dr Kristy Jackson and Dr Pamela Davern

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**Research Focus:**
The influence of the central nervous system on long-term blood pressure levels and the relationship between blood pressure and stress pathways in the brain is a major focus of the Neuropharmacology Lab’s studies. Research in Neuropharmacology centres on cardiovascular neuroscience and fills a niche between the clinic and basic research.

**Keywords**
Hypertension, brain, immunohistochemistry, pharmacology

**Project description:**
The Schlager BPH/2J mice is a model of hypertension which is caused by overactivity of the sympathetic nervous system (SNS) driven by greater activity of neurons in the medial amygdala, a brain region most notable for its role in stress. The brain regions downstream of the medial amygdala which result in SNS overactivity likely include projections to the hypothalamus but to date these pathways have not been assessed.

**Part 1** of this student project will determine these downstream brain pathways involved in causing the hypertension in BPH/2J mice. This will be achieved by injecting a tracing compound into the medial amygdala and tracking where in the brain these neurons project using immunohistochemistry. In particular we will identify brain regions involved in hypertension by colocalising with another immunohistochemical marker of neuronal activity (Fos).

**Part 2** of this student project will be to pharmacologically inhibit one of the important brain regions (identified in part one of this study) and measure the effect on blood pressure in conscious BPH/2J mice via radiotelemetry probes.

**Project related methods/skills/technologies:**
- Animal handling and surgery
- Immunohistochemical analysis of brain regions
- Direct measurement of blood pressure in conscious freely moving mice

**References:**
**Project title:**
Central mechanisms underlying obesity related hypertension: trans-generational effect on cardiovascular events

**Laboratory:**
Neuropharmacology laboratory

**Primary Supervisor(s)**
Prof Geoff Head, Dr Joon Lim (Kyungjoon Lim) and Dr Pamela Davern

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pamela.davern@bakeridi.edu.au        03 8532 1330

**Research Focus:**
The influence of the central nervous system on obesity related hypertension and the relationship between trans-generational effect of obesity and blood pressure. Research in Neuropharmacology centres on cardiovascular neuroscience and fills a niche between the clinic and basic research.

**Keywords**
Obesity, Hypertension, Developmental Programming, Brain, Physiology, Pharmacology, Leptin

**Project description:**
It is increasingly apparent that the high rate of hypertension in many societies can be attributed to an equally alarming rate of obesity. The sympathetic nervous system (SNS), responsible in part for control of blood pressure, is known to be overactive in obese humans. In our laboratory, we have shown that the levels of plasma insulin and leptin increase for up to 3 weeks after 1 week of high-fat feeding, accompanied by elevated blood pressure and renal sympathetic nerve activity. This study will investigate changes in leptin and insulin signalling when rabbits are born from obese mother where breeder rabbits are fed with a high-fat-diet. This project will involve surgical implantation of an intracerebroventricular catheter (for delivering drugs directly to the brain) and implantation of a renal sympathetic nerve electrode (nerve activity recording). Also, immunohistochemistry and real-time PCR will be used to identify the signalling pathways that may be associated with obesity-related hypertension.

**Project related methods/skills/technologies:**
- Animal handling and surgery
- Immunohistochemical analysis of brain regions
- Direct measurement of blood pressure and renal sympathetic nerve activity in conscious rabbits

**References:**
1. Kyungjoon Lim, Sandra L. Burke and Geoffrey A. Head (2013). “Obesity related hypertension and the role of insulin and leptin in high fat fed rabbits” Hypertension 61; 628-634, selected for evaluation by Faculty of 1000 (F1000), Top 2 % in all Biological & Medical Journals in the world).
2. Kyungjoon Lim, Sandra L. Burke, James A. Armitage, Geoffrey A. Head (2012). “Comparison of blood pressure and sympathetic activity of rabbits in their home cage and the laboratory environment” Experimental Physiology 97 (12):1263, selected for evaluation by Faculty of 1000 (F1000), Top 2 % in all Biological & Medical Journals in the world).
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<th><strong>Project title:</strong></th>
<th>Central effects of chronic stress and mild activation of the renin angiotensin system on blood pressure</th>
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<td><strong>Laboratory:</strong></td>
<td>Neuropharmacology laboratory</td>
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<tr>
<td><strong>Primary Supervisor(s)</strong></td>
<td>Prof Geoff Head and Dr Pamela Davern</td>
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| **Contact:**     | geoff.head@bakeridi.edu.au 03 85321332  
pamela.davern@bakeridi.edu.au 03 85321330                                                   |

**Research Focus:** The influence of the central nervous system on long-term blood pressure levels and the relationship between blood pressure and stress pathways in the brain is a major focus of the Neuropharmacology Lab's studies. Research in Neuropharmacology centres on cardiovascular neuroscience and fills a niche between the clinic and basic research. Work is carried out to understand the mechanisms that trigger cardiovascular diseases through environmental factors. Stress is a main area of investigation and research is also being conducted on the effects on the central nervous system in response to mild activation of the renin angiotensin system.

