MONASH University

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Opportunities for Translational Research

Southern Clinical School

Excellence in Care, Learning and Discovery

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www.med.monash.edu.au/scs

Contents

Overview

Southern Clinical School (SCS) is a health professional school based at the Monash Medical Centre (MMC), a Monash Health Hospital and Victoria's largest hospital network. In addition to training, the School is a vibrant hub of research via strong collaborations between Monash University and Monash Health. SCS is at the forefront of clinical translational research with demonstrated research strengths in cardiovascular disease, inflammatory diseases, nutrition, women's and children's health and neurosciences. Our senior academic staff are mostly health professionals who work closely with colleagues in Monash Health, translating scientific discoveries into clinical practice in an innovative and collaborative environment to shape the health professionals of the future. The Monash Health Translation Precinct (MHTP) is based at MMC and consists of SCS, MIMR and Prince Henry's Institute and provides exceptional collaboration opportunities.

A message from the Head of School, Professor Eric Morand

The Southern Clinical School of the Faculty of Medicine, Nursing & Health Sciences comprises the Faculty's academic departments based at Monash Health. It is the Faculty's largest medical clinical school and also hosts its Nutrition & Dietetics department (based at Notting Hill). There is close integration between Monash Health clinical services and the departments including Medicine, Surgery, Paediatrics, Obstetrics & Gynaecology and Nutrition and Dietetics. Moreover, the School has extensive laboratory based research programs that are integrated with clinical research activities across multiple disciplines, and also hosts three major University Centres of Excellence, the Centre for Inflammatory Diseases, Ritchie Centre for Baby Health Research (jointly with MIMR), and the Cardiovascular Research Centre. Many group leaders are recognised as international leaders in their areas of expertise.

As a result, there is a strong focus on both basic and translational research with real clinical issues driving research questions addressed in the laboratories. Similarly, laboratory derived discoveries can be rapidly tested in relevant clinical settings.

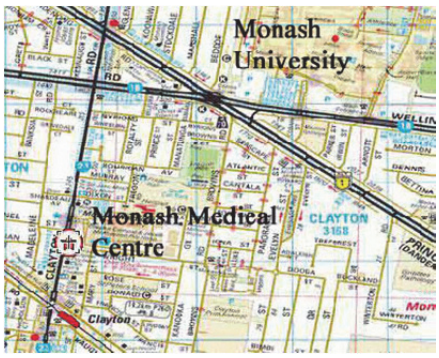
The School has a strong track record of welcoming and supporting Biomedical Science research students and BMedSci students in productive graduate (honours and doctoral) programs within the School. A growing number of gifted students have progressed from Honours or BMedSci through successful PhDs, postdocs to become successful, independent researchers and biomedical professionals in the Southern Clinical School and beyond.

What's at SCS–MMC?

A HUB of activity

In conjunction with our collaborators MIMR and PHIMR, SCS provides world class equipment and facilities similar to other Monash sites, but also offers student rooms, and a clinically grounded context. Monash Medical Centre has a gymnasium, on site ATM and bank, and café, and is a short walk to all the cafes and shops in the Clayton mall precinct.

Our Location



The Southern Clinical School incorporates the four hospitals of Monash Health but is principally based at Monash Medical Centre (MMC), Clayton. This is approximately a 15 minute walk (south) from the main Monash University campus at Clayton. The Clayton railway station is only a 5 minute walk away, and a number of bus services stop at MMC. The main School administration centre is located in Block E, Level 5, MMC.

Facilities

Over 15 000 people work at Monash Health and there are a large number of facilities available. There is an extensive education program run both by Monash University and Monash Health on campus at MMC with daily meetings covering all areas of medicine and biomedicine.

Library MMC

The MMC Clayton library has a collection of 16,000 books, approximately 700 journals and access to around 1,500 electronic journal titles. The library cooperates with the other Monash Health libraries located at Dandenong, Moorabbin, Kingston, and Casey as well as the Monash University Library. Opening hours are 8.00am - 5.30pm Monday to Friday.

Honours Information

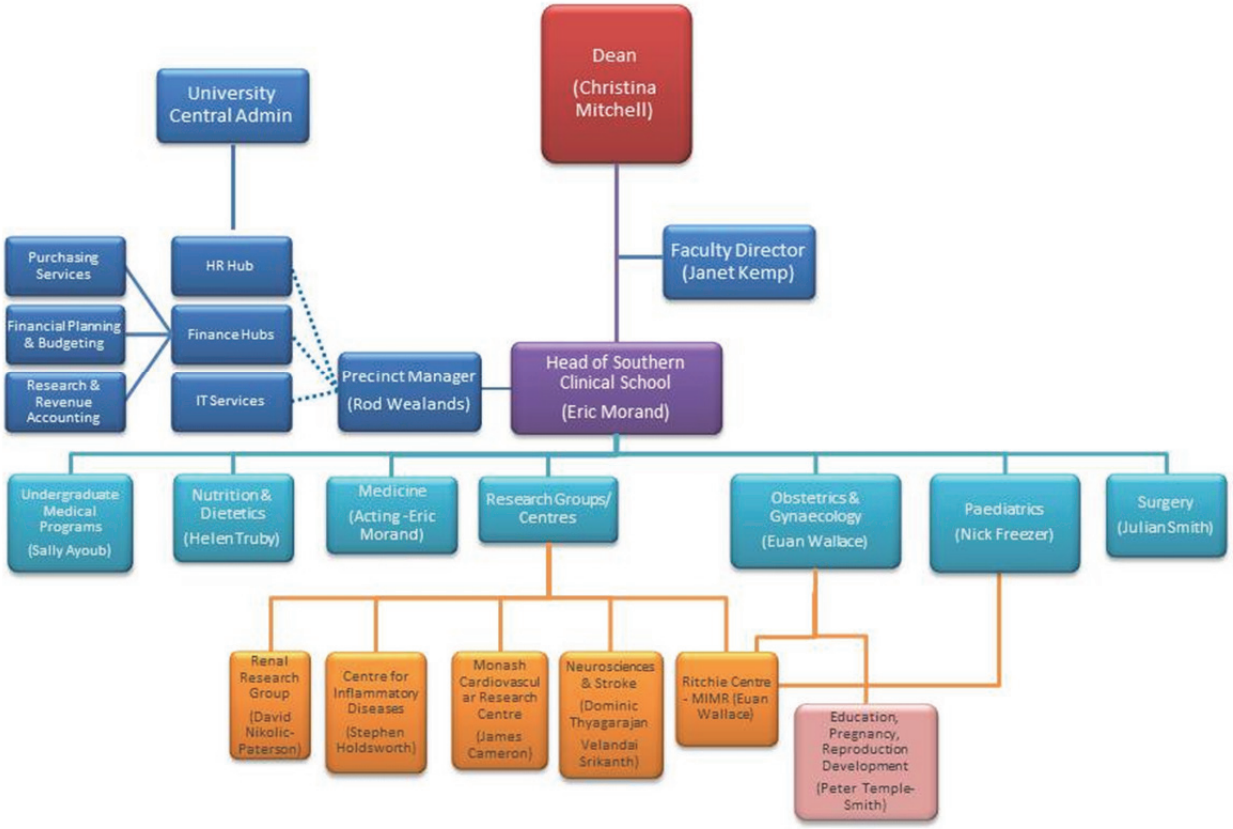
If you are thinking of a career in biomedical research, Southern Clinical School is a great place to start. The School is within easy walking distance of Monash University's Clayton Campus.

Our research staff undertake internationally recognised basic and clinical/translation research. Many are recognised as international leaders in their areas of expertise. Our research covers a broad range of topics including inflammatory and cardiovascular diseases, and neurosciences to name a few. Southern Clinical School has an outstanding track record in successful supervision of honours students, many of whom have gone on to PhD studies and successful careers.

Scholarships

Southern Clinical School can offer scholarships to exceptional Honours, BMedSci and PhD students.

Southern Clinical School Organisational Chart



Work with the best…

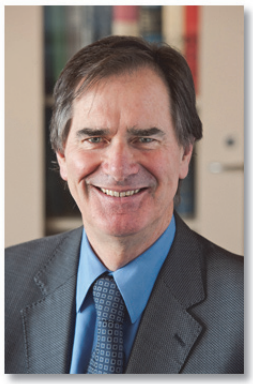
Some of the supervisors at Monash Medical Centre, Southern Clinical School:

Head of School / Centre for Inflammatory Diseases - Arthritis
Professor Eric Morand

Professor Eric Morand trained as a specialist rheumatologist in Melbourne and at the Royal National Hospital for Rheumatic Diseases, Bath, UK, gaining Fellowship of the Royal Australasian College of Physicians in 1992. Overlapping with this, he began research training at the Bath Institute for Rheumatic Diseases in 1991 and continued working towards a PhD granted by Monash University in 1995. The Arthritis group was founded during this period and has since held continuous funding from bodies including the NH&MRC, NIH (USA), and Arthritis Australia. The group led by Professor Morand has trained many successful PhD and MD candidates. His main interests are molecular mechanisms of action of glucocorticoids, and biomarkers of SLE. He holds multiple patents. Professor Eric Morand was appointed Head, Southern Clinical School in 2011.

Head, Department of Surgery MMC
Professor Julian Smith

Professor Smith has broad basic and clinical research experience in general and cardiothoracic surgery including organ transplantation and minimally invasive surgical techniques. Current research areas include cardiac surgery without the use of cardiopulmonary bypass, new devices in artificial heart technology, and the evaluation of outcomes in cardiothoracic surgery especially with respect to new technologies such as microsurgery, minimally invasive and robotic-assisted surgery.



Director, Centre for Inflammatory Disease
Professor Stephen Holdsworth

Professor Stephen Holdsworth is the Director of the Centre for Inflammatory Diseases, Head of Clinical Immunology and Director of Research Strategy at Monash Health. He is a clinician-scientist who is a nephrologist, clinical immunologist and career academic. His long-standing research interests have focussed on the mechanisms in immune glomerular injury relevant to understanding and treating human vasculitis and glomerulonephritis (GN). His work has substantially contributed to revelations that cell-mediated immunity and pathological coagulation induce crescentic GN. The evidence substantiating this assertion derives from key in vivo studies in animals models bracketed with human observations confirming the relevance of experimental discoveries to human disease.

Centre for Inflammatory Disease - Leukocyte Recruitment
Associate Professor Michael Hickey

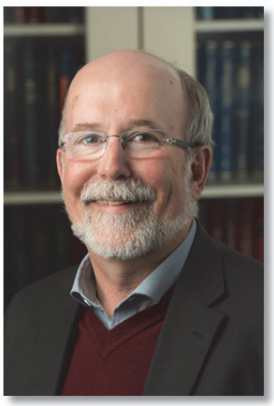
Associate Professor Michael Hickey is an NHMRC Senior Research Fellow. His laboratory examines leukocyte recruitment in inflamed tissues, a process which underlies the pathogenesis of most inflammatory diseases. His research examines the control of leukocyte-endothelial cell interactions and leukocyte migration in the inflamed microvasculature, using intravital (in vivo) microscopy to examine the functional microvasculature in models of inflammation. Current diseases examined include contact sensitivity, glomerulonephritis, systemic lupus erythematosus, arthritis and cerebral inflammation. An additional focus is human endothelial cell biology.

Centre for Inflammatory Disease - Renal
Professor Richard Kitching

Professor Richard Kitching is a clinician-scientist, his Clinical Specialty being nephrology. His research helped established that the T-helper cell subsets (Th1, Th2 and most recently Th17) are applicable to glomerulonephritis. He studies mechanisms of autoimmune renal disease and explore hypotheses related to the pathogenesis of immune and autoimmune renal injury. Professor Kitching is a member of the Editorial Board of the Journal of the American Society of Nephrology and is a Section Editor on the board of Nephrology. He was awarded the Australian and New Zealand Society of Nephrology TJ Neale Award for Outstanding Contribution to Nephrological Science in 2007. He has teaching and leadership roles in the Monash University, Faculty of Medicine Nursing and Health Sciences in the MBBS degree and the Bachelor of Biomedical Sciences degree.

Centre for Inflammatory Disease - Autoimmunity
Professor Ban Hok Toh

Professor Ban-Hock Toh leads the Centre for Inflammatory Diseases Auto-Immunity team. He held appointments at Universities in Singapore and Malaysia, before joining Monash University in 1972. Professor Toh was the Head of the Department of Immunology and Senior Staff Specialist in Immunology at the Alfred Hospital. He was Chief Examiner for the Royal College of Pathologists Australia in Immunology, Regional Editor (Australasia) for Autoimmunity, Commonwealth Medical Fellow, MRC Immunology Unit, London, Fogarty Visiting Scientist, National Institutes of Health, USA, Visiting Professor, University of Singapore and University of Innsbruck, Austria.



Centre for Inflammatory Disease - Gastroenterology
Professor William Sievert

Professor William Sievert is a Professor of Medicine in the Department of Medicine and Director of the Gastrointestinal and Liver Unit at Monash Health. Professor Sievert has a long-term interest in liver disease and directs an active clinical research unit comprising physician-scientists, clinical research nurses and research students. The Clinical Research Unit has been continuously active over ten years and regularly contributes to international trials of new antiviral agents for hepatitis B and C in addition to developing and leading national investigator-initiated studies. He also directs a basic research laboratory investigating mechanisms of inflammatory liver injury and hepatic fibrogenesis, with a translational focus on identification and development of potential hepatic antifibrotic agents.

Centre for Inflammatory Disease - Renal
Dr Shaun Summers

Dr Summers is a clinician -scientist who works as a Consultant Nephrologist in the Dept. of Renal Medicine at Monash Health and as a Senior Research Fellow at Monash University. His clinical and research interests focus on glomerulonephritis and acute kidney injury. Dr Summers leads the Monash Glomerulonephritis clinic and has established a specialist vasculitis clinic, with a particular focus on patients with anti-neutrophil cytoplasmic antibody associated vasculitis. In addition to ensuring best clinical practice this clinic serves as an important research and training facility. Dr Summers also directs laboratory research studying how the immune system, in particular innate immunity, drives autoimmunity, renal vasculitis and acute kidney injury. His laboratory aims to better understand the pathogenesis of kidney disease, with an aim to identify new treatments for clinical use.

Renal Research

Associate Professor David Nikolic-Paterson

Associate Professor David Nikolic-Paterson runs a research program investigating the signaling pathways (JNK, p38 MAPK, Syk, c-fms) that regulate inflammation, fibrosis and apoptotsis in the pathogenesis of kidney disease. He is based in the Department of Nephrology at Monash Medical Centre and his studies use conditional gene deletion and pharmacologic kinase inhibitors in mouse models of kidney disease, as well as cell culture studies.

Centre for Inflammatory Disease – Respiratory Diseases

Professor Phil Bardin

Professor Phil Bardin obtained a PhD from Southampton University (UK) working under Stephen Holgate, an eminent researcher in allergy and asthma. His field of study was viruses (particularly rhinovirus), their interaction with asthma and role in exacerbations. In 2000, he accepted a position as Director of Respiratory Research at Monash Medical Centre and commissioned a virus research laboratory. The laboratory is one of only a handful worldwide that is able to conduct studies of RV and its impact on allergic diseases. Recent research has also included studies of RSV in collaboration with David Jans at Monash University and innate immune responses with Bryan Williams at Monash Institute of Medical Research.

Vascular Brain Ageing

Associate Professor Velandai Srikanth

Associate Professor Velandai Srikanth is an NHMRC/NHF Career development Fellow. He is the Head of the Stroke and Ageing Research Centre based in Southern Clinical School, Monash Medical Centre. He is the overall head of the centre and also leads the Vascular Brain Ageing division with an emphasis on the vascular determinants of dementia, falls and gait disorders. He is a specialist geriatrician in the Department of Neurology at Monash Health (MMC) involved in the post-acute care of patients admitted to the acute stroke unit. He conducts a comprehensive stroke clinic aimed at rapid assessment and secondary prevention of transient ischaemic attack (TIA) and stroke, and a cognitive disorders clinic.

Head of Epidemiology & Prevention Unit, Stroke & Ageing Research Centre

Professor Amanda Thrift

Professor Amanda Thrift is the Head of the Epidemiology & Prevention unit of the Stroke & Ageing Research Centre Department of Medicine (Monash Medical Centre), Monash University. She is a career epidemiologist, having gained her PhD in epidemiology in 1995. Her long-standing research interests are in the field of epidemiology of stroke and vascular disease, particularly relating to developing countries. She has ongoing research studies on the prevention and management of stroke in the community, and the identification of risk factors for stroke and vascular diseases in those living in deprived settings (including Iran, India and Vietnam).

Acute Stroke and Imaging
Professor Thanh Phan
Professor Phan is Head of Stroke at Monash Medical Centre and has developed a first class stroke team, providing stroke services in the areas of Transient Ischemic Attack, acute thrombolysis, interventional radiology and stroke unit care. He is actively involved in the teaching of Advanced Physician Trainees in both Neurology and Stroke. He leads the Acute Stroke and Imaging division within the research group. He conducts cutting edge research involving brain imaging in stroke, and also in developing computational models of the cerebral circulation. He is at forefront of research into service delivery systems for stroke and TIA.

Public Health and Translation
Associate Professor Dominique Cadilhac
Associate Professor Cadilhac is the inaugural Head of the Translational Public Health Research Unit at the Centre. She is an expert in public health research, particularly in the areas of health service delivery models, translational research, economic evaluation, program evaluation and chronic disease prevention in vascular disease, in particular stroke. She is one of the lead investigators to have established the Australian Stroke Clinical Registry. She has also contributed to more than 100 'quality of stroke care' individual hospital reports to facilitate direct translation of evidence into practice. She was awarded the 2010 top ranked National Heart Foundation Research Fellow for Victoria.

Monash Cardiovascular Research Centre
Professor James Cameron
Professor James Cameron is Director of the Monash Cardiovascular Research Centre and Associate Director (Research & Education) of MonashHEART. He holds senior medical staff appointments with MonashHEART and Epworth Hospital. Since 2006 he has been Professor of Electronic Engineering (Biomedical) at La Trobe University. Currently he is Vice-President of The International Society for Vascular Health (ISVH) and Chairman of the Australasian Regional Committee of the ISVH. Professor Cameron acts as principle investigator in a number of pharmaceutical industry studies. He has developed clinical laboratory systems used extensively for assessment of arterial properties in Australia and overseas. The arterial assessment techniques he has developed have provided important evidence demonstrating the concept of the systemic arterial stiffness as a valid therapeutic target.

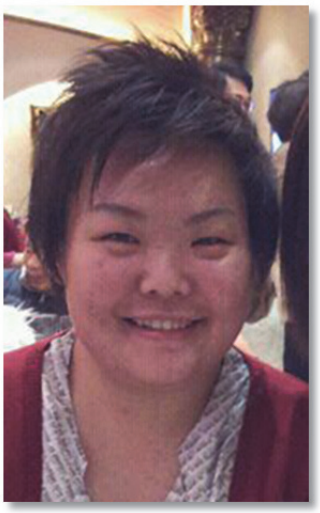
Head of Department of Nutrition and Dietetics
Professor Helen Truby
Professor Truby is a nutrition scientist and clinical dietitian with extensive experience in conducting dietary studies including randomized controlled trials and intervention protocols in adults and children. Current research areas include energy expenditure and appetite control in children with chronic diseases and in obesity.

Emergency Medicine and Clinical Toxicology Research
Professor Andis Graudins

Professor Andis Graudins is the coordinator of emergency medicine research across the Monash Health Emergency Medicine program as well as a consultant emergency physician and clinical toxicologist at Monash Health and clinical toxicologist working for the NSW and Victorian Poisons Information Centres. Professor Graudins is a clinical and basic science toxicology researcher. Clinical research interests include paracetamol poisoning and pharmacokinetics of modified- release paracetamol formulations in humans. Basic science research utilises in- vivo animal models to assess treatment of cardiovascular drug poisoning with novel inotropic and antidote agents such as levosimendan, fructose-1,6-diphosphate and 4-aminopyridine. Dedicated laboratory space for emergency medicine and toxicology basic science research is located in the Monash University Department of Pharmacology.

Student Snapshot

Honours students - Where are they now?



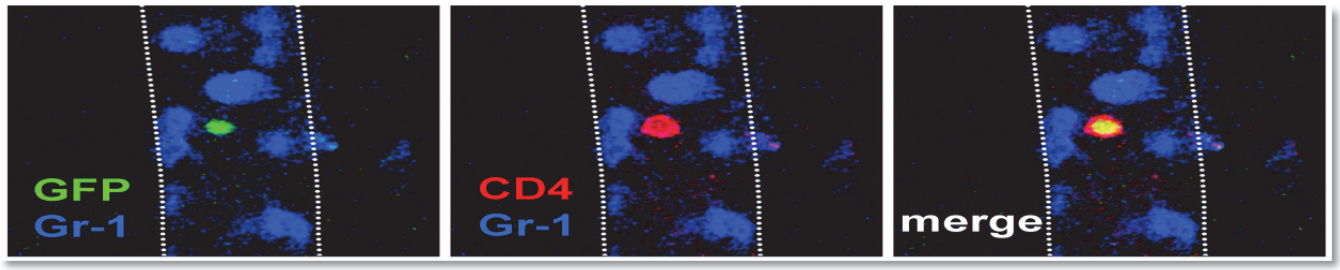
Many honours graduates of SCS have gone on to exceptional careers.