**Keywords**
Hypertension, Chronic stress, Renin angiotensin system, Central nervous system

**Project description:** The effects of acute stress have been well documented in the literature but the mechanisms by which chronic stress or repeated daily exposure to acute stress contributes to sustained elevations in blood pressure is not well understood. The critical factor leading to a marked amplification of cardiovascular responses does not appear to arise from chronic stress per se but requires a combination with either an acute novel stress experience or low subpressor increases in circulating angiotensin II. Our laboratory has data that indicates overexpression of neuronal nitric oxide synthase and NADPH oxidase in neurons that are activated in response to novel stress. This observation is also associated with elevated blood pressure and identified in brain regions such as the amygdala and hypothalamus that are known to regulate sympathetic output to influence the kidney. In this study we will repeatedly expose mice administered a mild dose of angiotensin II or vehicle to a stress on a daily basis over two weeks and record their blood pressure, heart rate and activity continuously via radiotelemetry devices. The effect of stress on cardiovascular parameters and neuronal activation and associated neurochemical signatures will also be determined using immunohistochemistry.

**Project related methods/skills/technologies:**
- Animal handling and surgery
- Direct measurement of blood pressure in conscious freely moving mice
- Stress tests to measure reactivity to aversive and non-aversive stress
- Immunohistochemical analysis of brain regions

**References:**
### Project title:
Mechanisms responsible for neuronal synaptic plasticity influencing blood pressure regulation

### Laboratory:
Neuropharmacology laboratory

### Primary Supervisor(s)
Prof Geoff Head, Dr Kristy Jackson and Dr Pamela Davern

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### Research Focus:
The influence of the central nervous system on long-term blood pressure levels and the relationship between blood pressure and stress pathways in the brain is a major focus of the Neuropharmacology Lab's studies. Research in Neuropharmacology centres on cardiovascular neuroscience and fills a niche between the clinic and basic research.

### Keywords
Hypertension, brain, synaptic plasticity, tissue plasminogen activator, stress, immunohistochemistry

### Project description:
Tissue plasminogen activator (tPA) is very highly expressed in the brain where it is an important mediator of synaptic plasticity. One of the brain regions which displays pronounced expression of tPA is the medial amygdala which is a brain region crucial for regulating cardiovascular responses to stress and mediating neurogenic hypertension in Schalger BPH/2J mice.\(^1\) tPA is likely to play an important role in mediating the maladaptive effects of chronic stress in stress related brain regions and subsequently contribute to hypertension. Therefore this project aims to determine whether tPA influences neuronal plasticity in cardiovascular regulatory brain regions such as the medial amygdala which may ultimately affect blood pressure. Mouse strains genetically modified to over or under-express tPA will be exposed to chronic stress and a Golgi-Cox staining technique used to visualize morphological changes in dendritic spines to indicate synaptic plasticity. Immunohistochemistry will also be used to label for stress hormones and other markers and radiotelemetry devices will record cardiovascular parameters including blood pressure and heart rate in conscious freely moving mice.

### Project related methods/skills/technologies:
- Animal handling and surgery
- Immunohistochemical analysis of brain regions
- Direct measurement of blood pressure in conscious freely moving mice

### References:
Project title: The role of caveolae in hypertension-induced inflammation

Laboratory: Vascular Pharmacology

Primary Supervisor (s): Dr Karen Andrews & Professor Jaye Chin-Dusting

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Research Focus: Hypertension induced inflammation, specifically investigating the effect of high blood pressure on leukocyte adhesion which leads to atherosclerosis.

Keywords: hypertension, inflammation, caveolae, leukocyte adhesion

Project description: Despite the widespread availability of blood pressure lowering medications, high blood pressure (hypertension) remains responsible for more deaths and disease globally than any other biomedical risk. While numerous studies identify hypertension as a potent contributing factor in the development of coronary artery disease (CAD), the exact mechanism by which this occurs is not known. We have shown that high intraluminal pressure per se causes leukocyte to endothelium adhesion, a hallmark of vascular inflammation which leads to CAD. We have also shown that high intraluminal pressure alters caveolae (50- to 100-nm flask-shaped invaginations of the plasma membrane) structure, where pressure decreases caveolae number (Figure). Caveolae mediate vesicular transport and house many proteins relating to cholesterol metabolism and cell signaling. This project aims to determine the mechanisms by which high intraluminal pressure modulates caveolae. The effect of pulsatile pressure on leukocyte adhesion, using algorithms of blood pressure of hypertensive and normotensive patients, will be investigated in rat carotid arteries. The effect of pressure on caveolae number and function will be analysed in vessels subjected to different conditions. These studies may lead to new paradigms in the management of cardiovascular risk commonly seen in many individuals.