Department of Medicine/Centre for Inflammatory Diseases

Dr Connie Wong
ARC DECRA Fellow, School of Biomedical Sciences, Monash University
Connie Wong undertook her PhD jointly in the Centre for Inflammatory Diseases and the Monash Institute of Medical Research, studying control of reactive oxygen species in experimental stroke. She then took up a postdoctoral fellowship at the University of Calgary in Canada, where she used in vivo imaging to reveal novel mechanisms of immune suppression in stroke. During her fellowship she produced publications in *Science* and *Nature Immunology* and *Cell Host Microbe*. Upon returning to Monash University, she was awarded an ARC DECRA Fellowship to continue her work in systemic regulation of the immune response.

Dr Michael Kuligowski
Postdoctoral Fellow, Centenary Institute, Sydney
Michael undertook his PhD at the Centre under the joint supervision of Associate Professor Michael Hickey and Professor Richard Kitching. He performed some ground-breaking imaging studies which revealed a novel mechanism whereby neutrophils undergo adhesion in inflamed glomerular capillaries, leading to publications in the leading international journals Blood & Journal of Immunology. After completing his PhD, Michael took up a postdoctoral position at the Immune Disease Institute at Harvard Medical School, where he underwent training in advanced new imaging techniques including in vivo multiphoton confocal microscopy, by internationally-leading researchers. He has since returned to Australia and is now based at the Centenary Institute.

Project Areas



The Southern Clinical School offers projects in a wide variety of different areas of medicine and biomedical science. Projects are classified into different research areas listed on the following pages:

Centre for Inflammatory Diseases

The Centre for Inflammatory Diseases (CID) concentrates on a wide variety of inflammatory diseases including kidney disease, vasculitis, arthritis, trafficking of cells and cardiovascular disease. Our research seeks to bridge the gap between basic experimental biology and clinical research. Both clinical and laboratory based experimental techniques are employed to explore the mechanisms of inflammatory injury in these important human diseases. In particular, we are interested in defining the roles of leukocytes (particularly lymphocytes and macrophages), resident cells, cytokines and coagulation proteins. These participants in inflammation may be common to injury in a variety of organs or in contrast, possess roles uniquely relevant to particular organs. In the long term, all our research is dedicated to developing novel and effective therapeutic strategies. Research projects are based at the Monash Medical Centre in the Centre for Inflammatory Diseases, Department of Medicine, Southern Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University.

The main research themes in CID are:
Theme 1: Mechanisms of immune injury in autoimmune vasculitis and glomerulonephritis
Theme 2: Molecular mechanisms controlling inflammation and autoimmune diseases
Theme 3: Control of leukocyte recruitment and microvascular permeability during inflammation
Theme 4: Mechanisms of liver fibrosis
Theme 5: Atherosclerotic vascular disease: Role of the immune system
Theme 6: Respiratory infection
Theme 7: Inflammation in Type 2 diabetes and its complications
Theme 8 Haematology

Theme 1: Mechanisms of immune injury in autoimmune vasculitis and glomerulonephritis

Research Leaders:

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Description: Glomerulonephritis (GN) is the most common cause of end stage renal failure in Australia and world-wide. The overall aim of this theme is to further our understanding of key events in the generation of nephritogenic immune responses, autoimmunity as it pertains to the kidney and effector responses in the kidney, so that potential therapeutic targets can be identified. Research in our laboratories covers a range of key questions as to why the kidney can be a target of immune attack. It uses a variety of techniques that involve models of disease, transgenic and knock out mice, molecular biology, cell culture, analysis of immunological endpoints, and histological and functional readouts.

Our laboratories work to define mechanisms of immune renal injury, with a particular focus on the role of T cells. Glomerulonephritis (GN) is a common cause of end stage renal failure. The overall aim of this theme is to further our understanding of key events in the generation of nephritogenic immune responses, autoimmunity as it pertains to the kidney and effector responses in the kidney, so that potential therapeutic targets can be identified. Research in our laboratories covers a range of key questions as to why the kidney can be a target of immune attack. We are well funded and publish regularly in the best journals in the field.

We perform our research using a range of classical immunological techniques in murine models of renal disease. We use a variety of techniques that involve models of disease, transgenic and knock out mice, molecular biology, cell culture, analysis of immunological endpoints, and histological and functional readouts. A variety of projects are available - examples of specific currently available projects are given below

The laboratory is made up of postdoctoral scientists, research assistants, and several PhD students and in most years one or two BMS honours students. As we don't have a regular BSc Honours stream, we can devote more time and effort to helping BMS honours students achieve high standards. A number of our honours students have gone on to undertake PhD studies with us, and two Postdoctoral Career Scientists are BMS graduates.

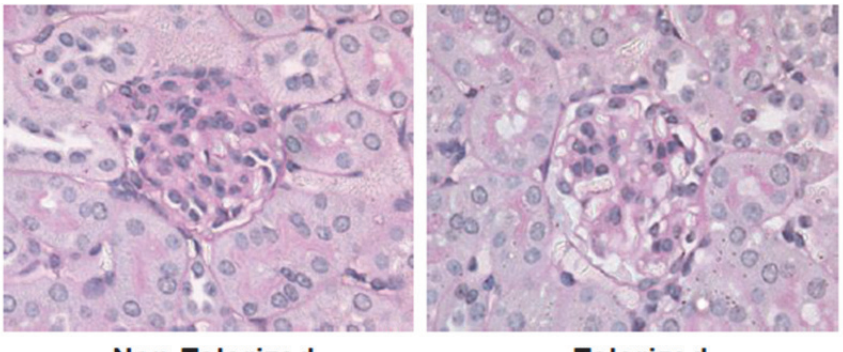
Theme 1 projects include:

1. Treating Autoimmune Anti-Myeloperoxidase (MPO) ANCA Associated Glomerulonephritis (GN) by Inducing Nasal Tolerance

Supervisor: Professor Stephen Holdsworth
Associate Supervisor: Dr Joshua Ooi

Crescentic Glomerulonephritis (GN) is a major cause of renal failure around the world. We now know that in most patients this disease results from the development of autoimmunity to a lysosomal enzyme in neutrophils called myeloperoxidase (MPO). The disease is best known for its associated autoantibody, anti neutrophil cytoplasmic antibody (ANCA).

Our group has recently discovered the four peptide sequences of MPO that are immunodominant and capable of inducing kidney damaging (nephritogenic) autoimmunity in a mouse model of autoimmune anti MPO ANCA associated GN . The major immunodominant peptide has remarkable homology with the major human MPO peptide that is recognized by ANCA from patients with autoimmune anti MPO ANCA associated GN. Thus our model appears highly relevant and learning how to induce tolerance using immunodominant peptides in mice is likely to rapidly translate to new human treatments. We have studied the effects of nasal insufflation of the dominant MPO peptide and been able to induce tolerance that both protects from, and treats murine autoimmune anti MPO ANCA associated GN.



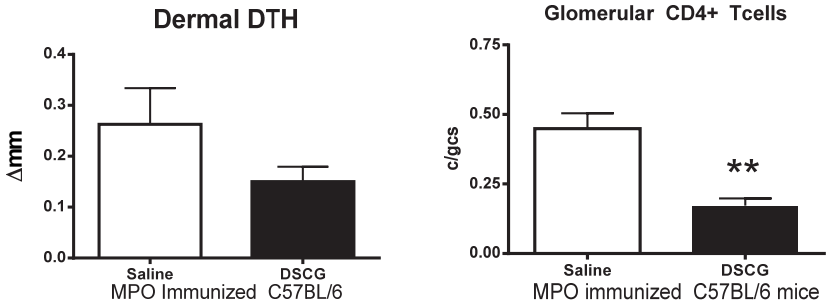
While this tolerance is significant it is not complete. We now plan, in this project, to assess the effects of inducing nasal tolerance with the other 3

immunodominant MPO peptides. The hypothesis to be tested is that a tolerising "cocktail" of peptides will act synergistically to produce maximum protection against, and optimal treatment of, murine autoimmune anti MPO ANCA associated GN.

2. Developing Mast Cell (MC) Based Treatments for Autoimmune anti Myeloperoxidase (MPO) ANCA associated Glomerulonephritis (GN)

Supervisor: Professor Stephen Holdsworth
Associate Supervisor: Dr Poh Yi Gan

Mast cells (MCs) are best known for their role in allergy. We now know that MCs also play important roles in host defense and many chronic diseases including atherosclerosis, Type II diabetes and autoimmune anti Myeloperoxidase (MPO) ANCA associated glomerulonephritis (GN), a major cause of chronic renal failure worldwide. We have developed a murine model of autoimmune anti MPO ANCA associated GN that allows us to study the mechanisms of renal injury and to develop new therapies.
We have recently found that a commonly used asthma drug (chromoglycate; DSCG)that stabilizes MCs preventing their degranulation significantly prevents the development of autoimmune anti MPO ANCA associated GN. To prove that the drugs effects are MC specific we compared the effects of chromoglycate) on MC intact wild type (WT) and MC deficient mice (both treated with DSCG and WT untreated mice all induced with autoimmune anti MPO ANCA associated GN. Use of the drug attenuated autoimmunity and GN in WT mice but had no effect on disease in MC deficient mice proving that its effects are MC specific.



Effects of chromoglycate on Murine Autoimmune anti MPO ANCA associated GN

In this project we will define the mechanisms of action of chromoglycate on both the induction of autoimmunity by MC activation of Dendritic cells as well as the role of MCs in the effector phase by recruiting leukocytes to the kidney. We will also assess the capacity of chromoglycate to have similar effects on other models of autoimmune renal injury.
A new monoclonal antibody, Masitinib has recently been developed to specifically deplete MCs by targeting the key MC growth factor receptor cKit. In this study we will assess the capacity for this biological modifier to abrogate the injurious effects of MCs in autoimmune anti MPO GN thereby advancing its clinical application.

3. The role of γδ T cells in experimental crescentic glomerulonephritis

Supervisor/s: Professor Stephen Holdsworth
Associate Supervisor: Dr Poh Yi Gan

Crescentic glomerulonephritis (GN) is the most severe and destructive form of kidney disease. Current therapies of crescentic GN involve serious immune suppression with low specificity and considerable toxicity. New targeted less toxic therapies are badly needed. Experimental anti-glomerular basement membrane (GBM) GN is the best characterized and most widely studied model of crescentic GN which also models human anti glomerular basement membrane (GBM) GN. The nature of adaptive immune response is characterised by the accumulation of delayed type hypersensitive effector cells; CD4 T cells, macrophages and fibrin. Much of the literature regarding pathogenic role of T cells refers almost entirely to αβ T cells. However, data is emerging suggesting

innate T cells including γδ T cells may play important roles in facilitating and regulating αβ T cells in adaptive immune responses.

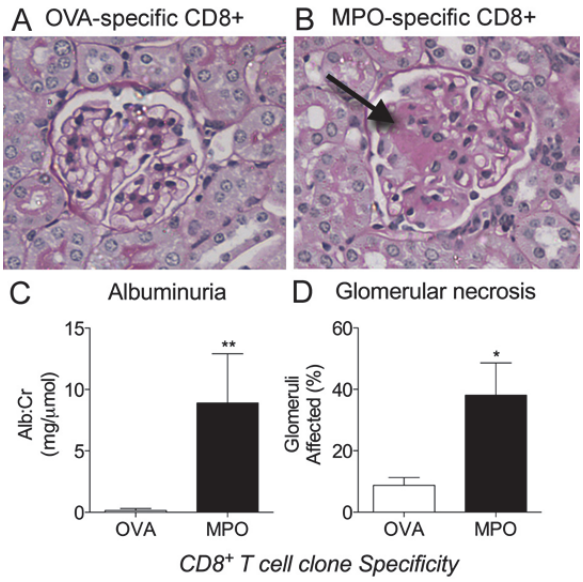
This project will assess the role of γδ T cells in experimental anti GBM GN using genetically modified γδ T cell deficient mice (Tcrd-/-). Furthermore, we will transfer genetically manipulated γδ T cells deficient in likely candidate molecules responsible in regulating αβ T cell responses (ie. IL-17A-/- γδ T cells → Tcrd-/-).

This project will allow honours students to gain skills in important laboratory techniques; in vivo experimental disease models, cell culture, flow cytometry, PCR, in vitro assays of T cell function - ELISPOT, histological staining as well as gaining publishable novel data.

4. Mechanisms of CD8+ cell mediated involvement in autoimmune vasculitis

Supervisor: Professor Richard Kitching
Associate Supervisor: Dr Joshua Ooi

Rapidly progressive forms of glomerulonephritis have a poor outcome and treatments have substantial toxicities. They commonly feature autoimmunity to myeloperoxidase [MPO], a prominent neutrophil granule protein, with the development of anti-neutrophil cytoplasmic antibodies, known as ANCA. We have recently shown that in addition to a role for ANCA, cellular immune effectors are important in ANCA-associated GN (Ooi JD et al, Proc Natl Acad Sci USA, 2012). Observations in humans and our preliminary data imply that MPO-specific CD8+ T cells play an important role in this important human disease.



Transfer of MPO-peptide specific CB8+ cells can induce glomerulonephritis
After disease was triggered by depositing MPO in glomeruli, CD8+ $MPO_{431-439}$ specific cells induced significant disease, with segmental glomerular necrosis and pathological albuminuria (Chang J, Ooi JD, Kitching AR, unpublished data).

CD8+ cells can induce injury by MHCI-peptide mediated lysis or by cytokine secretion. This project will define key mediators of CD8+ cell directed injury in experimental anti-MPO GN. Several molecules will be studied: t-bet, a key transcription factor, key CD8+ cell cytokines, IFN-□ and TNF and key mediators of cytotoxicity, perforin and granzyme B.

Initial studies will induce active anti-MPO autoimmunity in mice deficient in these candidate molecules. However, these molecules may have other roles outside of CD8+ cells (e.g. TNF is expressed by a range of cells). Therefore, the first series of studies will be followed by studies examining the effect of deficiency confined to the CD8+ T cell. For this the project will use naive cell reconstitutions and transfers. These disease models reconstitute mice *Rag1*$^{-/-}$ mice that lack adaptive immunity with naïve wild type CD4+ cells, and also with naïve CD8+ cells derived from wild type or from knockout mice that lack the mediator of interest. In this way, the only cell type lacking the mediator of interest is the CD8+ T cell. Naive, genetically intact CD4+CD25- cells (or our CD4+ T cell clone specific for MPO) will be transferred into *Rag1*$^{-/-}$ mice, together with CD8+ cells from either WT mice, or mice deficient in the selected molecules.

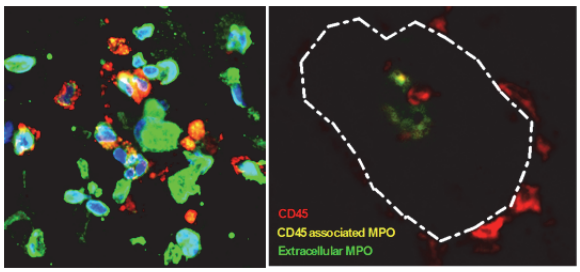
The project centres on murine models of autoimmune anti-MPO glomerulonephritis. It offers opportunities to gain skills in a variety of techniques: in vivo models of disease, flow cytometry, molecular biology, In vitro assays of T cell function, cell culture and working with T cell clones, histological staining, immunofluorescence and immunoperoxidase staining and ELISA/ELISPOT.

5. Do microvascular endothelial cells present autoantigens in the glomerulus?

Supervisor: Professor Richard Kitching
Associate Supervisor: Dr Joshua Ooi

Autoimmunity to myeloperoxidase (MPO) is a common cause of rapidly progressive glomerulonephritis. MPO is a neutrophil granule protein, and with autoimmunity to MPO comes the development of anti-neutrophil cytoplasmic antibodies, known as ANCA. We have recently shown that in addition to a role for ANCA, cellular immune effectors are important in disease. We have proven that ANCA-activated neutrophils release MPO that is deposited in glomeruli. Although MPO is recognized in an antigen specific manner by antigen-specific CD4+ and by CD8+ cells, we do not know which cells are involved and how this happens.

Glomerular microvascular endothelial cells are primary targets of injury in ANCA-associated renal vasculitis. They express MHC I, and can express MHC II under inflammatory conditions, meaning that if they take up MPO released by neutrophils, they may be able to present MPO peptides via MHC I and/or MHC II. Therefore, theses endothelial cell victims may in fact be critical to disease as they may be the cells that allow antigen specific CD4+ and CD8+ cells to localize to the kidney.



Free MPO is present in glomeruli of patients and mice with ANCA-associated GN
Two and three colour confocal microscopy of glomeruli show that non leukocyte associated MPO is present in glomeruli of humans (far left, MPO is red [unpublished data]) and mice (near right, MPO is green, [PNAS, 2012]).

We have human conditionally immortalised glomerular endothelial cells, and murine microvascular endothelial cells. The project will use these cells to define whether MPO peptides are presented and whether this leads directly or indirectly to injury by:

- Studying the expression of MHC I and MHC II under different conditions
- Examining MPO uptake by endothelial cells in vitro
- Defining MHC I and MHC II MPO peptide display
- Studies in CD8+ cell clone/endothelial cell co-cultures will determine whether and how MPO-specific CD8+ T cells injure the endothelial cell.

This project will focus on cell culture, cell imaging in vitro, immunological and biochemical techniques together with T cell (MPO-specific co-cultures) and flow cytometry.

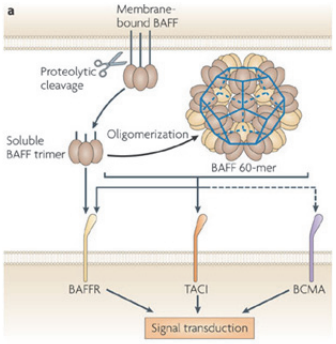
REFERENCE: Ooi JD, Chang J, Hickey MJ, Borza DB, Fugger L, Holdsworth SR, Kitching AR: The immunodominant myeloperoxidase T-cell epitope induces local cell-mediated injury in antimyeloperoxidase glomerulonephritis. Proc Natl Acad Sci USA 2012, 109:E2615

6. The role of BAFF in the production of anti-neutrophil cytoplasmic antibodies and autoimmune vasculitis

Supervisor: Professor Richard Kitching
Associate Supervisor: Dr Joshua Ooi

Rapidly progressive forms of glomerulonephritis have a poor outcome and treatments have substantial toxicities. They most commonly feature autoimmunity to myeloperoxidase (MPO), a prominent neutrophil granule protein, with the development of anti-neutrophil cytoplasmic antibodies, known as ANCA. Treatments that target BAFF(also known as BLyS), a B cell stimulating cytokine, are registered for use in human systemic lupus erythematosus, but apart from two interesting descriptive studies in humans, we have no understanding whether anti-BAFF treatments have a rationale in ANCA-associated vasculitis.

BAFF can be released by neutrophils, a target of anti-MPO antibodies (ANCA). Two human studies have shown that after ANCA stimulation in vitro, human neutrophils release BAFF that can prolong B cell survival, implicating BAFF in this disease.



(BAFF and its ligands. from Mackay and Scheider, Nat Rev Immunol, 2009)

The project will use models of autoimmunity to MPO with genetically modified mice (eg *Taci*$^{-/-}$ mice, and *Baff* transgenic mice [from Professor Fabienne MacKay, Dept Immmunology] and antibodies to study the contribution of BAFF to MPO autoimmunity and ANCA-associated vasculitis, using MPO immunization, transfer studies, and *in vivo* models.

We are establishing a collaboration in this area with Professor Peter Heeringa, from the university town of Groningen in The Netherlands, with the aim of commencing a joint PhD program in the future.

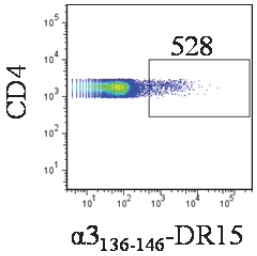
REFERENCES:

1) Holden NJ et al. ANCA-stimulated neutrophils release BLyS and promote B cell survival: a clinically relevant cellular process. Ann Rheum Dis. 2011 70: 2229-33.
2) Mackay F, Schneider P. Cracking the BAFF code. Nat Rev Immunol. 2009; 9:491-502.

7. The role of human MHC II molecules in shaping the autoreactive T-cell repertoire

Supervisor: Dr Joshua Ooi

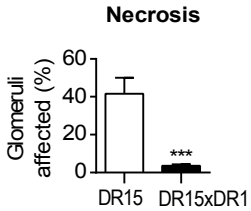
Most autoimmune diseases are associated with specific MHC class II alleles which can either predispose to disease or confer protection. Understanding this association is of basic importance to health and disease. Based on recent discoveries in this laboratory and newly generated human MHC class II tetramers, this project aims to identify the TCR sequences of tetramer-specific T cells selected in the context of a MHC class II that generates pathogenic effector T cells or a MHC class II that generates regulatory T cells.



8. The role of autoantigen specific T regulatory cells in suppressing autoreactive T effector cells

Supervisor: Dr Joshua Ooi

Regulatory T cells are vital for the maintenance of tolerance. In experimental autoimmune anti-GBM disease, we have shown that inheritance of a specific human MHC II can dominantly protect from disease. This project aims to test the hypothesis that protection from disease is conferred via the generation of regulatory T cells. Furthermore, this project will seek to determine the mechanism by which autoantigen specific T regulatory cells prevent the activation of pathogenic T effector cells.



9. Novel treatments for Acute Kidney injury-targeting the innate immune system

Supervisor: Dr Shaun Summers and Dr Maliha Alikhan

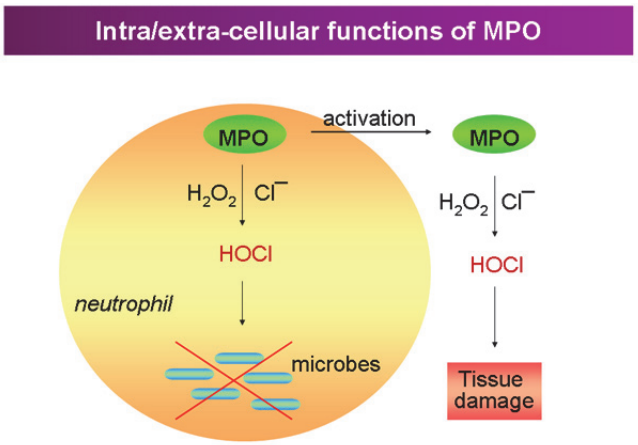
Acute kidney injury (AKI) is an important clinical condition, which significantly increases morbidity and mortality. Two important causes of AKI are ischaemic injury and damage by nephrotoxins. These forms of human AKI are well modeled experimentally by ischaemia reperfusion injury and cisplatin nephrotoxicity. Both of these models are well established in our laboratory. In preliminary studies we have shown important roles for innate immune, pattern recognition receptors, i.e. Toll like receptors (TLRs) and the Inflammasome in driving AKI. This is an interesting and important finding. In this project we plan to investigate the usefulness of novel monoclonal antibodies, TLR and inflammasome inhibitors, to prevent AKI. In addition to learning in vivo and in vitro

techniques, student will have good opportunities to work in research, which is likely to have important translational applications.

10. The Role of Myeloperoxidase in Acute Kidney Injury

Supervisor: Dr Dragana Odobasic

Myeloperoxidase (MPO) is a major protein of neutrophils, the most abundant leukocyte in humans. In the presence of hydrogen peroxide (H_2O_2) and chloride (Cl^-), it catalyses the formation of powerful reactive oxidants including hypochlorous acid (HOCl) which can have profound biological effects by altering proteins, lipids and DNA. Intracellularly, MPO plays a major role in microbial killing. However, MPO can be also released outside following neutrophil activation and cause organ damage, as has been demonstrated in many human inflammatory diseases. We have shown, using MPO-deficient (Mpo-/-) mice and/or MPO inhibitors, that MPO affects tissue inflammation and damage in various models of glomerulonephritis and rheumatoid arthritis.



Acute kidney injury (AKI), resulting from different factors including toxic effects of drugs and various infections, is one of the major causes of morbidity and mortality in patients. Direct tissue-damaging effects and inflammation, mediated by kidney-infiltrating leukocytes such as neutrophils, play a key role in the pathogenesis of AKI. In animals, AKI (with features resembling those of the human condition) can be induced by a single injection of the chemotherapeutic agent, cisplatin. Cisplatin is used in cancer patients, but causes renal damage via direct effects on kidney cells and subsequent accumulation of injurious leukocytes.

Neutrophils and MPO are present in kidneys of animals with cisplatin-induced AKI, suggesting that MPO has the potential to contribute to renal damage in this model. These studies will explore the role of MPO in cisplatin-induced AKI by using Mpo-/- mice and MPO-specific inhibitors. They are aimed at providing a better understanding of kidney-damaging effects of MPO and, consequently, the development of novel therapies for the treatment of AKI.

11. The role of neutrophils in experimental crescentic glomerulonephritis

Supervisor: Dr Dragana Odobasic

Neutrophils have been well known as first responders in innate immunity against invading pathogens at local inflammatory sites. As part of the innate immune system, they also play a key role in tissue inflammation and damage in various immune-mediated diseases. Neutrophils express a vast array of mediators including reactive oxygen species, cytokines and chemokines which mediate their functions. However, more recent studies have revealed that neutrophils also have novel immunoregulatory functions as they can, in contrast to their pro-inflammatory effects at local sites of inflammation, migrate to lymph nodes and suppress the development of adaptive immunity.

Crescentic glomerulonephritis (GN) is a major cause of end-stage-renal-failure. Evidence in patients with the disease suggests that it is driven by CD4 T cells, the major component of the adaptive immune system. The best-characterized and well-established model of crescentic GN is anti-glomerular basement membrane (GBM) GN, which has been used in our laboratory for many years. It is mediated by CD4 T cells and macrophages. Neutrophil accumulation is also markedly upregulated in secondary lymphoid organs (where adaptive immunity is generated) and in the kidney (where the disease develops) during disease progression. However, the role of

neutrophils in this model is unknown. These studies will explore the role of neutrophils in anti-GBM GN by depleting them with a neutrophil-specific monoclonal antibody during the priming (early) and effector (late) phases of the disease. We will assess the effects of neutrophils on the adaptive immune response in secondary lymphoid organs and on disease severity in the kidney. In addition, the mechanisms of their action will be explored using mice deficient in mediators known to be produced by neutrophils. These studies will add to our understanding of the pathogenesis of crescentic GN and, therefore, the improvement of therapeutic strategies.

Theme 2: Molecular mechanisms controlling inflammation and autoimmune diseases

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Description: We are interested in identifying novel therapeutic strategies for treatment of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). We aim to study the biological processes that are faulty in these autoimmune diseases and to identify components of these processes that can be therapeutically targeted to treat disease. One such candidate is the glucocorticoid-induced leucine zipper (GILZ), which we are finding has multiple anti-inflammatory effects in the immune system. We are working to discover the mechanisms by which GILZ mediates these effects and to design a therapeutic to target GILZ in the treatment of RA and SLE. In addition, we are interested in the cellular process of autophagy and its capacity to degrade pro-inflammatory cytokines before they are released by cells. We believe that enhancing autophagy will be an effective means of reducing inflammation in diseases such as RA and SLE. In the lab, we use a range of molecular biology, biochemistry and cellular biology techniques and have access to mouse models and patient samples. Our group contains leading physicians and scientists whose knowledge and expertise combine to place the lab in a strong position to translate basic discoveries into meaningful clinical interventions.

Theme 2 projects include:

1. Defining the mechanisms of action of GILZ to design a therapeutic strategy for targeting GILZ

Supervisors: Professor Eric Morand, Dr Colin Cheng, Dr Huapeng Fan

Rheumatoid arthritis (RA) patients are routinely treated with synthetic glucocorticoids and while these have excellent anti-inflammatory effects, they also induce damaging metabolic effects. To avoid these adverse effects, we aim to identify a novel therapy that specifically dampens inflammation. Expression of the glucocorticoid-induced leucine zipper (GILZ) is correlated with reduced disease severity in arthritis and we are working to create a therapeutic strategy for specifically inducing or stabilising GILZ activity. This project aims to define the molecular mechanisms of action of GILZ and the means by which it mediates its anti-inflammatory effects and protection against arthritis. GILZ interferes with the functions of NFkB and alters histone marks and expression of

a range of inflammation genes by mechanisms we do not yet understand. As well as elucidating these mechanisms, this project aims to create a therapeutic to stimulate the effects of GILZ for use as a treatment for inflammatory diseases such as RA.

2. The role of GILZ in adaptive immunity and autoimmunity

Supervisors: Professor Eric Morand, Dr Sarah Jones

An essential process in the development of RA and SLE is the formation of autoantibodies, the proteins that trigger these diseases. For autoimmune disease to arise, B cells firstly recognise the antigen to which their surface antibody, or B cell receptor, is complementary. Secondly, B cells must receive help signals from activated T cells. Once these requirements are fulfilled, B cells can mature and undergo the germinal centre reaction, then become a persisting source of pathogenic, disease-driving autoantibody. We are learning that the molecule GILZ has profound effects on the capacity of T cells to respond to particular stimuli. When GILZ is deleted, T cells are better able to become activated and to stimulate B cell responses and germinal centre formation. In addition, we have evidence that GILZ is an important limiter of T cell maturation to Th17 cells, and this has implications for the generation of damaging autoimmune responses. The intersection of Th17 cells and the germinal centre reaction is a new and highly interesting field of research, and studying the functions GILZ will give some insight into how these pathways intersect. Moreover, these studies will provide evidence to support the notion that targeting GILZ will be beneficial in reducing pathogenic germinal centre reactions and Th17 responses and therefore be an effective point at which to interrupt autoimmune disease.

3. Role of Autophagy in Autoimmune Diseases

Supervisors: Dr Jim Harris, Professor Eric Morand

Autophagy is an important homeostatic mechanism common to all cells that is involved in the degradation and recycling of cellular constituents. It also has important roles to play in immune cell function and, consequently, in infection and inflammation. This project will look at the role of autophagy in regulating cytokines and chemokines relevant to inflammatory autoimmune diseases like arthritis and systemic lupus erythematosus (SLE). In particular, the project will concentrate on Type I IFNs (IFNα and IFNβ), IL-10 and a range of different chemokines. This project will seek to uncover the mechanisms of autophagic regulation of cytokines and chemokines using a variety of Immunological and cell biological techniques, including ELISA, Western blot, confocal microscopy, quantitative PCR and flow cytometry. The work will concentrate initially on innate immune cells such as macrophages and dendritic cells, but will eventually encompass numerous immune cell types, including T and B cells. Finally, the role of autophagy in models of autoimmune disease will be tested *in vivo* and on human samples *ex vivo*. The data will inform on the potential of autophagy as a therapeutic target in inflammatory diseases, leading to highly novel new data in this increasingly popular and fast-moving area of research.

4. Role of Annexin AI in the Autophagic Regulation of Inflammation

Supervisors: Dr Jim Harris, Dr Yuan Yang

Annexin A1 (ANXA1, lipocortin 1) is endogenous anti-inflammatory molecule that binds to the formyl-peptide receptor 2 (FPR2). In particular, AnxA1 inhibits leukocyte recruitment, pro-inflammatory cytokine expression, phospholipase A2 activity, NF-κB activation and apoptosis. Endogenous AnxA1 exhibits anti-inflammatory effects in mouse models of arthritis and mice deficient in FPR2 develop more severe disease in the K/BxN serum transfer model of inflammatory arthritis. ANXA1 is induced by glucocorticoids and is of interest for the development of potential anti-cancer drugs. Recent evidence has suggested a role for ANXA1 in the regulation of autophagic degradation of cytosolic constituents. Our own research has demonstrated that autophagy targets the pro0inflammatory cytokine IL-1β for degradation and may similarly target other pro-inflammatory cytokines, as well as components of the inflammasome, involved in the maturation and secretion of IL-1β. Thus, ANXA1 may regulate inflammation through the autophagic degradation of pro-inflammatory molecules. This project will

characterize this process, examining the affects of ANXA1 and its deletion on the ubiquitination and degradation of these molecules in autophagosomes, using advanced microscopy techniques, alongside established biochemical analysis. In addition, the effects of other FPR2 ligands, including synthetic compounds, will be tested, with a view to developing novel treatments for the treatment of inflammatory diseases, including lupus and arthritis. Moreover, these compounds may offer new insights into the specific regulation of autophagic degradation in immune cells.

5. Role of Annexin A1 in Regulation of Regulatory T Cells in Inflammatory Diseases

Supervisors: Professor Eric Morand, Dr Yuan Yang

Chronic inflammatory diseases constitute a major health and economic burden. Rheumatoid arthritis (RA) is one of the most common of these diseases, affecting 1% of populations worldwide, and causing severe destructive inflammation of the joints accompanied by systemic complications and loss of life expectancy. It has become clear that in the majority of cases, a loss of tolerance to post-translationally modified host proteins and consequent T-cell-dependent inflammation is critical to the pathogenesis of RA. Therefore, research attention has turned to pathways that temper host immune responses, such as regulatory T cells (Tregs), in a search for the means to abrogate the consequences of unwanted T cell activation.
The importance of the glucocorticoid-induced protein annexin A1 (AnxA1) and its cell surface receptor FPR2 in the effects of glucocorticoids on inflammatory disorders has been increasingly recognized. We have strong evidence in AnxA1 research with respect to inflammatory arthritis and signaling path-ways, have recently demonstrated a previously undocumented inhibitory effect of endogenous AnxA1 in adaptive immunity. We demonstrate that AnxA1 expressed in CD4+ T cells is a key regulator of adaptive immune responses *in vivo* and hence of immune-mediated inflammatory disease. Given that small molecule AnxA1 receptor ligands are now emerging, AnxA1 regulation of immune-mediated inflammation via effects on Treg cells may represent a unique opportunity to move swiftly from scientific concept to Treg cell targeting therapy. The aim of this proposal is to bridge the gap between current knowledge and that required to support development of AnxA1 receptor ligands as inducers of Tregs for the therapy of diseases like RA.

6. Role of the TLR adaptor molecule MAL in the Regulation of Inflammation

Supervisors: Dr Jim Harris, Dr Ashley Mansell (MIMR)

MyD88 adaptor-like (MAL), also known as Toll-interleukin 1 receptor (TIR) domain containing adaptor protein (TIRAP) is an adaptor molecule involved in signalling via Toll-like receptors (TLR) 2 and 4. Different polymorphisms in MAL have been linked with both susceptibility and protection against tuberculosis, as well as protection against systemic lupus erythematosus (SLE). Through its interaction with TLRs, MAL regulates inflammatory responses to exogenous bacterial products. Our own recent findings also suggest a novel role for MAL in IFN-γ signalling, suggesting another important function in the regulation of inflammatory responses. This project will characterise the mechanisms through which MAL directs IFN-γ signalling and examine the consequences of this for inflammatory autoimmune diseases, particularly SLE, in which IFN-γ is known to be important. Using both animal models of disease and samples from SLE patients, the role of MAL and its potential as a therapeutic target to treat SLE will be explored. In particular, the role of MAL in driving inflammatory cytokine and chemokine production in SLE will be investigated. This project will also explore the effects of different polymorphisms in MAL in mouse models of lupus. The results from these studies will inform on the potential of MAL as a therapeutic target for SLE.

7. Autophagy and the Control of Intestinal Inflammation

Supervisors: Dr Jim Harris, Dr Gabrielle Belz (Walter and Eliza Hall Institute of Medical Research)

Autophagy is known to play an important role in the control of inflammation in inflammatory bowel diseases, including Crohn's disease, both through the regulation of inflammatory cytokines and the direct immune

response to enteric bacteria. *Citrobacter rodentium* is a Gram-negative member of the attaching and effacing (A/E) family of bacterial pathogens. Its host is mice, where it causes transmissible murine chronic hyperplasia and is responsible for high mortality in suckling mice. Moreover, *C. rodentium* offers a useful model for the study of bacteria-induced colonic inflammation. Recent studies have identified autophagy in macrophages and intestinal epithelium as an important mechanism for the intracellular killing of *C. rodentium*. This project will further assess the role of autophagy in immune control of this bacterium, as well as its role in the control of intestinal inflammation during infection. In addition, the role of autophagy in specific cell types, including macrophages and intestinal epithelial cells, in regulating the inflammatory environment (cytokine/chemokine secretion, activation of inflammatory signaling pathways, immune cell trafficking and the composition of lymphoid cell populations) will be assessed. This study will detail the specific roles and contributions of autophagy in the control of both inflammation and anti-bacterial immune responses, leading to a better understanding of how this process might be targeted for therapeutic potential. This project is being jointly run by Centre for Inflammatory Diseases at Monash and WEHI and will involve work at both institutes.

Theme 3: Control of leukocyte recruitment and microvascular permeability during inflammation

Research Leader:

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Theme 3 projects include:

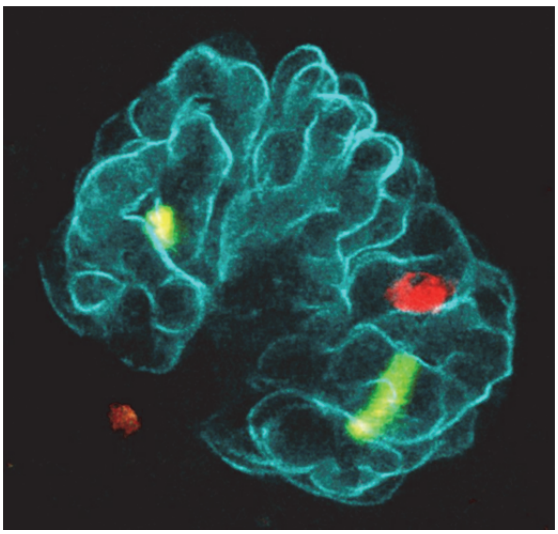
1. Mechanisms of regulatory T cell recruitment and migration

Supervisor: A/Prof Michael Hickey

Many skin diseases are caused by recruitment of T cells. While T cells exist in many subsets, regulatory T cells are unique in that they act to limit immune and inflammatory responses. We have been investigating how regulatory T cells exit the vasculature and home to the inflamed skin in order to control local inflammation. We have used advanced *in vivo* imaging in regulatory T cell reporter (Foxp3-GFP) mice to directly visualize these cells as they adhere and transmigrate in the skin microvasculature, and migrate throughout the dermis. However, the molecular mechanisms of these responses remain unclear. The aim of this work will be to examine the roles of several novel molecular pathways specifically in regulatory T cell recruitment and function – these pathways include adhesion molecules CLEVER-1 and VAP-1, and transcription factors IRF4 and Blimp-1. This project will utilise state of the art imaging approaches (e.g. multi-photon confocal microscopy, & spinning disk confocal microscopy) to examine regulatory T cell-endothelial cell interactions *in vivo* in the vasculature of the skin, and also investigate the mechanisms of T cell migration within the inflamed interstitium. In addition, this work will make use of novel mouse models including regulatory T cell reporter mice in which deficiency of IRF4/Blimp-1 is restricted to regulatory T cells.

2. Control of leukocyte-endothelial cell interactions in glomerular injury

Supervisors: A/Prof. Michael Hickey, Prof. Richard Kitching



Glomerulonephritis is a life-threatening inflammatory condition affecting the kidney, the most important forms of which are mediated by the recruitment of leukocytes to the glomerulus. In order to understand the immunological and molecular basis of glomerular inflammation, our laboratory uses *in vivo* multiphoton confocal microscopy of the kidney to directly image the glomerular microvasculature and examine leukocyte-endothelial cell interactions in this unique vascular bed. These experiments have revealed that numerous blood-borne leukocytes undergo interactions with the endothelium lining the glomerular capillaries, even in the absence of inflammation. However, the molecular basis of these interactions is unknown. The aim of this project is to investigate the role of the endothelial surface layer, a poorly understood structure present on the surface of the glomerular endothelium, in controlling intravascular leukocyte adhesion and crawling in the glomerulus. The main technique used for this project will be *in vivo* multiphoton confocal microscopy of the kidney in mice undergoing various forms of glomerular inflammation.

3. Tetraspanins as regulators of leukocyte migratory function

Supervisors: A/Prof. Michael Hickey & A/Prof. Mark Wright (Dept. of Immunology)

Tetraspanins are a family of leukocyte-expressed transmembrane proteins the functions of which have not been fully elucidated. We have recently demonstrated that the tetraspanin CD53 is important in promoting adhesion molecule expression by lymphocytes, suggesting that it might play key roles in inflammatory and immune responses. The aim of this project will be to investigate this issue *in vivo* by examining lymphocyte-endothelial cell interactions and migration in the microvasculature of wild-type and CD53-deficient mice. This project, which is a collaboration between the laboratories of A/Prof. Michael Hickey (Centre for Inflammatory Diseases) and A/Prof. Mark Wright (Dept. of Immunology), will utilise a wide range of techniques, including *in vivo* imaging in mice, as well as complementary immunological approaches to determine the role of CD53 in the immune response.

Theme 4: Mechanisms of liver fibrosis

Research Leader:

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Description: Liver fibrosis and cirrhosis is the common end stage to all liver diseases in humans (such as infection with viral hepatitis, excessive alcohol intake or metabolic diseases). In response to injury, it has been shown that the hepatic stellate cell (HSC), the vitamin A storing cell of the liver, is responsible for the development of liver fibrosis and cirrhosis. When HSC's become activated they produce excess collagen and other scar components that are deposited in the liver. Over-production of this matrix results in reduced liver function and liver failure. We study mechanisms of liver fibrosis and factors that determine its progression to cirrhosis. We use animal models of liver fibrosis and cirrhosis in our laboratory to enable us to determine which factors may be important in the development of this disease and identify new therapeutic targets. Several different but interrelated honours projects in Theme 5 are available. Projects will use a wide range of laboratory techniques including: Enzyme linked immunosorbent assays (ELISA), molecular biological techniques such as PCR and Real Time PCR, Western blot analysis, immunohistochemistry

Theme 4 projects include:

1. Activin A as a marker for liver fibrosis and cirrhosis in humans

Supervisor: Professor William Sievert

We have recently identified activin A, a reproductive protein, as being an important component in the development of liver fibrosis. This project will aim to identify the clinical utility of activin A as a surrogate marker for liver fibrosis in humans infected with viral hepatitis B and C. It will use a range of biochemical, molecular (such as real time PCR) and histological techniques to do so.

2. The coagulation pathway in liver fibrosis and cirrhosis

Supervisor: Professor William Sievert

It has recently been hypothesized that several blood coagulation factors, including plasminogen, plasmin and tissue factor, may be important in the development of liver fibrosis. This project aims to further analyse the importance of these coagulation pathway members in the development of liver fibrosis. It will use a broad range of histological, immunohistochemical and molecular biology techniques. This project will be performed in conjunction with Assoc. Prof. Peter Tipping.

3. The effect of hepatitis C virus viral replication on hepatic stellate cell biology

Supervisor: Professor William Sievert

This project aims to further characterize the effects of HCV infection in hepatocytes results in HSC activation by using a cell culture system with a non-infectious form of the Hepatitis C virus. It will use a range of cell culture, molecular (such as real time PCR) and histological techniques to do so.

4. Mechanisms of alcohol related hepatocyte apoptosis in patients infected with viral hepatitis C

Supervisor: Professor William Sievert

Patients infected with viral hepatitis C who also consume excessive quantities of alcohol typically have a poorer diagnosis and prognosis. This is likely due to the increased amount of liver cell apoptosis (cell suicide) occurring within the liver. This project will investigate the mechanisms behind this increased liver cell apoptosis. It will use a range of cell culture, molecular (such as real time PCR) and histological techniques to do so.

Theme 5: Atherosclerotic vascular disease: Role of the immune system

Research Leaders:
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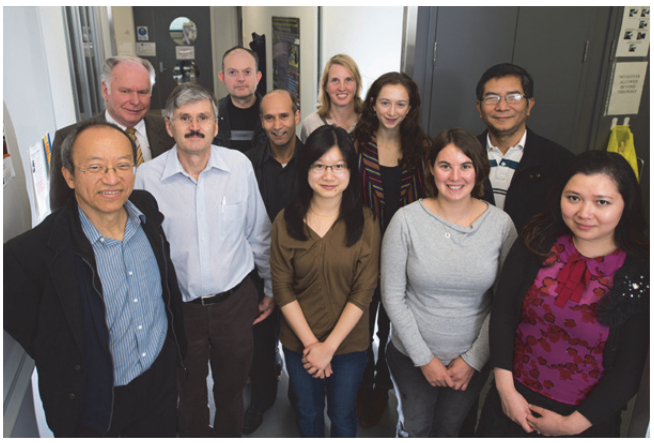

Atherosclerosis is an occlusive disease of arteries that causes heart attacks and strokes. Together, they constitute the number 1 killer in our community. While a high fat diet plays an important role, there is increasing recognition that inflammatory and immunological mechanisms play key contributing roles.

Immunity: Our studies are directed towards a precise understanding of the role of the innate and adaptive immune system in the initiation and progression of atherosclerosis in the ApoE-/- mouse model of this disease. In particular, our studies are focused on the role of macrophages, NKT cells, NK cells, CD4 T cells, regulatory T cells, B cells and the interplay between these lymphocyte subsets in this process. We have compelling evidence for a key role of the cytokine, MIF (Macrophage Inhibitory Factor) and for NKT cells in the initiation of atherosclerosis.

Significance: A precise understanding of the immunological processes leading to occlusive vascular disease can be expected to lead to novel treatment strategies to control atherosclerotic vascular disease that lead to heart attacks and strokes.

Working hypothesis: Lipids enter the vessel wall and are taken by antigen presenting cells (APCs such as macrophages, dendritic cells and B cells. These APCs present lipid antigen to NKT cells to initiate early lesions of atherosclerosis. Secretion of TH1 cytokines by NKT cells recruit NK cells and CD4 T cells that may themselves be activated by protein antigens such as HSP60, leading to lesion progression. Suppression by regulatory T cells is incomplete, contributing to lesion progression.

Students will be exposed to a unique intellectual environment that combines methods and expertise in *Immunology and Inflammation* at the Centre for Inflammatory Diseases, Department of Medicine, Southern Clinical School and in *Vascular Biology* at the Baker Heart Research Institute. Several of our PhD students are currently working on this project.

Performance of past honours students: Two of our current 3 PhD students were the top students in their honours year, attaining the top student Nairn medal.

Theme 6: Respiratory infection

Research Leader:

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Description: Respiratory bacterial infection is extremely common and is probably the most common cause for patients needing to go and seek medical attention. The outcome in respiratory infection is primarily determined by the interaction between the bacterial pathogen and host immune response. The nature of the protective immune response is generally not well understood.

We have a longstanding research interest in assessing the immune response to common bacteria. Our work has concentrated on clinical samples from patients and cell lines. We have expertise in wide variety of techniques including flow cytometry, molecular biology, confocal microscopy and intracellular survival assays.

Theme 6 projects include:

1. Defining intracellular behaviour of nontypeable Haemophilus influenza

Supervisor: Dr Paul King

Nontypeable Haemophilus influenzae (NTHi) is the dominant cause of respiratory bacterial infection including tonsillitis, sinusitis, ear infection and bronchitis. This bacterium has adapted to the human host and is found in the throat of most healthy adults. It only causes clinical disease in a minority of people it infects. One potentially important mechanism of causing disease is the ability to invade host cells and live intracellularly. This project will attempt to define the mechanisms of intracellular survival of NTHi using patient cells and cell lines. The techniques used will include confocal microscopy, flow cytometry and intracellular survival assays

2. Lung immune responses to bacteria in COPD

Supervisors: Dr Paul King and Professor Stephen Holdsworth

Chronic obstructive pulmonary disease (COPD) (which is also known by the lay term emphysema) is the 4th leading cause of death worldwide. This condition is characterized by chronic inflammation that persists after smoking cessation. Bacterial infection may have a role in driving the inflammation in this condition. This project will assess how the common bacterium Haemophilus influenzae, activates inflammatory lung cells in patients with COPD. To assess immune responses, we will use lung tissue taken from patients having curative surgery to treat lung cancer. Techniques used will include flow cytometry, tissue culture and bead array.

Theme 7: Inflammation in Type 2 diabetes and its complications

Research Leaders:

A/Prof David Nikolic-Paterson
Email: david.nikolic-paterson@monash.edu
Phone: +61 3 9594 3535

Dr Greg Tesch
Email: greg.tesch@monash.edu
Phone: +61 3 9594 3534

Description: The growing incidence of type 2 diabetes is a major medical concern. This metabolic syndrome is caused by the development of insulin resistance, which is normally a consequence of chronic obesity. During obesity, inflammation of adipose tissue (fat) and liver promote metabolic dysfunction and insulin resistance which results in type 2 diabetes. The onset of diabetes enhances the inflammatory response causing additional tissue damage to a number of organs including the heart, kidney, eye and nervous system.

The overall aim of this theme is to create a greater understanding of the inflammatory process which takes place in tissues during the development of type 2 diabetes and its complications. Our research examines the role of a specific inflammatory cell (macrophages) in the development of obesity, insulin resistance and diabetic nephropathy. Our lab uses genetically modified mice and pharmacological inhibitors in models of obesity and type 2 diabetes to explore the molecular mechanisms by which macrophages promote injury. Our analyses include metabolic readouts, gene and protein expression in tissues, immunohistochemical assessment of pathology and cell culture assays of inflammation and metabolism.

Theme 7 projects include:

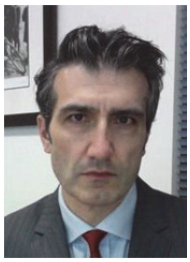
1. The role of JNK signalling in macrophage-mediated tissue injury in type 2 diabetes

Our animal studies have identified that obese mice which are genetically deficient in either JNK1 or JNK2 are protected from the development of insulin resistance and type 2 diabetes. This project will use previously collected tissues to examine how these deficiencies affect macrophage accumulation and their inflammatory responses in fat and the liver. Additional cell culture studies will utilise genetic deficiencies or pharmacological blockade to identify the importance of JNK signalling in specific interactions between macrophages and adipocytes or hepatocytes.

Theme 8: Haematology Research

Research Leaders:

Dr Ashish Banerjee
Email: ashish.banerjee@monash.edu
Phone: +61 3 9594 5660



Dr George Grigoriadis
Email:
george.grigoriadis@monash.edu
Phone: +61 3 9594 5660

Theme 8 projects include:

1. The role of NF-κB transcription factor RelA in regulatory T cell homeostasis and function.

Supervisors: Dr Ashish Banerjee, Dr George Grigoriadis

Regulatory T cells (Tregs) are a specialised subset of CD4+ T cells expressing the transcription factor Foxp3 that are essential for the maintenance of immune homeostasis by suppressing self-reactive and inflammatory T cells. The critical role Tregs serve in controlling T cell immunity is exemplified in mice and humans with a loss-of-function mutation in the *foxp3* gene that results in early-onset, multi-organ fatal inflammatory disease. Although Tregs play a pivotal role in preventing autoimmune disease and limiting chronic inflammation, they also impair beneficial responses by impairing sterilising immunity to certain pathogens and by limiting anti-tumour immunity. Given their key function in the immune system and the prospects of beneficially modulating Tregs in clinical practice, it is imperative to understand how Treg homeostasis and function is controlled. Results obtained so far indicate that the NF-κB transcription factor RelA (p65) plays a key role in Treg biology. Conditional knock-out mice that lack RelA only in Tregs present with a severe inflammatory disease within 6-8 weeks of age and get progressively unwell necessitating sacrifice. This project is aimed at understanding the precise cellular and molecular role of RelA in Treg homeostasis and function. As therapeutic agents that impact upon the RelA pathway are increasingly being utilised in the treatment of a diverse spectrum of diseases, research into how these drugs may impact on Treg differentiation, function or stability is urgently needed. We anticipate that the findings from this study will be beneficial to clinical practice and will help formulate novel therapeutic strategies to usefully manipulate Treg cells in human disease. This project will involve FACS analysis and sorting, Western blotting, QPCR, retroviral transductions and cell culture.

2. The role of iron chelation in myelodysplasia

Supervisors: Dr Ashish Banerjee, Dr George Grigoriadis

The myelodysplastic syndromes (MDS) are a group of clonal haematopoietic stem cell diseases characterized by cytopenia(s), dysplasia in one or more of the major myeloid cell lineages, ineffective haematopoiesis, and increased risk of developing acute myeloid leukaemia (AML). MDS occur principally in older adults with a median age of 70 years with an annual incidence of >20/100,000. Patients with MDS often require blood transfusion with a number of retrospective studies suggesting an adverse impact of transfusion dependence and iron overload on survival in lower risk MDS. Multiple uncontrolled studies attribute a survival benefit to iron chelation therapy in lower risk MDS. An unresolved and important question in MDS is whether survival is improved with iron chelation or whether this intervention merely lowers iron. If indeed a survival benefit is borne out in prospective placebo-controlled trials, the biological rationale for the observed clinical effects of iron chelation in MDS may be due to the role of iron in cell growth regulation. Excess iron may have deleterious effects including malignant transformation via as yet ill-defined mechanisms. More recently it has been demonstrated that targeting iron homeostasis induced blast differentiation of granulocytic/monocytic progenitors. Additionally, the iron chelator deferasirox has been shown to be an inhibitor of nuclear factor kappa light polypeptide gene enhancer in B-cells (NF-□B) in MDS cells. This activity of deferasirox is believed to be independent of its activity as an iron chelator as

it could not be recapitulated by other iron chelating agents. It is not entirely clear how deferasirox inhibits NF-□B; however identification of the mechanism and the patients who would benefit from this unique action would afford the opportunity to selectively utilize this compound in patients with MDS. This project is aimed at understanding the molecular mechanism of NF-κB inhibition by deferasirox. The project will involve cell culture, QPCR, Western Blotting, Immuno-precipitation and cell survival analysis.

3. Does Deferasirox alter T-cell subsets that results in reduced transfusion requirements in patients with myelodysplasia?

Supervisors: Dr George Grigoriadis, Dr Ashish Banerjee

The myelodysplastic syndromes (MDS) are a group of clonal haematopoietic stem cell diseases characterized by cytopenia(s), dysplasia in one or more of the major myeloid cell lineages, ineffective haematopoiesis, and increased risk of developing acute myeloid leukaemia (AML). MDS occur principally in older adults with a median age of 70 years with an annual incidence of >20/100,000. Patients with MDS often require blood transfusion and transfusion-induced iron overload is a frequent problem encountered in the clinic. An observational study recently demonstrated haematopoietic improvement following 'iron chelation' by deferasirox for transfusional iron overload in patients with MDS and aplastic anaemia (AA). Haematological responses occurred prior to significant falls in ferritin (a surrogate for iron levels) and at deferasirox doses considered inadequate for iron chelation. Therefore, it was speculated that the response to deferasirox may be independent of its Iron chelation activity.

Most recently Th1 and Th17 responses have been demonstrated to contribute to the pathophysiology of aplastic anaemia (AA), a disease characterized by peripheral blood pancytopenia and bone marrow (BM) hypoplasia. AA is an immune-mediated disorder in most cases with active destruction of hematopoietic cells by effector T lymphocytes. The production of interferon-γ (IFN-γ), TNF-α and IL-2 from T cells isolated from AA patients coupled with the responsiveness of these patients to immunosuppressive therapies indicate that the immune system which is Th1 skewed plays a pivotal role in the disease pathophysiology. It is widely accepted that there is a significant overlap in the pathophysiology of MDS and AA. Given that a subset of MDS and AA patients attain transfusion independence in response to deferasirox through as yet unclear mechanisms, we speculate that an immunosuppressive mechanism independent of iron chelation may be involved. In this project we will investigate the effects of deferasirox on Th1, Th2, Th17 and Treg cells in mitogen-stimulated human $CD4^+$ cells and study the mechanisms of deferasirox –mediated changes within the lymphocyte subpopulations. The *in vitro* findings will be correlated with the effects of deferasirox on Th1, Th2, Th17 and Treg lymphocyte distribution in MDS patients receiving deferasirox for transfusional iron overload. This project involves isolation of PBMCs from human peripheral blood, cell culture, FACS analysis, Cytokine ELISAs, QPCR and Western Blotting.

Neurosciences Research Group

The Stroke and Ageing Research Centre (STARC) is based in the Southern Clinical School, Monash Medical Centre. It consists of internationally recognised experts in clinical, epidemiological and public health aspects of stroke, dementia, and other brain ageing phenotypes.

Research Leaders include:





(from left: A/Prof Velandai Srikanth, Prof Thanh Phan, Prof Amanda Thrift, A/Prof Dominique Cadilhac, Dr Monique Kilkenny)

Projects available for potential honours students include:

1. The role of T-cells in acute stroke

Associate Professor Velandai Srikanth (velandai.srikanth@monash.edu)
Professor Thanh Phan (thanh.phan@monash.edu)

This is a project examining the role of T-lymphocytes in the evolution of acute ischemic stroke. It is unknown whether certain T-cells (Treg) have a protective role in stroke. This is an area that has generated significant interest in animal experimental models, and we aim to translate the findings from such animal models in human studies. The project involves laboratory measurement of several immune cell types in stroke patients.

2. Measuring ischemic stroke penumbra with high-resolution CT imaging

Professor Thanh Phan (thanh.phan@monash.edu)
Associate Professor Velandai Srikanth (velandai.srikanth@monash.edu)
Dr Henry Ma (henry.ma@monash.edu)

The ischaemic penumbra is that part of the brain affected by stroke that may be salvaged by acute treatments. Measuring the penumbra is challenging and this project aims to use a state-of-the-art CT scanner to achieve this goal. It involves working in the brain imaging laboratory.

3. Imaging approach to phenotyping lacunar stroke

Associate Professor Velandai Srikanth (velandai.srikanth@monash.edu)
Professor Thanh Phan (thanh.phan@monash.edu)

Lacunar stroke has been proposed to be due to small vessel disease. The aim of this study is to evaluate if this stroke mechanism holds true for all 'lacunar' strokes. This project involves working with stroke physicians and radiologists to phenotype patients.

4. Imaging amyloid angiopathy

Dr John Ly (john.ly@monash.edu)
Professor Thanh Phan (thanh.phan@monash.edu)

As a result of recent adances in ligand development, it is now possible to image amyloid binding in the brain in vivo using PET imaging. We have recently phenotype a TIA like presentation of amyloid angiopathy (the clinical implication is that these patients are treated differently from the typical TIA patients). We are planning to evaluate amyloid binding in a number of other stroke syndromes. This project involves working in the imaging laboratory in Neurosciences and state-of-the-art PET scanner.

5. Introduction to health services research in stroke

Associate Professor Dominique Cadilhac (dominique.cadilhac@monash.edu)
Dr Monique Kilkenny (monique.kilkenny@monash.edu)

In the public health division, there is potential for projects for suitable students based on access access to large datasets for undertaking research projects on stroke, as well as studies on blood pressure in the community. This will provide an insight into the usefulness of such work in translating evidence to practice, as well as enable skills in managing large datasets.

6. Shared Team Approach between Nurses and Doctors For Improved Risk factor Management (STAND FIRM)

Professor Amanda Thrift (Professor Amanda Thrift)
Phone: +61 3 9594 7567

This large-scale clinical trial is aimed at improving risk factor management in survivors of stroke. Time is one of the greatest barriers faced by General Practitioners (GPs) in assessing and providing ongoing monitoring of their patients' risk factors. In this research we overcome this barrier by preparing and providing individualised management plans to the patients' GPs. Chronic disease management plans, such as these, attract a Medicare benefit that provides an incentive for GPs to participate in the study, and further provides a mechanism for implementation/translation of our findings. There are many potential projects available within this clinical trial. These include assessing adherence to the management program by both GPs and patients, identifying factors associated with adherence to treatment and lifestyle advice, analysis of the effectiveness and cost-effectiveness of the treatment, and patient satisfaction with the program.

LINKS:
http://med.monash.edu.au/medicine/mmc/star/epidemiology/projects.html

7. Identifying factors associated with hypertension, and barriers to the control of hypertension in the setting of poverty, overcrowding and infection

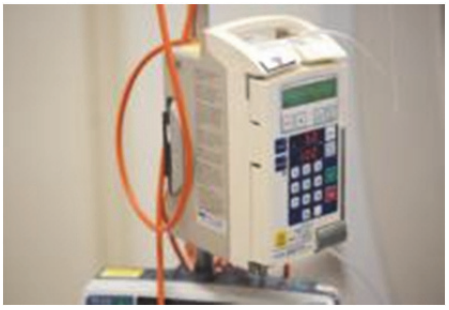
Professor Amanda Thrift (Professor Amanda Thrift)
Phone: +61 3 9594 7567

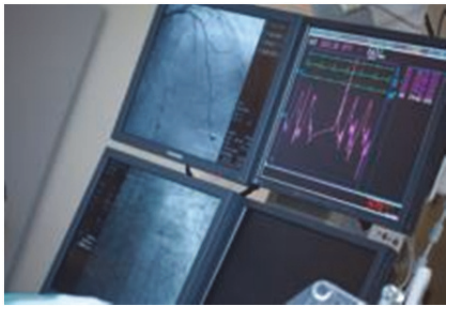
We know a lot about risk factors for hypertension in people who live in high income countries and in urban and relatively wealthy regions of low to middle income countries. However, the specific risk factors for hypertension in disadvantaged regions, and the barriers to control of risk factors, are largely unknown because most previous studies have been conducted in regions where obesity and physical inactivity are prevalent. Our preliminary work shows that people in rural disadvantaged regions are developing hypertension despite being thin and physically active. There is also evidence that those with hypertension are not adequately treated and their blood pressure is not controlled. We are therefore investigating what novel factors may be contributing to the development of

hypertension, and the barriers to control of hypertension, in a community that is subject to extreme poverty. There are many aspects to this study that are suitable for both Honours and PhD projects.

LINKS:
http://med.monash.edu.au/medicine/mmc/star/epidemiology/projects.html

The Monash Cardiovascular Research Centre





The Monash Cardiovascular Research Centre (MCRC) researches a wide variety of cardiac disease and is located at Monash Medical Centre. The Centre has an international reputation for excellence and achievement in basic and translational research, supporting the uptake of state-of-the-art cardiovascular treatments into clinical service.

Project Research Leaders:

Professor James Cameron
James.cameron@monash.edu

Dr Sarah Hope
sarah.hope@monash.edu

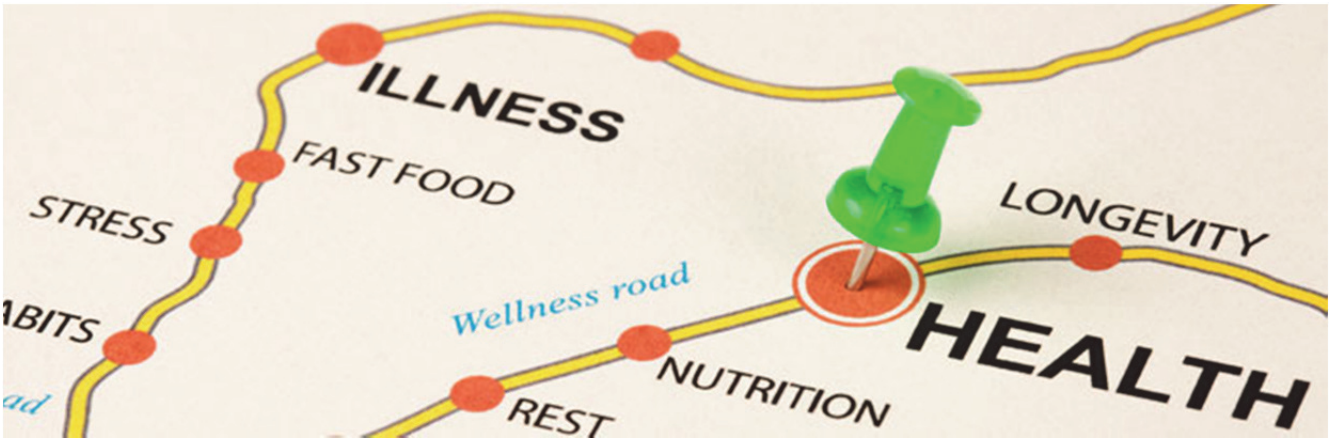
MCRC has potential BBiomedSc honours projects in a number of cardiological topics, including:

1. (Retrospective) Assessment of radiation dose in diagnostic angiography and percutaneous coronary intervention in a tertiary referral centre

2. Assessment of degree of stenosis in coronary artery disease as assessed by 3D quantitative angiography

http://www.med.monash.edu.au/medicine/mmc/mcrc/

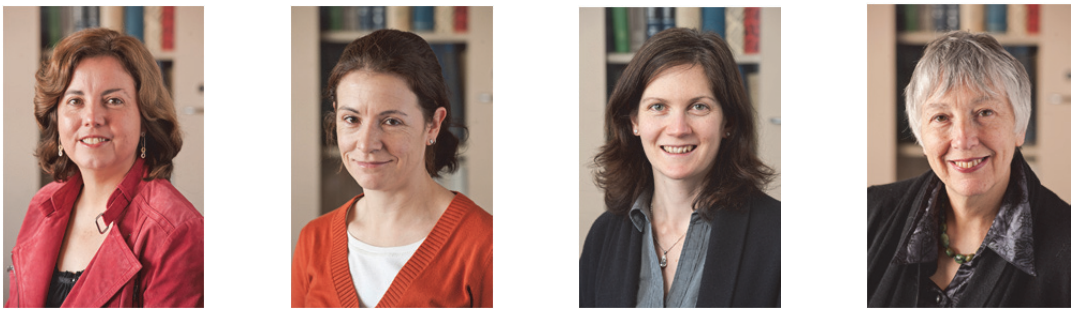
Nutrition, Dietetics and Sleep



2014 Projects for the Bachelor of Nutrition Honours and Bachelor of Medical Science

The Be Active Eat and Sleep (BASE) facility is a leading research facility in the Faculty of Medicine. Research (www.med.monaash.edu.au/base/). It provides facilities for a multidisciplinary group of Academics who conduct research across a wide range of areas that will educate the community with emphasis on the prevention of disease and maintenance of optimum health. With state of the art research equipment and facilities and highly qualified and experienced investigators, Human BASE is applying the integration of nutrition, sleep and exercise physiology research to address the needs of individuals, corporations, health professionals and the community at large.

Research Leaders include:



(left to right, Professor Helen Truby, Dr Maxine Bonham, Dr Cate Huggins & Dr Karen Walker)

Project areas:

- **Clinical dietetics including pediatrics**
- **Community and population nutrition**
- **Sport and exercise nutrition**
- **Sleep, nutrition and metabolism**

Projects offered include:

1. Exploring appetite and satiety responses

Food intake leads to the release of varied gut hormones that can suppress appetite. These hormones provide messages to the brain that in turn transmit signals effecting body metabolism and further food intake. A stronger understanding is needed of the impact of foods differing in macronutrient content, on appetite and satiety and whether effects differ in different population groups. Findings from studies of this type have particular relevance

to the growing problem of obesity. Several projects linked by the use of similar methodologies for studying satiety will be offered:

1.1. In clinical paediatric patients- to explore responses to dietary supplements

(dietetic student required)
Contact: Dr Zoe Davidson
Email: zoe.davidson@monash.edu

1.2. In healthy children of normal body weight

Contact: Dr Kate Huggins or Dr Elizabeth Barber
Email: catherine.huggins@monash.edu; elizabeth.barber@monash.edu

1.3. In overweight adults with sleep apnoea- to examine the effects of food on appetite and on sleep patterns

Contact: Dr Maxine Bonham
Email: maxine.bonham@monash.edu

2. Dietary and behavioural change in overweight adolescents following a 12-week commercial weight-loss program

Supervisors: Dr Maxine Bonham, Dr Aimee Dodrovich, Prof Helen Truby
Email: maxine.bonham@monash.edu

Adolescent overweight and obesity is increasing. Evidence suggests that obesity in adolescence tracks into adulthood and is a predictor of future chronic disease. Early lifestyle intervention with adolescents could help to avoid serious health events in early adulthood, which would ultimately alleviate some of the strain on the public health system due to obesity-related morbidity. Commercial weight loss programs are readily available in a community setting, and are successful in long term weight management in adults, beyond that of current public health care. This method of delivery of a weight management program has not been evaluated for adolescents. Monash University is currently evaluating the impact of the new 'JenMe' program for Jenny Craig Australia (http://www.jennycraig.com.au/health-conditions/adolescent-health). This project will assist with this evaluation and will specifically examine food and nutrient intake, physical activity levels and psychological outcome measures in overweight and obese adolescents taking part in the JenMe study. This project will investigate whether behavioural modification in overweight adolescents is associated with changes in measures of quality of life

3. Validation of bioelectrical impedance as a measurement of body fat and muscle in children with PKU

Supervisor team will include Prof Helen Truby, A/Prof Avihu Boneh, and Ms Maureen Humphrey.
Contact Helen Truby
e-mail: helen.truby@monash.edu

Phenylketonuria is an inborn error of metabolism diagnosed at birth via newborn screening. Children have a very restricted intake of natural protein to limit the accumulation of phenylalanine in the blood. We have a series of investigations underway in collaboration with the Victorian Clinical Genetics Services at the The Murdoch Children's Research Institute examining the effect of dietary intervention on body composition and growth in children with inborn errors of metabolism. This is a validation study designed to elucidate whether the bed side method of bioelectrical impedance can be used in this population group. This new non-invasive method will be compared with DXA and isotopic deuterium dilution to measure body composition. Food intake and energy expenditure will also be measured in a group of children (3-15 years of age) with PKU. Recruitment of subjects will take place at the Royal Children's hospital with clinical measures being carried out at within the Nutrition and Dietetics department (BASE facility) Notting Hill. Travel between these sites will be required.

4. The effect of fat type and fatty acid chain length on lipid uptake and appetite in healthy men and women

Supervisors: Dr Maxine Bonham and Dr Karen Walker
email: maxine.bonham@monash.edu; Karen.walker@monash.edu

High intakes of saturated fat are commonly associated with an increased risk of heart disease. However, there is evidence to indicate that it is not only the type of fat you eat that influences disease risk but also the relative length of the fatty acid chains that make up the fat molecule (or triacylglycerol). Fats are usually described as short chain (less than 6 carbons), medium chain (6-12 carbon atoms), long chain (14 – 22 carbon atoms) and very long chain (greater than 22 carbon atoms). Medium chain triacylglycerols tend to be broken down to fatty acids after digestion and are rapidly absorbed and transported to the liver via the portal vein for rapid oxidation. As a result little of this fat becomes stored in body fat. Medium chain triacylglycerols may therefore affect body composition through increased satiety and increased energy expenditure. Coconut oil is an important food oil throughout south Asia. Although it has been widely regarded with caution here due to its high content(> 85%) of saturated fat, over 60% of this saturated fat content is made up of medium chain fatty acids (MCFA). In contrast, butter which is also high in saturated fat has only about 10% of its saturated fat content as MCFA. The aim of this project is to examine the effect of a breakfast meal containing a high content of coconut oil on postprandial lipid absorption and appetite suppression in healthy men and women compared to a breakfast meal high in long chain fatty acids.

5. The glycemic and satiety effects of different Asian breakfasts

Supervisors: Dr Elizabeth Barber, Ms Tammie Choi, Dr Lisa Ryan
Email: Elizabeth.barber@monash.edu

Many Asian Australian patients with type 2 diabetes are advised to switch their traditional breakfast choices to the Western wholegrain bread and oat porridge, as evidence suggests the potential benefit of low glycemic index (GI) breakfast on stable blood glucose control. This dietary modification recommendation is not very culturally appropriate and may reduce compliance. By incorporating selective low GI Asian food choices, traditional breakfasts can be of low GI too. The aim of this study is to compare the effects of different modified Asian breakfast choices on glycemia and satiety. The study will involve recipe design, cooking, laboratory testing and questionnaire design to measure perceived satiety and dietary preference of the breakfasts. The anticipated results will inform dietetic practice with the Australian Asian community.

6. The impact of sleep during the last trimester of pregnancy and birth weight

Supervisors: Dr Sean Cain, (Senior Lecturer in Psychology) and Professor Helen Truby
Email: sean.cain@monash.edu

Insufficient sleep is associated with changes in metabolism that promote weight gain. These includes decreases in hormonal signals for satiety, increases in hormonal signals for hunger, decreases in resting metabolic rate and increased preferences for high fat foods. Sleep difficulties are highly common in pregnancy and may promote unhealthy weight gain. The consequences of gestational weight gain are not only important for the health of the mother (e.g., avoidance of gestational diabetes), but also the offspring. Maternal weight gain is associated with higher birth weight, which predisposes offspring to obesity throughout the lifespan. In this project, we will monitor sleep quality and quantity through the last trimester of pregnancy and relate it to maternal weight gain and the birth weight of offspring. This study will provide the evidence base for the development of interventions that promote improved sleep during pregnancy for the prevention of unhealthy weight gain in pregnant mothers and decrease the tendency toward weight gain due to excessive birth weight in their offspring. This project will be located at the new Be Active Eat and Sleep facility in Notting Hill (www.med.monaash.edu.au/base/)

7. Weight loss on Medicare…. What can we expect to deliver?

Supervisors: Professor Helen Truby, Dr Tracy McCaffrey, Dr Kevin Lee, and Mr Nathan Givoni (exercise physiologist and APD)
E-mail: Helen.truby@monash.edu

Offering effective treatment for overweight and obesity in Australia is a problem that our health services struggle to deliver due to demand for services. Currently, adults can access 5 visits to allied health practitioners (dietitian, physiotherapy, exercise physiology) to assist them with weight loss and lifestyle change - which remains the first line intervention for prevention of diabetes. No one has reported as to how effective this package of visits may be or what weight loss patients may be expected to achieve. This study will set up and deliver a weight management program using both diet and exercise over a 12 week period using the Medicare model. The aim of the study is to test the effectiveness of this program on weight and body composition changes in healthy adults. It will provide a unique insight as to how dietitians and exercise physiologists may work collaboratively to provide a weight loss service within the Medicare framework. It will provide clinical experience to those who wish to work in the health services or in private practice.

8. Do certain fruits and vegetables really result in a negative energy balance?

Supervisors: Dr Lisa Ryan and Dr Maxine Bonham
Email: l.ryan@monash.edu

Reducing energy intake and increasing physical activities are the main approaches recommended to prevent and control obesity in most weight loss programmes. However, there is increasing interest in finding specific dietary substances that may have beneficial effects on energy expenditure (EE) and metabolism. Diet induced thermogenesis (DIT), also recognised as the thermal effect of foods (TEF) is the increase in the energy expenditure above basal metabolic rate after food ingestion. DIT accounts for approximately 3-10% of the total EE depending on the macronutrient content of the ingested meal. Old wives tales dictate that the energy cost of consuming certain fruits and vegetables (such as grapefruit and celery) is greater than the energy gained from consuming it. The current project will test this theory by examining the effect of identified fruits and vegetables on DIT (indirect calorimetry) and subjective satiety (VAS scales) in healthy subjects

9. The use of phytochemicals to increase the satiating effect of beverages

Supervisors: Dr Lisa Ryan and Dr Kate Huggins
Email: l.ryan@monash.edu

Soft drinks and fruit juices are commonly consumed energy-containing beverages that also play a major role in providing optimum hydration. Paradoxically, the consumption of these beverages has been implicated in the development of obesity. Human studies have reported that energy-containing beverages generally induce less satiety (i.e. feeling of fullness) than solid foods of equal energy content, which may lead to a daily over-consumption with a resultant risk of obesity. It is known that the energy content, palatability and physical properties of foods are influential in determining appetite.
Animal studies have suggested that certain polyphenols and flavonoids may induce increased satiety. Additionally, the levels of fruitiness, sourness and bitterness, and the addition of medicinal plant extracts have all modified palatability in nutritive drinks. The present study aims to explore the use of natural polyphenols in beverages, to determine if their inclusion may maintain the facilitation of hydration, while simultaneously increasing levels of satiety. Previously, green tea (catechins) and also beverages with oats (β-glucans) have improved energy regulation, while reducing the tissue concentrations of triglyceride and cholesterol in hamsters and humans.
The main aim of this study will be to test a range of beverage formulations, with varying amounts and types of polyphenols, in order to:
Determine the role that certain polyphenols may play in reducing satiety after the ingestion of a beverage system.

Develop a beverage with increased satiety and optimum hydration.
The hypothesis is that the phytochemicals in beverages should increase the satiety level of the beverage, while still maintaining the optimum level of hydration.

10. Testing the precision of the Monash University low FODMAP diet iPhone and Android app "traffic light system" in guiding patients with irritable bowel syndrome toward adequate symptom control.

Supervisors: Dr Jane Muir, Dr Jaci Barrett and Prof Peter Gibson
Email: jacqueline.barrett@monash.edu

Department of Gastroenterology, Monash University, Central Clinical School, Alfred Campus.
One in seven Australians suffer from irritable bowel syndrome (IBS), a condition that is characterized by abdominal bloating, pain, and irregular bowel habit. Our research team has identified dietary triggers that might be responsible for the induction of symptoms in the majority of patients with IBS. These triggers involve a group of small carbohydrates that are commonly found in a wide variety of foods and can be poorly absorbed in the small intestine and include; fructose (in apples, pears and fruit juice, high fructose corn syrups), lactose (milk), fructans (onions, garlic, wheat), galacto-oligosaccharides (legumes) and sugar alcohols [sorbitol (pears & apple) and mannitol (mushroom, celery, cauliflower)]. We have named this group of compounds *FODMAPs*-Fermentable Oligo-, Di- and Mono-saccharides And Polyols.

In order to deliver low FODMAP diet information to the public, our team created the Monash University low FODMAP diet iPhone and Android apps. They include a traffic light system to help guide patients to understand which foods are suitable (green), generally tolerated in small amounts (amber) and those which should be avoided (red). This system is based on arbitrary cut off values created through clinical experience, but the accuracy of these cut off levels and the benefit of planning the diet around this "traffic light system" have not been tested. This study aims to test the hypothesis that patients with IBS require a "green" low FODMAP diet, that "amber" foods can only be tolerated in small amounts and "red" foods induce symptoms.

11. Consumer's perceptions of Australian Dietary Guidelines and their influence on food choice

Supervisors: Dr Claire Palermo, Prof Helen Truby
Email: claire.palermo@monash.edu, helen.truby@monash.edu

The Australian Dietary Guidelines provide recommendations about the types and amounts of foods, food groups and dietary patterns. They aim to promote health and well being and prevent diet related disease. There is little evidence on how consumers view these guidelines. The increasing prevalence of nutrition related disease may indicate that they do not influence food and eating behaviour. After a systematic review of the evidence the guidelines were recently revised (June 2011). This study will explore consumer's perspectives and views of the revised dietary guidelines, specifically about how they help or hinder their food selection. Consumer attitudes and beliefs around the guidelines and whether any key messages are missing will also be explored. A qualitative ethnomethodological (study of social practice) approach using focus groups and in-depth interviews will be used. The findings may be used to inform dietitians and government on more appropriate use of the guidelines to improve the diets of individuals and populations.

12. Gut training: Can the gut cope with increased food intake during exercise in thermoneutral and extreme environmental conditions with exposure to repetitive gut challenge?

Supervisor: Dr Ricardo Costa
E-mail: ricardo.costa@monash.edu

Providing carbohydrate during endurance exercise is of fundamental importance in order to attenuate fatigue and maintain exercise workload. Guidelines and recommendations for carbohydrate intake during exercise have previously been established from original investigations to guide sport & exercise nutrition practice. However, previous research has identified difficulties in achieving proposed carbohydrate intake recommendations during

exercise, predominantly due to gastrointestinal symptoms reported by athletes, especially in hot ambient conditions. This project aims to determine if greater carbohydrate intake during exercise can be achieved after a period of gut training. This project will be located at the new Be Active Eat and Sleep facility in Notting Hill (www.med.monaash.edu.au/base/)

13. Extent of disordered eating amongst male athletes: Is there cause for concern?

Supervisor: Dr Ricardo Costa
Email: ricardo.costa@monash.edu

Recently, there has been growing concern into the reports of male athletes developing eating disorders, with the aim of achieving greater muscular physique. Certain disordered lifestyle and dietary behaviours, adhered to by recreational and elite male athletes, have been associated with the drive for muscularity and image of ideal physique. However, the extent of such behaviours is currently unknown, and the degree of dietary imbalance (if any) has not been identified in the target population. This project aims to assess exercise training habits, dietary intake and habits, and supplement use of male athletes from a wide range of sports. The project will determine dietary intake of athletes, and identify is any nutritional imbalances exist. This project will be located at the new Be Active Eat and Sleep facility in Notting Hill (www.med.monaash.edu.au/base/)

14. Impact of exercise-induce dehydration on gastrointestinal symptoms, intestinal endotoxin leakage, and systemic endotoxaemia.

Supervisor: Dr Ricardo Costa
Email: ricardo.costa@monash.edu

Intestinal endotoxin leakage and systemic endotoxaemia is a common feature of exertional-heat stress, stemming from circulatory and thermal disturbances of the splanchnic region. Such responses have been associated with gastrointestinal symptoms leading to reductions or withdrawal from exercise activity, and contributing to the aetiology of heat illnesses (i.e., heat stroke) and fatal systemic inflammatory syndrome. Maintaining euhydration during exertional-heat stress has been shown to reduce both cardiac and thermoregulatory strain, and thus may benefit gastrointestinal integrity during exposure to such stressors. To date, the role of hydration in regulating the degree of intestinal endotoxin leakage, systemic endotoxaemia and gastrointestinal symptoms is unknown. This project aims to assess the impact of a euhydration and dehydration on gastrointestinal symptoms, intestinal endotoxin leakage, and systemic endotoxaemia. This project will be located at the new Be Active Eat and Sleep facility in Notting Hill (www.med.monaash.edu.au/base/)

15. Does milk as a recovery beverage after exercise prevent the post-exercise decrease in immune function?

Supervisor: Dr Ricardo Costa
E-mail: ricardo.costa@monash.edu

Previous studies have shown that the consumption of a carbohydrate and protein supplement beverage after prolonged strenuous exercise prevented the reduction in some aspects of immune function; which are essential for reducing illness/infection risk, and tissue healing, repair and growth. Milk is a natural food source, and in a sufficient volume, contains the right quantity and quality of carbohydrate and protein to potentially stimulate the immune system. However, to date this has not been tested in the research setting. This project aims to determine the role of a milk based recovery drink on bacterially-stimulated neutrophil degranulation. This project will be located at the new Be Active Eat and Sleep facility in Notting Hill (www.med.monaash.edu.au/base/)

16. The effects of short-term vitamin D supplementation on vitamin D status

Supervisors: Dr Maxine Bonham and Dr Lisa Ryan
Email: Maxine.bonham@monash.edu

According to data released in 2011, it is estimated almost one third of adults (31%) in Australia and New Zealand have a vitamin D status classified as inadequate (Daly et al, 2011). Vitamin D status is a reflection of dietary intakes, supplement usage and UVB exposure with UVB exposure the most important determinant. With increasing latitude and a more seasonal exposure to UVB radiation, southern states (such as Victoria) have estimated levels of inadequacy as high as 50%.

Extensive work has been undertaken to identify the cut offs for inadequacy, deficiency and sufficiency (IOM, 2010) and a variety of recommendations exist regrading proposed supplemental doses to improve vitamin D status. However there is wide disagreement about dosing protocols. Well controlled RCTs in the US and Ireland (Aloia et al, 2008, Cashman et al, 2008) observed different requirements for vitamin D to maintain the same levels of sufficiency indicating that population derived outcomes may not be applicable outside of that particular country. This basic, but critical study design has not yet been undertaken in Australia where currently the high levels of deficiency and inadequacy are unexpected. This project will involve undertaking a short-term (8 week) randomized, placebo-controlled, double-blind intervention at supplemental levels of 0, 20, and 40 ug vitamin D3/d. Vitamin D status will be examined pre and post intervention from small blood samples taken from volunteers Factors known to influence vitamin D status such as body adiposity dietary intake and sun exposure will also be assessed.

17. The effect of dietary fats on appetite, lipid metabolism and energy expenditure in obese women

Supervisors: Dr Maxine Bonham, Dr Kate Huggins, Kay Nguo
Email: Maxine.bonham@monash.edu

High intakes of saturated fat are commonly associated with an increased risk of heart disease. However some interesting evidence is emerging to suggest that the association between saturated fat and heart disease is not as strong as once thought, and that not all food sources of saturated fats possess the same atherogenic properties. Saturated fats can be described as short chain (3-7 carbons), medium chain (8-13 carbons) and long chain (14-20 carbons). Shorter chain fats have a tendency to be broken down to fatty acids after digestion and are rapidly absorbed and transported to the liver via the portal vein for rapid oxidation. As a result little of this fat becomes stored in body fat. Much of this evidence has resulted from experiments using individual fats as the test meal; little research has been done on investigating whole foods of various saturated fat chain length. This project will involve undertaking a postprandial study in overweight women to examine the role of saturated fats of different chain lengths on energy expenditure, appetite and lipid metabolism. You will be involved in all aspects of running the clinical trial including recruitment of participants, preparation of study food, administering questionnaires, processing of biological samples, anthropometric measures, data entry and statistical analysis. You will learn specialized techniques such as the measurement of body composition using Bioelectrical Impedance and also measurement of energy expenditure using the indirect calorimetry. Understanding how whole food sources of different fats influence appetite and energy expenditure rather than just individual fatty acids will ultimately better facilitate translation of research into clinical practice.

18. The effect of shift work on dietary patterns and quality of life

Supervisors: Dr Maxine Bonham, Dr Kate Huggins
Email: Maxine.bonham@monash.edu

Industrial and consumer benefits of a 24 hour work-force are self-evident, yet the 1.4 million Australians who engage in shift work are more likely to suffer from health issues such as obesity, sleep disorders and cardiovascular disease compared with workers conforming to the normal sleep-wake cycle. This increased risk is thought to be a result of disruption to the internal body clock resulting in a mismatch between our body's internal timing system and our behaviour. Eating and sleeping at irregular times (overnight) can lead to disturbances in metabolism and energy imbalance promoting obesity, cardiovascular disease and diabetes. A cross-sectional study will be undertaken to ascertain dietary intakes, timing of eating events and metabolic rate in a group of shift workers. These findings will help to inform the content of a health education program.

Surgery

The Department of Surgery (Monash Medical Centre) offers research projects centred around both the laboratory and clinical domains, which ultimately aim to improve our understanding and the practice of surgery. Students with special surgical interests are invited to discuss these with Professor Julian Smith.

Professor Julian Smith
Email: julian.smith@monash.edu
Phone: +61 3 959 45500

Surgical anatomy projects

Description

Projects are available within all the surgical disciplines to explore the anatomical basis of surgical conditions and of the practice of surgery. Examples include:

- Studies of regional anatomy relevant to surgery
- Studies of regional anatomical variations relevant to surgery
- Methods of teaching and of learning of surgical anatomy

Projects may be conducted in association with the Department of Anatomy and Cell Biology. There may be a dissection, investigational and/or clinical basis to each of these projects.

Cardiothoracic surgery projects

Supervisors: Professor Julian Smith, Mr Aubrey Almeida, A/Prof. Andrew Cochrane, Mr Adrian Pick
Location: Monash Medical Centre, Clayton
Tel: 03 9594 5500 **Email:** Julian.Smith@monash.edu
03 9594 3017 Aubrey.Almeida@monash.edu
03 9594 4515 andrew.cochrane@southernhealth.org.au
03 9594 4515 apick1@optusnet.com.au

Projects include:

1. Robotic cardiac surgery – clinical application, early follow-up of results; robotic, micromanipulation and nanotechnology research in association with the Department of Mechanical Engineering.
2. Cognitive function after cardiac and thoracic surgery – measurement of subtle changes in cognitive function, with a computer based test.
3. ASCTS Victorian Cardiac Surgery Database project – development of a risk adjustment model for outcomes of cardiac surgery and the assessment of other cardiac surgical outcomes.
4. Markers of renal dysfunction after cardiac surgery
5. A comparison of the outcomes of the surgical treatment of atrial fibrillation utilising radiofrequency, cryotherapy or high intensity focused ultrasound
6. Trials of 3f, Medtronic Mosaic and Edwards bioprostheses in the aortic position
7. Minimally invasive lung resections compared with open thoracotomy – evaluation of post-operative pain and quality of life

Dental and oral maxillofacial surgery projects

Supervisor: Associate Professor Geoff Quail
Location: Monash Medical Centre, Clayton
Tel: 03 9594 5493 **Email:** geoffrey.quail@monash.edu

Description:
Dental and Maxillofacial Surgery Unit provides a 24-hour service to Monash Health including inpatient and outpatient services and receiving specialist referrals from the primary dental care clinics. It is staffed by specialist consultants, a full-time hospital dental officer and a maxillofacial surgery registrar.

1. Surgical & dental implications of Thalassaemia A Major

Monash Health has the largest cohort of thalassaemia patients in Australia.

This study will examine:

- The prevalence of blood bone and viral infections in patients requiring repeated blood transfusions since infancy.
- Jaw bone density in these patients compared with matched controls.
- Effect of the condition on dental eruption and cranio-facial skeletal morphology.

2. Sleep Apnoea therapy

A mandibular advancement splint is an effective non-invasive technique for treating this troublesome condition. This study will assess subjective changes in day time somnolence and alertness and document changes in oxygen saturation through the use of the appliance.

3. Cleft palate condition

Monash Health has one of the largest multidiscipline and busiest cleft lip and palate clinics in Australia. This study will evaluate the nature of congenital defects referred for assessment and management and the stability of palatal expansion prior to alveolar bone grafting, the integrity of the alveolar graft, the effectiveness of pharyngoplasty and patient and parent appreciation of the condition and compliance with treatment.

4. The incidence of cleft lip and palate related to soil contaminants in a Third World Country.

Intensive Care Unit projects

Supervisor: Associate Professor Geoffrey Parkin
Location: Monash Medical Centre, Clayton
Tel: 03 9594 3276 **Email:** Geoffrey.parkin@southernhealth.org.au

Description:

- The open and closed loop control of water balance.
- The open and closed loop control of the volume state.
- Open and closed loop control of vasodilator and inotropic therapy.
- Measurement of the cardiac output from the airway in intubated patients.
- Ambulant control of the glucose in diabetes mellitus.

Orthopaedic surgery projects

Supervisors: Mr Simon Bell, Mr Minoo Patel
Location: Monash Medical Centre, Clayton
SB Tel: 03 9592 8028 **Email:** SNBell@bigpond.net.au
MP Tel: 03 9429 8084 **Email:** minoo.patel@monash.edu

Projects include:

1. Membrane guided bone regeneration

Prospective randomised animal study.

2. Bone length multiplier

A long term prospective human observational study

3. Lateral epicondylitis (tennis elbow)

A human cadaveric, retrospective and prospective human biomechanical study.

4. Pronator quadratus compartment syndrome

A human cadaveric and retrospective study.

5. Club foot

A human retrospective study.

6. Perthes disease

A human retrospective and prospective (multicentre) study.

7. Spina bifida

Establishment of a data base and ongoing analysis.

8. Tibial fracture IMN versus TSF

Multicentre prospective human study.

9. Growth factors associated with adhesive capsulitis.

10.The effect of the addition of Cortisone to the distension fluid during Hydro- dilatation for adhesive capsulitis

11. Correlation and validation of shoulder scoring between medical practitioners, physiotherapists and patient self assessment

12. Correlation between the outpatient assessment of patients clinically for power and strength and versus the use of strength measurement devices – shoulder or elbow or knee

13. Rotator cuff

Correlation of the response to local anaesthetic for impingement tendinitis and strength testing.
Correlation of pathology on X-Ray and local anaesthetic response.
Long term benefits of cortisone.

14. Evaluation of the benefits and costs of pre-operative education for patients undergoing surgery. Comparison of the private and public sector

15. Efficacy of the pre-emptive injection of Ropivacaine to the operative site given prior to surgery versus prior to or immediately post closure

16. Efficacy of the use of Parecoxib peri-operatively versus no Parecoxib for post operative pain relief

17. Evaluation of post operative recuperative support systems for urban versus rural patients

18. Evaluation of the long term outcome of compensation patients following surgery according to employment classification and other factors

Plastic surgery projects

1. Neurovascular island flap perfusion study

Supervisor: Mr John Crook
Location: Monash Health hospital network
Tel: 03 9899 6144/ 0412 001 380 **Email:** john@johncrock.com

Description:
The concept of vascular flaps has burgeoned since McGreggor first published his axial pattern flap concept last century. Since the advent of microvascular and musculocutaneous flap surgery in the early 1970's work in this field escalated. Behan and Wilson, Taylor et al, O'Brien et al, Crock and Taylor, and Cormack and Lamberty have all defined and re-defined the concept of vascular territories. Now Behan has pioneered neurovascular island flaps in the clinical setting, which has in many cases reduced the need for more complex microvascular surgery. His work has been clinically focused, and the emphasis has always been on solving specific reconstructive conundrums.

This study aims to explain the vascular phenomenon that allow neurovascular islands of tissue to be defined and transferred to create predictable, durable and sensate reconstructions in many areas of the body with a minimum of equipment and within a short operation window.

This is a project that has potential to convert into a higher degree, and will be valuable to anyone interested in pursuing a career in plastic and reconstructive surgery.

2. Comparative study for small bone fixation

Supervisor: Mr John Crook
Location: Monash Health hospital network
Tel: 03 9899 6144/ 0412 001 380 **Email:** john@johncrock.com

Description:
A comparative study of all the small bone fixation sets looking at torque strength, load strength, compressive strength, ease of use and overall kit design. The researcher will require assistance from the engineering department and will also need volunteer medical students in order to complete the study, in particular when assessing the ease of use of the particular sets.

This is a well encapsulated project that is easily to design and carry out, and will be valuable to anyone interested in pursuing a career in hand surgery, plastic surgery or orthopaedic surgery.

Emergency Medicine and Clinical Toxicology

Monash Health and Monash University Emergency Medicine and Clinical Toxicology Research Group Projects for BMedSci and Honours Students

Contact: Professor Andis Graudins
Location: Emergency Department, Monash Medical Centre, Clayton
Tel: +61 3 9594 6666 Email: andis.graudins@monash.edu

The Monash Health Emergency Medicine Research Group is coordinated by Professor Andis Graudins and comprised of medical, nursing and allied health researchers affiliated with the Southern Clinical School of Monash University and the three hospital campuses of the Monash Health Emergency Medicine Program (Monash Medical Centre, Dandenong Hospital and Casey Hospital). Research interests of the group are wide-ranging both in the areas of clinical research in emergency medicine, and toxicology as well as applied basic-science research in various aspects of clinical toxicology.

Specific projects for 2014 Academic year are based at a number of sites. Clinical projects are offered at all of the Monash Health Emergency Departments. Laboratory research is also possible in toxicology research in a dedicated laboratory in the Department of Pharmacology at Monash University, Clayton campus:

Toxicology Projects

1. Development of an animal model of oral drug toxicity to assess the effectiveness of intravenous lipid emulsion (ILE) therapy in the reversal of cardiovascular toxicity of lipophilic drugs implicated in severe human poisoning

Supervisor: Professor Andis Graudins
Site: Toxicology Laboratory in Department of Pharmacology, Monash Clayton Campus.

ILE therapy has been touted as a novel antidote in severe CVS toxicity resulting from lipophilic drug poisoning. Several animal studies have suggested a positive effect when toxins are administered intravenously. Human case report data is not as compelling in the degree of effectiveness of this therapy. Using an established animal model, this project aims to investigate whether the effectiveness of ILE is less significant in a controlled environment of oral poisoning than that seen with intravenous toxin administration utilising a range of drugs implicated in human poisoning.

2. A retrospective review of digoxin poisoning and Digoxin Fab antibody use at Monash Health hospitals

Supervisor: Professor Andis Graudins
Site: Emergency Department, Monash Medical Centre, Clayton, ED

Supratherapeutic digoxin concentrations are not an uncommon finding in elderly patients presenting to the ED with a multitude of medical problems. Many patients exhibit signs of digoxin toxicity. This chart review aims to

correlate the incidence of symptomatic patients with elevated digoxin concentrations and define the appropriateness of use of digoxin specific Fab antibodies in patients with increased serum digoxin concentrations and suspected digoxin toxicity.

Emergency Medicine Projects

1. Qualitative study on what factors influence patients' decisions to present to the Emergency Department (ED) with Stroke

Contact: Andis Graudins
Supervisors: Professor George Braitberg and Assoc/Professor Ian Mosely
Site: Emergency Department, Monash Medical Centre Clayton ED.

The treatment time to maximize survival or morbidity from acute stroke is known as the door to thrombolysis time, which measures the time it takes for the occluded artery to be opened up by the administration of tissue plasminogen activator, a thrombolytic agent. This time frame is less than 4.5 hours. From previous research it has been shown that only a small proportion of patients present to the ED within this time frame. In this study we will interview people when they arrive in the Emergency Department and determine what key decisions the patient and/or their family made prior to arrival and what influenced the decisions they made. This data will support a wider range of research we are undertaking with the National Foundation to evaluate and inform behavior of patients having a stroke.

2. The development and implementation of a 'real time' adverse event monitoring system in the emergency department.

Contact: Andis Graudins.
Supervisor: Dr Robert Meek/ Professor Andis Graudins
Site: Dandenong Hospital ED

The Emergency Department, with its large undifferentiated patient load, high staff numbers with varying levels of experience, long hours and frequent interruptions is likely to have the highest rate of adverse events within a hospital. Despite this concern, research in ED adverse events is lacking, which means that evidence based planning of corrective interventions is almost impossible. The development of an adverse event monitoring system will be followed by appropriate data analysis and preparation of a report which will explore the nature of some possible interventions to reduce identified types of adverse events.

3. Evidence-based analgesia in the emergency department:

A. An assessment of intranasal ketamine as primary analgesia for adults with moderate to severe pain in the ED – a prospective observational study

Contact: Andis Graudins
Supervisors: Professor Andis Graudins / Dr Diana Egerton-Warburton / Associate Professor Ed Oakley
Site: Adult Emergency Department, MMC, Clayton

Ketamine is a potential alternative analgesic agent to opioids in moderate to severe pain. To date, there is little controlled evidence assessing the efficacy of ketamine in emergency department acute pain scenarios. This project utilises sub-anaesthetic doses of intranasal ketamine in an assessment of reduction of pain scores and patient satisfaction in adult patients with moderate to severe pain.

B. Intranasal ketamine in paediatric musculoskeletal injury pain – dose-finding study

Contact: Andis Graudins
Supervisors: Professor Andis Graudins / Associate Professor Ed Oakley / Dr Diana Egerton Warburton
Site: Paediatric Emergency Medicine Department, MMC, Clayton

Ketamine is a potential alternative analgesic agent to opioids in moderate to severe pain. To date, there is little controlled evidence assessing the efficacy of ketamine in emergency department acute pain scenarios. In paediatric patients, the optimal dose of intranasal ketamine resulting in analgesia without marked sedation is not well characterised. This study utilises an observational sequential dose-finding methodology in assessing the most effective dose of IN ketamine not resulting in sedation in moderate to severe musculoskeletal pain in the ED.

C. An assessment of three oral analgesic regimens in the treatment of moderate pain from musculoskeletal injuries in adult patients in the emergency department

Contact: Andis Graudins
Supervisors: Dr Alastair Meyer / Professor Andis Graudins
Sites: This is a cross campus study at all three Monash Health emergency departments. Study is based at MMC, Clayton and Casey Hospitals.

Current analgesic guidelines suggest that patients with moderate pain should have an opioid analgesic included in their medication regimen. Oxycodone is suggested over codeine given that it does not need to be metabolised to gain analgesic effectiveness and also because a significant proportion of patients given codeine are poor metabolisers of this drug. However, some studies suggest that many patients respond well to simple analgesia with paracetamol and ibuprofen alone. This study examines the effectiveness of three drug regimens in the treatment of moderate pain in a double-blind randomised controlled fashion.

Department of Obstetrics and Gynaecology/The Ritchie Centre

Head of Department/Centre Director: Professor Euan Wallace

The Ritchie Centre is one of four Research Centres within Monash Institute of Medical Research and is affiliated with the Monash University Southern Clinical School through the Department of Obstetrics and Gynaecology, and the Department of Paediatrics. The Ritchie Centre has a world-leading reputation in women's health research; fetal development and neonatal research; sleep medicine; and stem cell biology. The Ritchie Centre is one of the few research units that have world-class laboratories and access to clinical patients (women and babies) in a major teaching hospital, allowing seamless translation of experimental work to clinical trials and healthcare.

There are four *Research Themes* in The Ritchie Centre:

- Women's Health
- Fetal and Neonatal Health
- Infant and Child Health
- Cell Therapy and Regenerative Medicine

Honours and PhD Projects are available in all of these themes and some projects involve more than one theme. Some examples of projects are listed below, with more detailed information following.

- Causes of apnoea and its consequences on heart, lung and brain function
- Causes and treatment of obstructive sleep apnoea in infants and children
- Disorders of the circulation and breathing during sleep in preterm infants
- Endometrial regeneration and regulation
- Fetal and neonatal development of the lungs, heart, brain and kidney
- New therapies for preterm lung disease
- Novel bedside tests of brain function in extremely low birth weight babies
- Pathophysiology of preeclampsia and the development of new therapies
- Prevention of perinatal brain injury (cerebral palsy)
- Role of endometrial stem cells in endometriosis
- Stem cell therapies in lung disease, pelvic floor prolapse, and spinal surgery disc injury and degeneration
- Transition of the cardiorespiratory system at birth
- Understanding sudden infant death syndrome

Research Group: Women's Health Group

1. Wnt signalling in regenerating endometrium (lining of the uterus)

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Associate Professor Caroline Gargett, Dr James Deane and Dr Helen Abud**

Email: *caroline.gargett@monash.edu*
Phone: 03 9902 4712 (Caroline)

Project Description: Human endometrium is highly regenerative, growing 1 cm of mucosal tissue each menstrual cycle. The thin endometrium of postmenopausal women also regenerates and can support pregnancy after hormone replacement therapy. We discovered endometrial epithelial progenitor cells and mesenchymal stem cells in human endometrium, likely responsible for this remarkable regenerative capacity and we have identified markers to purify them. We also found 22 differentially expressed WNT-signalling pathway molecules in pre- and postmenopausal endometrium. This project will examine the role of the Wnt signalling pathway in regulating human endometrial epithelial progenitor cell populations in in vitro and in vivo studies.

Index: Endometrium, stem cells, Wnt signalling

2. Testing the in vivo regenerative potential of putative stem cell populations from the endometrium

Suitability: PhD

Location: Level 3, MIMR

Project Leaders: **Associate Professor Caroline Gargett and Dr James Deane**

Email: *caroline.gargett@monash.edu*
Phone: 03 9902 4712 (Caroline)

Project Description: The endometrium is the lining of the uterus and contains adult stem cells that are thought to be responsible for its ability to rapidly regenerate during each menstrual cycle. Finding markers to identify endometrial stem cells is an important area of research. We are investigating candidate endometrial stem cells using cells surface markers in human tissue, and transgenic reporters in mice. The ultimate test of stem cell potential is whether these cells can form endometrium. To answer this question, we will assess the ability of putative endometrial stem cells from mouse and human to produce endometrium when transplanted into a mouse.

Index: Endometrium, stem cells, transplantation

3. Telomerase activity as a stem cell marker in the endometrium

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Dr James Deane and Associate Professor Caroline Gargett**

Email: *james.deane@monash.edu*
caroline.gargett@monash.edu
Phone: 03 9902 4778 (James)
03 9902 4712 (Caroline)

Project Description: Stem cells are believed to be responsible for the regeneration of the endometrium, but markers for mouse endometrial stem cells are required to study this process. To this end, we have investigated the endometrial activity of the telomerase complex which allows stem cells to divide indefinitely by maintaining telomere length. We have used transgenic mice expressing telomerase reporter constructs to identify putative stem cells in the endometrium. This project will use telomerase reporter mice to study stem cells in normal

endometrial cycling, endometrial shedding and repair (as in the human menstrual cycle), and endometrial repair and regeneration after pregnancy.

Index: Endometrium, stem cell, telomerase

4. Role of human endometrial stem/progenitor cells in endometriosis

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Associate Professor Caroline Gargett and Dr Kjiana Schwab**

Email: *caroline.gargett@monash.edu*
Phone: 03 9902 4712 (Caroline)

Project Description: We discovered that human endometrium has a population of epithelial progenitor cells and mesenchymal stem cells (MSC), which can be identified by several novel markers: W5C5 for endometrial MSC and H3D12 and AdM2 are candidates for epithelial progenitor cells. Our preliminary data shows that $W5C5^+$, $H3D12^+$ and $AdM2^+$ cells are shed in menstrual blood and that significantly more of these cell populations gain access to the pelvic cavity in women with endometriosis than normals, suggesting that these cells initiate endometriosis. This project will undertake gene profiling on endometrial stem/progenitor cells purified with our markers from endometrial samples of women with and without endometriosis a common disease affecting 6-15% of young women. For PhD project the role of Wnt4, a susceptibility gene will also be examined.

Index: Endometrium, adult stem cells, endometriosis

5. Role of endometrial stem/progenitor cells in endometrial receptivity

Suitability: Honours, B Med Sci

Location: Level 3, MIMR

Project Leaders: **Associate Professor Caroline Gargett**

Email: *caroline.gargett@monash.edu*
Phone: 03 9902 4712 (Caroline)

Project Description: Some women have a thin, inadequate endometrium that cannot support pregnancy and for whom IVF procedures fail. An endometrial biopsy during the cycle before embryo transfer in these women doubles the pregnancy rate. This project will examine whether biopsy-induced tissue damage-activates endometrial stem/progenitor cells producing an overabundance of new endometrial cells generating an endometrium thick enough to support pregnancy in subsequent cycles. Endometrial stem/progenitor cells will be quantified using our novel markers for identifying epithelial and mesenchymal stem cells in biopsy samples from women undergoing IVF and correlated with endometrial thickness measured by ultrasound and pregnancy outcomes.

Index: Mesenchymal stem cells, epithelial progenitors, IVF

6. Do endometrial mesenchymal stem cells (eMSC) have anti-inflammatory and immunomodulatory properties? Investigating their use in cell based therapies for non identical individuals?

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Associate Professor Caroline Gargett, Dr James Deane and Dr Rebecca Lim**

Email: *caroline.gargett@monash.edu*
Phone: 03 9902 4712 (Caroline)

Project Description: Mesenchymal stem cells (MSC) are rare populations of undifferentiated cells found in many tissues that are capable of self renewal and differentiating into multiple mesodermal lineages. We discovered a novel MSC population in the endometrium, the highly regenerative lining of the uterus, (eMSC). Our tissue engineering studies have shown that eMSC have anti-inflammatory properties. Bone marrow and fat MSC have immunomodulatory properties, making them ideal for cell based therapies in non-identical individuals. In order to use eMSC in non-identical individuals (allogeneic) it is necessary to characterise their anti-inflammatory and immune properties to determine their utility for allogeneic use in regenerative medicine applications.

Index: Mesenchymal stem cells, cell-based therapy, regenerative medicine

7. Pelvic Organ Prolapse - developing an autologous, pre-clinical large animal model for a cell based therapy

Suitability: PhD

Location: Level 3, MIMR and also CSIRO, Clayton

Project Leaders: **Associate Professor Caroline Gargett, Dr Jerome Werkmeister (CSIRO) and Dr Anna Rosamilia (Obstetrics and Gynaecology)**

Email: *caroline.gargett@monash.edu*
Phone: 03 9902 4712 (Caroline)

Project Description: Pelvic organ prolapse (POP) results from childbirth injury, affecting 25% of all women. It causes incontinence and sexual dysfunction. POP is treated by surgery using mesh, but complication rates are high. We are investigating a tissue engineering approach to improve treatment outcomes using a cell-based therapy delivered in novel mesh fabricated by CSIRO. Our studies in a rat xenograft model show that endometrial mesenchymal stem cells (eMSC) improve the biocompatibility and biomechanical properties of implanted mesh by modulating the inflammatory response to implanted mesh, promoting blood vessel growth and minimizing fibrosis. This project aims to develop sheep models of POP and birth injury and will use sheep eMSC.

Index: Animal model; mesenchymal stem cells, cell-based therapy, regenerative medicine

8. Pelvic organ prolapse – computer simulation of new treatments

Suitability: Honours, PhD

Location: Anatomy and Cell Biology, Monash University Clayton campus and Level 3, MIMR

Project Leaders: **Dr Colin McHenry and Associate Professor Caroline Gargett**

Email: *caroline.gargett@monash.edu*
colin.mchenry@monash.edu
Phone: 03 9902 4712 (Caroline)

Project Description: Pelvic organ prolapse (POP) results from childbirth injury, affecting 25% of all women. It causes incontinence and sexual dysfunction. POP is treated by surgery, but failure rates are high. We are investigating a regenerative medicine approach to improve treatment outcomes using cell based therapy delivered in novel scaffold materials fabricated by CSIRO. This project will use virtual testing of the scaffolds to examine the impact of biomechanical loads simulating daily activities on their performance. Normative data will be collected from a sheep and human pelvis using high resolution MRI and CT imaging to generate models predicting biomechanical responses of the pelvic tissues. This multidisciplinary project involves the use of engineering software and supercomputers.

Index: Prolapse, computational biomechanics, simulation

9. Creatine and human pregnancy – it's time we knew more

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Dr Hayley Dickinson, Dr Miranda Davies-Tuck, Professor David Walker and Professor Euan Wallace**

Email: *hayley.dickinson@monash.edu*
Phone: 03 9594 5394 (Hayley)

Project Description: Creatine is obtained from the diet (meat and dairy) and synthesized by the kidney and liver in an approximately 50:50 ratio. Vegetarians have lower levels of creatine stored in muscle than non-vegetarians. During periods of high-energy demand, the creatine/phosphocreatine system is able to readily resynthesize ADP to ATP replenishing energy levels. We have experimental evidence to show that high maternal creatine intake is associated with positive outcomes (improved survival rates and prevention of neurological, muscular and renal injuries) in newborn animals. There are no data on the levels of creatine during pregnancy in humans. This project will: 1) Define the normal range of creatine levels during pregnancy and the early postnatal period and correlate these with dietary intake of creatine. 2) Determine whether higher levels of maternal creatine are associated with better pregnancy outcomes for the mother and baby.

Index: Creatine, pregnancy, diet

Research Group: Fetal and Neonatal Health

10. Overcoming the 4-cell block in spiny mouse embryo culture

Suitability: Honours

Location: Level 5, Monash Medical Centre, Clayton

Project Leaders: **Dr Hayley Dickinson**

Email: *hayley.dickinson@monash.edu*
Phone: 03 9594 5394

Project Description: The spiny mouse (*Acomys cahirinus*) is regularly used as a model of development physiology in preference to traditional rodents, such as mice or rats, as it mirrors the stages of human development more accurately. In the earliest stages of embryogenesis this is also believed to be the case, however the conditions required to culture the spiny mouse embryo *in vitro* require further investigation. At present, embryos fail to progress past the 4 – 8-cell stage when cultured *in vitro*. We hypothesise that this '4-cell block' coincides with the embryonic genome activation (EGA) and requires supplementation of the standard culture medium to support this stage of growth. This is very similar to the addition of EDTA to culture medium required to support human embryos through the EGA. This project will determine the culture conditions necessary to culture spiny mouse embryos *in vitro* through all stage of embryogenesis, and will characterise the EGA in this species.

Index: Embryo, in vitro, culture, embryonic genome activation

11. Supplementing the diet with creatine at the end of pregnancy: a possible treatment to prevent perinatal brain damage in preterm and term lambs?

Suitability: Honours, PhD

Location: Level 5, Monash Medical Centre, Clayton

Project Leaders: **Associate Professor David Walker, Dr Syed Baharom, Dr Suzie Miller and Dr Graeme Polglase**

Email: *david.walker@monash.edu*
Phone: 03 9594 5372

Project Description: The aetiology of brain damage that manifests itself in some infants after birth is still not understood. Current treatments such as head cooling, or use of noble gases such as xenon or argon are "rescue" treatments with limited effectiveness. Our recent work in pregnant sheep and a precocial rodent shows that adding creatine to the maternal diet in the latter stages of pregnancy protects the fetal brain against the effects of severe hypoxia at birth. The aim of our on-going studies is to show that this creatine treatment improves the resuscitation and development of locomotor function in lambs delivered preterm or at term, with or without the additional challenge of birth hypoxia.

Index: Bone marrow, stem cells, brain repair, cerebral palsy

12. Creatine transport across human amnion and chorion

Suitability: Honours

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor David Walker, Dr Hayley Dickinson and Professor Euan Wallace**

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Project Description: Creatine is an essential intracellular metabolite involved in the maintenance of ATP. In adults creatine is obtained after synthesis by the kidney and liver from amino acid precursors, and also from the diet. The source of creatine for the fetus is unclear, but probably depends on placental transfer and/or transfer across the chorion and amnion. We have identified the creatine transporter-1 protein in the human placenta and membranes. In this project we will study transport of creatine cross the human chorion and amnion using an

Ussing chamber. This project will provide new information on the role of the chorio-amnion in the regulation of fetal creatine homeostasis in human pregnancy.

Index: Creatine transport; fetus; placenta; chorio-amnion

13. Brain steroidogenesis in the fetal spiny mouse

Suitability: Honours

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor David Walker, Dr Hayley Dickinson and Ms Tracey Quinn**

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Project Description: This project investigates the consequence of excess maternal glucocorticoids on brain development in the spiny mouse; specifically, on steroidogenesis and neurosteroid synthesis. We have used dexamethasone to mimic glucocorticoid stress by treating pregnancy spiny mice at either 0.5 or 0.75 of gestation, and found this produces quite different effects on adrenal gland structure and function. We hypothesise that increased glucocorticoids of maternal origin will also permanently alter neurosteroid synthesis in the fetal brain, with consequences for postnatal behaviour.

Index: Glucocorticoids, pregnancy, stress, fetus, brain, behaviour

14. Endothelial progenitor cells (EPCs) in fetal blood and brain – role in repair and recovery from developmental brain injury

Suitability: Honours, PhD

Location: Level 5, Monash Medical Centre, Clayton

Project Leaders: **Associate Professor David Walker, Professor Euan Wallace, Associate Professor Caroline Gargett and Dr Margie Castillo-Melendez**

Email: *david.walker@monash.edu*
Phone: 03 9594 5372 (David)

Project Description: We hypothesise that EPCs from bone marrow are recruited in the developing brain following hypoxic and/or ischaemic (HI) injury, and determine the capacity of the fetal and newborn brain to limit and repair this damage caused by HI and inflammation. Specifically, we propose that EPCs are mobilised from fetal bone marrow following HI and limit brain damage by promoting vascularisation of injured regions. EPCs derived from umbilical cord blood may be useful for therapeutic repair of brain injury in the postnatal brain following HI. By investigating preterm and term fetal sheep, we will provide new insights into the role of circulating EPCs in the developing brain under hypoxic conditions, explore the potential of circulating EPCs to serve as a prognostic marker of brain injury, and determine the therapeutic potential of EPCs for promoting recovery from perinatal brain injury.

Index: Bone marrow, stem cells, brain repair, cerebral palsy

15. Impact of dopamine in the immature brain

Suitability: Honours, PhD

Location: Level 5, Monash Medical Centre, Clayton

Project Leaders: **Dr Flora Wong, Professor Adrian Walker, Professor David Walker and Dr Suzie Miller**

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Project Description: Dopamine is commonly prescribed to preterm babies to raise their blood pressure, but its effect in the immature brain is uncertain. New data suggest that dopamine may improve brain oxygenation. This

project aims to define the effects of dopamine in the immature brain using a preterm lamb model, to evaluate the therapeutic potential of dopamine in improving brain oxygenation and reducing brain injury in preterm babies. In preterm lambs receiving dopamine, we will correlate changes in blood pressure, cerebral blood flow and metabolism with histopathology in brain slides, in order to assess the effect of dopamine in reducing brain injury.

Index: Preterm, brain injury, infants

16. Novel approaches to bedside monitoring of cerebral oxygenation in infants with HIE undergoing therapeutic hypothermia

Suitability: Honours

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Dr Flora Wong, Dr Alex Veldman and Professor Adrian Walker**

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Project Description: Hypoxic ischaemic encephalopathy (HIE) is major problem worldwide, with significant mortality and morbidity. Based on recent evidence that therapeutic hypothermia is beneficial to term newborns with HIE, neonatal units now offer cooling as recommended therapy. This project aims to improve and refine the cooling therapy, by using the tissue oxygenation index measured by near infrared spectroscopy (NIRS). We plan to continuously monitor the cerebral oxygenation of HIE infants by NIRS, and relate the measurements to neurodevelopmental outcome. The study will provide bedside information to aid clinical assessments with the potential to guide therapeutic interventions in these critically ill infants.

Index: Brain injury, infants, birth asphyxia

17. Are sick preterm infants sleeping in prone position at risk of low brain oxygen levels?

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Dr Flora Wong and Professor Rosemary Horne**

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Phone: 03 9594 5482 (Flora)

Project Description: It is common practice for sick, preterm babies receiving intensive care to sleep on both their front (prone) and back (supine) alternately while in hospital. However, our recent study shows that healthy term babies sleeping prone have lower brain oxygen levels. Preterm babies receiving intensive care are particularly vulnerable to brain injury due to low brain oxygen levels. We therefore aim to determine whether the current practice of prone sleeping in sick babies is compromising the developing brains of these vulnerable babies, by measuring brain oxygen at the babies' bedside with a spectrometer (near infrared spectroscopy).

Index: Preterm, brain injury, infants

18. Use of activated protein C (aPC) to reduce brain injury from birth asphyxia

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Dr Flora Wong, Professor David Walker and Dr Hayley Dickinson**

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Project Description: Birth asphyxia leads to significant brain injury and long term neurodevelopmental problems, including cerebral palsy, cognitive and other neurological dysfunction. Activated protein C (aPC) is a vitamin K-dependent plasma glycoprotein, and has been shown to be neuroprotective in adult animal models of brain injury and stroke. We propose to explore aPC as a possible new therapy for brain injury following birth asphyxia. We will use our well-validated model of birth asphyxia in the spiny mouse to determine if treatment of birth-asphyxiated pups with aPC prevents the neuropathology in brain slides, and improves postnatal behavioural deficits.

Index: Brain injury, infants, birth asphyxia

19. Do cord blood stem cells reduce brain injury after birth asphyxia?

Suitability: Honours, PhD

Location: Level 3, MIMR, and Large Animal Facility, Monash Medical Centre

Project Leaders: **Dr Suzie Miller and Professor Graham Jenkin**

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Phone: 03 9902 4795 (Suzie)
03 9902 4736 (Graham)

Project Description: It is now appreciated that the parents of many Australian children with cerebral palsy are taking their children overseas to undertake cord blood stem cell therapy, despite a lack of published data that such therapy will be beneficial. We plan to undertake a project that will directly address the question of whether cord blood stem cells reduce perinatal brain injury, caused by a severe asphyxic event at birth, and the mechanisms of protection. This project will utilise our established term lamb model of birth asphyxia, with state-of-the-art neonatal care and magnetic resonance imaging to track the cells.

Index: Perinatal brain injury, stem cells, newborn lambs

20. Novel treatments for preterm brain injury

Suitability: Honours, PhD

Location: Level 3, MIMR and Large Animal Facility, Monash Medical Centre

Project Leaders: **Dr Suzie Miller, Professor Graham Jenkin, Dr Margie Zakhem and Dr Tamara Yawno**

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Project Description: In Australia, a baby is born with the brain injury that underlies cerebral palsy every 15 hours. Improvements in newborn care mean that most babies that are born preterm will survive, but prematurity remains linked to cerebral palsy. Although umbilical cord blood derived stem cells are being used to treat cerebral palsy, there is currently insufficient evidence that such treatment will improve the underlying brain injury. This project will examine whether melatonin, a free radical scavenger, and/or umbilical cord blood stem cells can reduce brain damage caused by preterm lack of oxygen. Treatments will be administered to preterm (fetal) lambs following hypoxia. The active constituents of cord blood will also be investigated in vivo and in vitro.

Index: Prematurity, cerebral palsy, stem cells

21. Novel treatments for preeclampsia

Suitability: Honours, PhD

Location: Level 3, MIMR and main campus, Clayton

Project Leaders: **Dr Rebecca Lim and Professor Euan Wallace**

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Project Description: Preeclampsia is a serious pregnancy-specific condition affecting approximately 5% of pregnancies worldwide. It is a leading cause of maternal and fetal, morbidity and mortality. To date, there is no cure for preeclampsia. Resveratrol is becoming increasingly well known for its protective effects against cancer, cardiovascular disease, inflammation, obesity, age-related deteriorations and ischaemic injuries, such as myocardial infarctions and stroke. Its potential as a therapeutic for preeclampsia is yet to be investigated in detail. Using a rat model of preeclampsia, we will determine the efficacy of resveratrol as a novel therapy. This project involves small animal surgery and molecular techniques.

Index: Preeclampsia, pregnancy, oxidative stress

22. Reparative effects of human amnion epithelial cells in hyperoxia-induced brain injury

Suitability: Honours, PhD

Location: Level 3, MIMR and Monash University, Clayton

Project Leaders: **Dr Rebecca Lim, Dr Courtney McDonald and Professor Euan Wallace**

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Project Description: Our research focuses on the wellbeing of mother and child, with particular interest in pulmonary distress. Recently, human amnion epithelial cells (hAEC) have attracted a lot of attention as a cell source for regenerative therapies. This project will investigate the therapeutic benefits of hAEC in reducing brain inflammation, oxidative stress and neuronal cell death in a neonatal mouse model of bronchopulmonary dysplasia. Various techniques will be employed such as small animal surgery, stem cell culture, immunohistochemistry, ELISA, FACS, real-time PCR and Western blotting. This project will provide valuable preclinical data to support future human clinical trials of hAEC therapy.

Index: Neonatal lung injury, stem cells, regenerative medicine

23. Exploring a new frontier: The immune and coagulation systems of the premature infant and their relevance for the risk of the major diseases of prematurity

Suitability: Honours

Location: Level 3, MIMR

Project Leaders: **Associate Professor Marcel Nold and Dr Claudia Nold**

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Project Description: Surprisingly little is known about the immune and coagulation system of preterm infants, which therefore represent problematically blank pages for clinicians on the one hand, but a true frontier for researchers on the other. Preterm immunity and coagulation are also a new frontier, because only very recently has technology advanced enough to allow us to extract large amounts of information from sample volumes as small as 0.5 ml - which in fact is a significant volume of blood to take from the tiny patients, considering that the total blood volume is as small as 35 ml in some of the babies. Our laboratory has obtained approval to conduct an exciting study in which blood is taken from extremely premature infants at 5 timepoints, thus allowing for a unique longitudinal view at plasmatic and cellular immunity as well as coagulation. To explore these systems in depth, we use cutting edge methods such as protein arrays and multi-colour flow cytometry. Since we also have access to the babies' clinical data, we will be able to perform correlation analyses and draw conclusions about the relevance of our findings to the major diseases of prematurity such as bronchopulmonary dysplasia, intracranial

haemorrhage and necrotising enterocolitis. These insights may lead to the identification of biomarkers and/or new therapeutic targets, which are direly needed as several of these diseases are clinically highly problematic and currently untreatable.