Project related methods/skills/technologies:
- Ex vivo: vessel chamber
- Electron microscopy
- Molecular techniques: gene expression via real-time PCR, protein expression via flow cytometry and western blot analysis

References:
Project title: Understanding the energy pathways regulating monocyte subsets and their recruitment to the atherosclerotic plaque

Laboratory: Vascular Pharmacology

Primary Supervisor(s): Dr Andrew Murphy and Professor Jaye Chin-Dusting

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Research Focus: The effects of atherosclerosis on energy metabolism in monocyte subsets.

Keywords: atherosclerosis, monocytes, energy metabolism

Project description: Cardiovascular disease (CVD) is the leading cause of death worldwide. Atherosclerosis, a chronic inflammatory disease of the arterial wall is the main contributor of this disease. This process begins with excess cholesterol depositing into the arterial wall which recruits circulating monocytes into the sub-endothelial space where they differentiate into macrophages and engulf cholesterol. When macrophages become overloaded with cholesterol, they are unable to emigrate out of the vessel wall and thus become trapped, contributing to the atherosclerotic plaque. There are three subpopulations of circulating blood monocytes (classical – CD14+, intermediate - CD14+/CD16+ & non-classical – CD16+) and recent clinical observations indicate that of these the non-classical subset is significantly elevated in patients with CVD. Thus, targeting non-classical monocytes in circulation may hold key to regressing the atherosclerotic plaque. New evidence now suggests that the energy status of immune cells in chronic inflammatory diseases such as atherosclerosis plays a critical role and that manipulating their energy pathways may hold the therapeutic key to the regression of atherosclerotic plaques. We have shown for the first time that non-classical monocytes isolated from healthy blood donors meet their normal energy needs through increased mitochondrial respiration compared to the classical and intermediate subset (Figure). Whether their energy metabolism is altered after exposure to high cholesterol or high glucose, as seen in atherosclerosis or diabetes, remains to be determined. This project will involve the use of an atherosclerotic mouse model to understand how the metabolic requirements of monocyte subsets differ to healthy control mice, and whether manipulating their energy pathways may prevent them from entering the sub-endothelial wall and feeding into the atherosclerotic plaque.

Project related methods/skills/technologies:
- Flow cytometry
- RT-PCR
- Seahorse extracellular flux analyser
- Transmigration assays

References:
**Project title:** Exploring mechanisms of T cell mediated vascular inflammation

**Laboratory:** Vascular Pharmacology

**Primary Supervisor(s):** Dr Karen Andrews, Dr Andrew Murphy & Professor Jaye Chin-Dusting

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**Research Focus:** To explore how T cells contribute to hypertension.

**Keywords:** T cells, inflammation, hypertension

**Project description:** The most common medical ailment managed by physicians globally is high blood pressure (hypertension) with greater than 2 million Australians diagnosed with this condition. Chronic high blood pressure is accountable for more deaths and disease globally than any other biomedical risk (including obesity and diabetes) and is the single biggest contributor to the incidence and progression of coronary artery disease (CAD), the underlying cause of heart attack and stroke. Inflammation is primarily a necessary and beneficial defense mechanism against foreign insult (such as germs and bacteria), tissue damage or injury. It localizes and eliminates the insult while repairing surrounding tissue. However, it is now thought that inflammation plays a role in the initiation and progression of hypertension and that vascular inflammation is a significant component of immune-mediated hypertension. As important recruiters of other white blood cells (leukocytes), T cells are integral drivers of vascular inflammation. However the mechanisms underlying T cell-driven vascular leukocyte recruitment and inflammation have not been well-defined. We propose that T cell-mediated activation of endothelial cells is a key driver of vascular inflammation, through the induction of vascular-derived chemokines and vascular adhesion molecules. The aim of this project is to determine how T cells perpetuate vascular inflammation, which may help identify new therapeutic targets for hypertension.

**Project related methods/skills/technologies:**
- **In vitro:** blood vessel organ bath
- **Molecular techniques:** gene expression via real-time PCR, protein expression via flow cytometry and/or western blot analysis.
- **Migration assays.**

**References:**
**Project title:** Lipid profiling in acute inflammatory bowel disease  

**Laboratory:** Vascular pharmacology  

**Primary Supervisor(s)**  
Prof. Anthony Dart, Dr. Lu Fang, Prof. Jaye Chin-Dusting  

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**Research Focus:**  
We aim to examine lipid profiling and inflammation in acute inflammatory bowel disease  

**Keywords:** Lipidomics, inflammation, inflammatory bowel disease  

**Project description:**  
Inflammatory bowel disease (IBD) is a chronic inflammatory disorder, encompassing two related and distinct forms of intestinal inflammation: ulcerative colitis (UC) and Crohn’s disease (CD). The development and course of IBD are affected by several factors, including genetic predisposition, the intestinal microbiota, other environmental factors and a dysregulated host immune response. However, the precise etiology of IBD remains unknown. Lipid metabolism and signalling are suggested to play important roles in inflammation with significant implications for IBD. We have recently examined plasma lipid profiling on patients with IBD at the chronic phase. We have demonstrated that a number of ether lipids (including alkylphospholipid and plasmalogens), a type of membrane phospholipids, are significantly and inversely associated with CD, but not with UC. Ether lipids possess anti-oxidant properties. Ample evidence has indicated that oxidant-mediated injury plays an important role in the pathogenesis of IBD. The decrease of ether lipids may lead to impaired antioxidant defence, thus contributing to the pathology of IBD. Since patients in our previous study were in remission, we plan to recruit IBD patients with acute inflammation and examine plasma lipid profiling and inflammatory markers in these patients. We will compare lipid profiling and inflammatory markers between healthy controls and patients with UC and CD.  

**Project related methods/skills/technologies:**  
- Recruit patients from Alfred Hospital  
- Measure inflammatory markers by Elisa assay, and measure microparticles by flow cytometry  
- Measure plasma lipids by lipidomics  
- Analyze data and perform statistical tests  

**References:**  
**Project title:** Investigating the therapeutic potential of targeting the bone morphogenetic protein signalling pathway to combat skeletal muscle wasting

**Laboratory:** Muscle Research and Therapeutics

**Primary Supervisor(s):** Dr Paul Gregorevic

**Contact:** email: paul.gregorevic@bakeridi.edu.au  phone: 8532 - 1224

**Research Focus:** Developing molecular interventions to dissect mechanisms controlling skeletal muscle attributes and generate gene therapies for conditions of muscle wasting.

**Keywords:** Skeletal muscle, cell signaling, growth regulation, gene therapy, wasting, cancer cachexia, sarcopenia, muscular dystrophy, aging.

**Project description:**

Skeletal muscle comprises approximately 40% of our body mass and performs a number of crucial bodily functions. Loss of muscle mass and strength is a serious and unmet health risk associated with disability, illness and premature death, having serious consequences on the vast majority of society.

The Laboratory for Muscle Research and Therapeutics Development aims to identify the molecular mechanisms that control muscle mass and manipulate cellular signalling pathways to promote muscle hypertrophy, metabolic function and strength in disease.

Our lab specialises in the delivery of genes to the striated muscle using recombinant viral vectors. This cutting edge technology allows us to reveal the basic biological characteristics of skeletal muscle in vivo in addition to providing a platform to investigate gene therapies in mouse models of skeletal muscle wasting.

A particularly novel signalling pathway controlling skeletal muscle mass is the bone morphogenetic protein (BMP) signaling pathway which was originally discovered for its role in stimulating bone formation. We have recently shown that this pathway plays a vital role as a positive regulator of skeletal muscle mass. Increasing BMP signaling in muscle can promote muscle growth, and counter protein breakdown. Based on these exciting results, we are now seeking to investigate whether gene-delivery and drug based interventions can be developed which target this pathway, as new therapeutics for muscle wasting.

The central aim of this project will be to use a number of molecular approaches to increase or reduce BMP signalling in skeletal muscle and accompanying cell types in mouse models of disease, to determine if this impacts on the loss of muscle mass associated with muscle wasting conditions, and impacts on lifespan. Additional studies will examine the signaling and gene regulation associated with these effects. Research projects are available for Honours, Masters and PhD students.