Index: Preterm babies, immune system, coagulation, clinical study

24. Molecular tracking of the cytokine IL-37 in anti-inflammatory signalling

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Associate Professor Marcel Nold, Dr Claudia Nold and Dr Camden Lo**

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Project Description: The focus of this study is on elucidating the molecular mechanism of signalling cascades triggered by the anti-inflammatory cytokine interleukin 37 (IL-37). We have recently described IL-37's powerful beneficial effects, which endow this cytokine with a vast potential for therapeutic application. This project continues our research on IL-37 by utilising sophisticated high resolution microscopy and live cell imaging techniques to observe and track IL-37 and its signalling cascades in real time. Students will have the opportunity to learn and use methods involving tissue/cell culture, molecular engineering, micrometer-scale resolution imaging as well as statistical analysis of the results.

Index: New anti-inflammatory interleukin, high-resolution microscopy, live cell imaging

25. Novel anti-inflammatory approaches for currently untreatable diseases of the preterm baby: IL-1Ra and IL-37 in animal models of bronchopulmonary dysplasia and necrotising enterocolitis

Suitability: Honours

Location: Level 3, MIMR

Project Leaders: **Dr Claudia Nold, Associate Professor Marcel Nold and Dr Philip Berger**

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03 9902 4723 (Claudia)
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Project Description: The severe chronic lung disease bronchopulmonary dysplasia (BPD) of the preterm newborn causes considerable suffering for affected children and families and contributes substantially to health care costs. Necrotising enterocolitis (NEC) is a disease of the premature gut that is very poorly understood and that carries a high mortality. Importantly, no effective therapy is known for either of these devastating diseases. Neonatal immunity has been neglected by biomedical research; therefore, the immense importance of inflammation for BPD and NEC is only beginning to be recognised. In this study, we will assess the therapeutic potential of two innovative anti-inflammatory mediators, interleukin 1 receptor antagonist (IL-1Ra) and IL-37, in established animals models of BPD and NEC. A BPD-like lung disease will be triggered in newborn mice and we will investigate whether increased levels of IL-1Ra or IL-37 can protect the young mice from developing lung pathology. To assess such BPD-like pathology, we will analyse biochemical and cellular markers of inflammation as well as histological slides for alveolarisation and vascularisation on day 2, 5, 14 and 28 of life. To mimick NEC, newborn mice will not be allowed to breast-feed, but will be fed an equivalent to formula for 3 days. In addition, they will briefly be exposed to cold and hypoxia. The resulting pathology in the gut resembles human NEC, and

again we will assess the protective properties of IL-1Ra and IL-37 on the cellular level by histology and flow cytometry and on the molecular level by analysis of various biochemical markers.

Index: Animal models of disease, preterm babies, anti-inflammatory interventions

26. Molecular characterisation of regulation and mechanism of action of the anti-inflammatory cytokine interleukin 37

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Dr Claudia Nold, Dr Ina Rudloff and Associate Professor Dr Marcel Nold**

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Project Description: Interleukin (IL)-37 was discovered in silico in 2000, but received very little attention (not even 10 publications) in general and nothing at all was known about its function until 2010, when our group described the powerful anti-inflammatory properties of this cytokine. IL-37 belongs to the IL-1 family of cytokines and imparts a strong inhibition of the production of pro-inflammatory cytokines. Interestingly, this protection from inflammatory responses is not limited to one or a few triggers, but covers a wide spectrum of inflammatory assaults - a rare property, which renders IL-37 a prime candidate for clinical use. However, further research on the mechanism of action of this unusual cytokine is required before such steps can be taken. In this project, we will characterise several aspects of regulation and function of IL-37, including the mRNA and protein expression profile of IL-37 across a spectrum of cell types and the effect of IL-37 on an important molecular regulator of inflammation, the inflammasome. Students will have the opportunity to learn and apply methods of tissue/cell culture, protein detection (ELISA, immunoblot), quantitative real-time PCR and more.

Index: New anti-inflammatory interleukin, RNA and protein detection, inflammasome

27. Oxygen therapy for preterm infants – optimising delivery

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leader: **Dr Kenneth Tan**

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Project Description: Premature infants with respiratory distress syndrome require oxygen treatment. Risks associated with oxygen therapy require bedside nurses to try to maintain oxygen saturation within a tight target range. However, manual control often fails to achieve oxygen saturation targeting. Automation of the control process may improve oxygen saturation targeting and reduce the adverse outcomes that accompany low or high oxygen levels. This project has two objectives that will involve collaboration with Monash Newborn and Department of Electrical and Computer Systems Engineering: 1) Development of (mathematical) models of oxygenation in preterm infants with RDS. 2) Development of controller device for oxygen delivery.

Index: Respiratory distress, oxygenation, automated control

28. Transition to life after birth

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor Stuart Hooper, Dr Kelly Crossley, Dr Graeme Polglase and Dr Melissa Siew**

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Project Description: The transition to life after birth is one of the greatest physiological challenges that humans face. At birth, the airways are cleared of liquid, to allow the entry of air, which increases pulmonary blood flow and closes vascular shunts that by-pass the lungs during fetal life. Most infants smoothly make this transition, but many don't, which can be life threatening and cause life-long problems. The aim of this project is to study the changes that occur at birth and to identify factors that both facilitate and impede these changes to reduce the risks that newborn infants face.

Index: Onset of air-breathing at birth, premature birth, cardiovascular changes at birth

29. Imaging the entry of air into the lungs at birth

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor Stuart Hooper, Dr Melissa Siew and Dr Marcus Kitchen (Physics)**

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Project Description: The transition to air-breathing at birth is dependent upon airway liquid clearance, which allows gas exchange to commence. This occurs smoothly in most infants, but preterm infants have difficulty in clearing their lungs of liquid. Using a synchrotron, we can image the entry of air into the lungs at birth and the simultaneous changes in blood flow to the lungs. The aim of this project is to identify factors that promote air entry into the lungs and the increase in pulmonary blood flow at birth in premature animals.

Index: Onset of air-breathing at birth, premature birth, lung imaging

30. Preventing lung disease in very premature babies

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Dr Megan Wallace and Dr Annie McDougall**

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Project Description: Very premature babies are born with immature lungs, so they often need respiratory support. However, this can injure their lungs and lead to abnormal lung development called bronchopulmonary dysplasia (BPD). There are no treatments to prevent or reverse BPD, because the mechanisms leading from injury to abnormal lung development are not known. We have recently identified several factors that are activated by injury and that may lead to BPD, suggesting they could be future therapeutic targets to prevent BPD. Several projects are possible to prove the involvement of these factors and could involve studies in premature rabbits and cell culture.

Index: Fetal and neonatal development, lung injury, lung disease

31. Optimising lung growth and maturation for premature babies

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leader: **Dr Megan Wallace and Dr Annie McDougall**

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Phone: 03 9902 4761 (Megan)

Project Description: At birth the lungs must take on the role of gas-exchange, a role they have never performed before. To survive, the lungs must be appropriately grown and mature by the time of birth. Babies born prematurely, before the lungs have had time to develop, are at high risk of death or disease. To improve the outcome for these babies we must understand the mechanisms that regulate normal lung development, so that we can find new ways to accelerate it. This project will investigate factors that are likely candidates for mediating lung growth using cell culture and molecular biology approaches.

Index: Fetus, newborn, lung development

32. Amniotic fluid infection/inflammation: effects on brain development and postnatal behaviour

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Associate Professor Tim Moss, Dr Hayley Dickinson, Dr Mary Tolcos and Dr Graeme Polglase**

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Phone: 03 9594 5392 (Tim)

Project description: Bacterial infection of amniotic fluid is a major cause of preterm birth, and is associated with a number of adverse neurodevelopmental outcomes, including cerebral palsy and autism. At present there is no animal model of amniotic fluid infection that allows investigation of the neurodevelopmental and postnatal behavioural outcomes. The spiny mouse (*Acomys cahirinus*) is particularly suitable as a model of human pregnancy, and postnatal outcomes can be assessed using a battery of neurobehavioural tests. This project is aimed at determining the effects of experimental amniotic fluid infection on brain development and postnatal neurobehaviour in spiny mice.

Index: Neurodevelopment, infection, inflammation

33. Optimising bubble CPAP for preterm infants

Suitability: Honours

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Associate Professor Tim Moss, Dr Graeme Polglase and Professor Stuart Hooper**

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Phone: 03 9594 5392 (Tim)

Project Description: The optimal means of providing breathing support to preterm newborn babies is unknown. We do know, however, that the risk of long-term lung disease can be minimised by providing support in the form of continuous positive airway pressure ventilation (CPAP); but we understand very little about how CPAP works to support breathing. This project has two components suitable for student research projects. One will use newborn lambs to investigate the transmission of pressures delivered by CPAP throughout the respiratory

system. The other will use newborn rabbits so that aeration of the newborn lungs can be visualised using synchrotron imaging.

Index: Newborn, lung, imaging

34. Fetal anti-inflammatory effects of human amnion epithelial cells

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton and Level 3, MIMR

Project Leaders: **Associate Professor Tim Moss and Professor Graham Jenkin**

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Project Description: Epithelial cells from the amniotic membrane have the pluripotent capacity of embryonic stem cells, and several other characteristics, which make them an attractive option for cell therapy. Amnion epithelial cells appear to exert their effects by modulating the immune response. This project is aimed at determining the effect of amnion epithelial cells on the fetal lung and systemic immune responses to intra-amniotic injection of the inflammatory agent lipopolysaccharide (LPS) in sheep.

Index: Inflammation, stem cells, fetus

35. Developing a model of cerebral palsy for rapid clinical translation of therapies

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton and the Australian Primate Facility, Monash University Churchill Campus

Project Leaders: **Dr Graeme Polglase, Associate Professor Tim Moss and Dr Mary Tolcos**

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Project Description: Cerebral palsy is a major complication of preterm birth, with 10% of infants born <30 weeks gestation being diagnosed. Exposure to inflammation within the womb is one of the main known causes of cerebral palsy. There are many antenatal therapies, including stem cells, melatonin and erythropoietin, that may prevent brain damage in preterm infants exposed to inflammation within the womb. However, current animal models are unsuitable for rapid translation of treatments into clinical practice, due to species differences in brain development. This project is aimed at developing a primate model of cerebral palsy, using first-world primates. We will assess the effect of inflammation on cardiovascular and brain inflammation and injury.

Index: Neurodevelopment, inflammation, cardiovascular

36. Protecting the brain from injury at preterm delivery

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Dr Graeme Polglase and Dr Kelly Crossley**

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Project Description: Brain injury is common in preterm infants and is a major cause of long-term adverse neurodevelopment, including mental disability and cerebral palsy. Human data and animal studies have shown that brain injury pertaining to preterm birth occurs through two major mechanisms: 1) an inflammatory cascade in the brain; and 2) alterations to cerebral blood flow.

Our current research is focused on understanding that events that occur in utero, during the time of birth, and upon subsequent respiratory support after birth, can lead to brain injury in preterm neonates. Several projects will focus on establishing techniques to reduce/prevent brain injury related to perinatal events. The experiments include whole-animal physiology, molecular biology and immunohistochemistry.

Index: Circulation, cardiovascular, preterm birth

37. Promoting myelination in the IUGR brain

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Dr Mary Tolcos and Professor David Walker**

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Project Description: Intrauterine growth restricted (IUGR) babies are often born with brain damage, and then grow up with disabilities such as cerebral palsy and/or learning and behavioural problems. This project will study the impact of IUGR on the developing oligodendrocyte, the cell responsible for myelin formation in the brain. We propose that the mechanisms which control oligodendrocyte development are impaired and that these mechanisms can be targeted therapeutically to promote myelination in the IUGR brain. This project combines animal surgery, brain histology, immunohistochemistry, western blot analysis and qPCR.

Index: Perinatal brain injury, growth restriction, myelination

38. Neuronal migration in the normal and prenatally-compromised brain

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton and Level 3, MIMR

Project Leaders: **Dr Mary Tolcos, Dr Megan Wallace and Dr Annie McDougall**

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Project Description: Neuronal migration is a fundamental biological process and is critical for the normal development of the brain. The molecular mechanisms which underlie neuronal migration are complex and involve a number of well characterised factors. When such factors as perturbed, possibly due to suboptimal intrauterine conditions, neuronal migration is impaired leading to abnormal brain development and adverse neurodevelopmental outcomes. Our group has recently identified a novel factor that is expressed in migrating neurons and along the migratory path. This project will combine small animal surgery, immunofluorescence, qPCR and tissue culture techniques to study neuronal migration during development and following prenatal compromise.

Index: Brain development, neuronal migration, prenatal insult

Research Group: Infant and Child Health

39. Postnatal consequences of intrauterine growth restriction on cardiovascular control during sleep in infants

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Dr Stephanie Yiallourou and Professor Rosemary Horne**

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Project Description: Intrauterine growth restriction (IUGR) has been associated with increased risk of hypertension later in life. The causes of this increased susceptibility remain unclear, however impaired autonomic cardiovascular control may play a role. Autonomic control undergoes dramatic maturational changes within the first 6 months of life and can be assessed during sleep in infants. To date there has been no description of the consequences of IUGR on the maturation of cardiovascular control within this window of maturation. In these novel studies, we will utilise clinical sleep studies to examine the effects IUGR on cardiovascular control within the first 6 months of life in an effort to identify underlying mechanism/s that contribute to cardiovascular complications later in life.

Index: Infant, sleep, intrauterine growth restriction, blood pressure

40. Understanding the relationship between childhood obesity and obstructive sleep apnoea

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor Rosemary Horne, Dr Gillian Nixon and Dr Lisa Walter**

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Project Description: Childhood obesity is reaching epidemic proportions in Western societies, with 1 in 4 Australian children being either overweight or obese. While obesity is well recognised as the primary cause of obstructive sleep apnoea (OSA) in adults, the relationship between the two disorders is less straightforward in childhood. In children, airway obstruction results primarily from enlarged adenoids and tonsils. With the rise in childhood obesity, however, more children are being seen clinically in whom obesity could significantly contribute to OSA, but the extent of this contribution is unclear. This study will answer important clinical questions. Does the added burden of OSA worsen any existing adverse cardiovascular or psychological outcomes in children with obesity? What factors are associated with a higher risk of OSA in obese children? The study involves polysomnography and MRI in obese and control children.

Index: Sleep, children, obesity

41. Obstructive sleep apnoea in children with Down Syndrome

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Associate Professor Gillian Nixon and Professor Rosemary Horne**

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Phone: 03 9594 5586 (Gillian)

Project Description: Obstructive sleep apnoea (OSA) affects 30%-80% of children with Down Syndrome (DS). Different countries have proposed different guidelines to clinicians for screening for the condition, with American

guidelines recommending routine sleep studies at 4 years of age and British guidelines recommending more simple overnight oximetry at home. As OSA can occur at any age, a single sleep study at a given age is an expensive and poorly targeted intervention. In addition, the benefits of treatment for OSA are poorly defined in children with DS, raising questions about the value of aggressive screening. We have recently shown that normally developing children benefit from treatment of OSA in terms of IQ, particularly in tasks associated with spatial visualisation, visual-motor coordination, abstract thought, and nonverbal fluid reasoning, and that elevated blood pressure returns to control levels. We now postulate that improvements in similar domains in children with DS might make substantial differences in adaptive functioning, the cognitive processes involved in carrying out tasks of daily living. The potential for such improvements is attractive, as better adaptive functioning translates into better social functioning and capacity for independent living in people with intellectual disability. In this study we will quantify the impact of OSA on children with DS, especially in terms of adaptive functioning, quality of life and cardiovascular functioning, and determine the effect of treatment of OSA on these parameters. This will provide crucial information to guide clinical recommendations for screening and treatment of OSA in DS. Collection of relevant clinical data will secondarily allow us to develop screening tools for OSA in this population.

Index: Children, sleep, down syndrome

42. Persistent desaturation following adenotonsillectomy for obstructive sleep apnoea in children

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Associate Professor Gillian Nixon and Professor Rosemary Horne**

Email: *gillian.nixon@southernhealth.org.au*
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Project Description: Obstructive sleep apnoea (OSA) is a common in childhood, occurring in about 2% of the population, with the peak occurrence between 2-8 years of age. The vast majority of cases are associated with adenotonsillar hypertrophy and most children are successfully treated by surgical removal of the tonsils and adenoids. However, children with severe OSA are at higher risk of respiratory complications in the post-operative period, ranging from the need for supplemental oxygen to emergency re-intubation and unplanned admission to the Intensive Care Unit. For this reason, children with the most severe OSA are usually monitored overnight for the first post-operative night in a tertiary centre with high nurse/patient ratios, using continuous oximetry recordings. Little is known however about which children treated in this way have complete resolution of their pre-existing hypoxia by the first night after surgery and thus could be safely managed in a less intensive setting. Knowledge of the normal pattern of resolution of OSA following surgery will help clinicians to plan post-operative care and more confidently assess risk of adverse outcomes. In this study we will carry out downloadable overnight oximetry on the first post-operative night in children with known severe OSA, comparing that result to the pre-operative study. We aim to determine predictors for persistence of severe desaturation, so that care of this group of children can be optimised.

Index: Children, sleep

43. What role do cerebral hypoxia and sleep disruption play in the neurocognitive effects of paediatric sleep disordered breathing?

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor Rosemary Horne, Dr Sarah Biggs and Associate Professor Gillian Nixon**

Email: *rosemary.horne@monash.edu*
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Project Description: Sleep disordered breathing (SDB) describes a spectrum of disorders caused by obstruction of the upper airway during sleep which ranges from simple primary snoring to obstructive sleep apnoea (OSA). Snoring is the most common clinical symptom of SDB and primary snoring has been reported to occur in up to

35% or over 4 million Australian children. Findings of our recently completed projects have provided strong evidence that all levels of SDB severity including primary snoring are associated with neurocognitive and behavioural deficits. Furthermore, we have shown that these deficits are age dependent, with preschool children exhibiting behavioural but not neurocognitive deficits, and primary school age children displaying both. The aim of this project is to examine the effects of SDB across the range of severities on cerebral oxygenation and sleep disruption using more sensitive techniques than routinely used, and relate these to neurocognition and behaviour in preschool and primary school aged children. We hypothesise that preschool children will exhibit less severe and fewer cerebral hypoxic episodes and less sleep disruption relative to older children and this will be related to the preservation of neurocognitive function observed in the pre-school age group.

Index: Children, sleep

44. Effects of caffeine on infant sleep and arousal: a further chance for intervention?

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor Rosemary Horne, Dr Flora Wong and Associate Professor Gillian Nixon**

Email: *rosemary.horne@monash.edu*
Phone: 03 9594 5100 (Rosemary)

Project Description: Around 10% of all births are preterm (infants born before 37 weeks of gestation); globally, this is estimated to be over 15 million annually. Owing to cardio-respiratory immaturity, 85% of infants born before 34 weeks of gestation suffer from apnoea of prematurity which is associated with prolonged arterial desaturation and bradycardia. This repeated exposure to hypoxia as been linked to adverse neurodevelopmental outcomes. The most effective treatment for apnoea of prematurity is the administration of caffeine to stimulate breathing. It is well known that caffeine promotes arousal and disrupts sleep in adults and adolescents. However, there have been limited studies of the effects of caffeine on sleep and arousal in infants and these have produced conflicting results. Thus it is not known if caffeine administration in the neonatal period alters sleep and arousal patterns or if the repeated caffeine exposure during the neonatal period can result in persistent alterations of sleep and arousal regulation. Impairment of the arousal process in conjunction with impaired cardio-respiratory control is believed to be the underlying mechanism for the Sudden Infant Death Syndrome (SIDS). This is important, as preterm born infants are 4 times more likely to die from SIDS than term infants.

This project will examine the short-term effects of caffeine exposure on the systemic and cerebrovascular circulations, sleep and arousal from sleep in preterm infants whilst in the neonatal unit, and then the long-term effects over the first 6 months of life when infants are at greatest risk for SIDS. We suggest that caffeine administration may be a safe method of improving arousability from sleep in preterm infants at increased risk for SIDS after they have been discharged home.

Index: Infant, sleep, SIDS

45. To what extent are the effects of childhood obesity and obstructive sleep apnoea cumulative: Implications for neuropsychological consequences, mood and quality of life

Suitability: Honours, PhD

Location: Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor Rosemary Horne, Dr Sarah Biggs and Associate Professor Gillian Nixon**

Email: *rosemary.horne@monash.edu*
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Project Description: Childhood obesity is reaching epidemic proportions in Western societies, and Australia is no exception, with 1 in 4 Australian children being either overweight or obese. The detrimental health consequences of obesity in childhood include adverse effects on behaviour and school performance with an overall reduction in quality of life for both the children and their families. Snoring and obstructive sleep apnoea

(OSA) are also very common in children