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**Healthy Muscle**

Nerve damage → Activation of muscle catabolism → **Muscle wasting**

Viral vector delivery → **Preservation of muscle mass**

Up-regulation of BMPs
### Project related methods/skills/technologies:

- Analysing skeletal muscle phenotypes *in vivo*
- Cell culture validation of viral vector plasmids
- Designing and administering viral vectors *in vivo*
- Using multiple mouse models of skeletal muscle wasting
- Immunofluorescent microscopy
- Physiological assessment of skeletal muscle function
- Molecular assays including western blotting and q-PCR
- Histological analysis of mouse skeletal muscle

### References:

Project title: Using gene therapy tools to study and treat skeletal muscle disease

Laboratory: Muscle Research and Therapeutics

Primary Supervisor(s): Dr Paul Gregorevic

Contact: email: paul.gregorevic@bakeridi.edu.au  phone: 8532 - 1224

Research Focus: Developing molecular interventions to understand mechanisms controlling skeletal muscle attributes and treat conditions of muscle wasting

Keywords: Skeletal muscle, cell signaling, growth regulation, gene therapy, wasting, cancer cachexia, sarcopenia, muscular dystrophy, aging.

Project description:

Physical frailty caused by loss of skeletal muscle mass and strength is one of the main factors contributing to disability, illness and premature death worldwide. Our goal is to elucidate how the cellular mechanisms that regulate muscle development and adaptation become perturbed in muscle wasting, and to develop new therapeutic approaches to reverse loss of muscle mass, strength and metabolic function.

What sets us apart is that we design and make recombinant viral vectors “in-house”, to regulate and interrogate the cellular mechanisms controlling muscle adaptation in vivo with a combination of precision, efficacy, and speed not offered by other methods. Our expertise in using gene delivery technologies to manipulate muscle is unparalleled in Australia, and undertaking research with us provides a unique opportunity to work with these cutting edge methods.

Opportunities are available to conduct studies within several of our research themes:

- How does the Transforming Growth Factor-β signalling network regulate muscle?
- Novel genes that control skeletal muscle growth and wasting
- Using vector-based delivery of genome editing technology to study and treat disease
- Novel gene therapies for neuromuscular disorders, and wasting in chronic illness
- Using gene therapies to treat diabetes & diabetic complications.

Students are also welcome to discuss other projects that may fall outside of these themes, or involve building collaborations with other teams possessing complementary expertise. Research projects are available for Honours, Masters and PhD students.

Figure 1: Recombinant viral vectors can be used as gene delivery tools to study the regulation of muscle attributes, and potentially to treat conditions associated with skeletal and cardiac muscle disease.
### Project related methods/skills/technologies:

- Analysing skeletal muscle phenotypes *in vivo*
- Cell culture validation of viral vector plasmids
- Molecular assays including western blotting and q-PCR
- Designing and administering viral vectors *in vivo*
- Using multiple mouse models of skeletal muscle wasting
- Histological analysis of mouse skeletal muscle
- Immunofluorescent microscopy
- Physiological assessment of skeletal muscle function

### References:

**Project title:** Regulation of skeletal muscle mass in health and disease

**Laboratory:** Muscle biology and therapeutics

**Primary Supervisor(s):** Dr Paul Gregorevic and Dr Kevin Watt

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**Research Focus:** Signalling pathways regulating skeletal muscle size, mechanisms promoting skeletal muscle atrophy in neuromuscular disease

**Keywords:** skeletal muscle, hypertrophy, atrophy,

**Project description:**
Physical frailty caused by loss of skeletal muscle mass and strength is one of the main factors contributing to disability, illness and premature death worldwide. The goal of our laboratory is to elucidate how the cellular mechanisms that regulate muscle development and adaptation become perturbed in muscle wasting, and to develop new therapeutic approaches to reverse loss of muscle mass, strength and metabolic function.

To do this we design and make recombinant viral vectors as a means to regulate and interrogate the cellular mechanisms controlling muscle adaptation *in vivo* with a combination of precision, efficacy, and speed not offered by other methods (Fig 1). Our expertise in using gene delivery technologies in skeletal muscle is unparalleled in Australia, and undertaking research with us is a unique opportunity to work with cutting edge methodology.

This project will interrogate the role of the Hippo signalling pathway (Fig 2) as a novel regulator of skeletal muscle size in health and disease. This pathway is currently generating much study with numerous examples of publications in the very highest impact journals. The Hippo signalling pathway is also a key regulator of skeletal muscle size. However, the mechanisms that drive this remain unclear. Using gene delivery technologies and a number of disease relevant models e.g. cancer cachexia and amyotrophic lateral sclerosis we will assess the interactions between the Hippo signalling network, and other key signalling pathways, as mechanisms governing skeletal muscle size in health and disease. Research projects are available for Honours, Masters and PhD students.
Project related methods/skills/technologies:

- Range of molecular biology methods (Western blotting, q-RT-PCR, Histology, Cell culture, In vivo manipulation of gene expression)
- Design, manufacture and administration in vitro and in vivo of recombinant viral vectors.
- Animal models of disease. Small animal handling, and surgical procedures.

References: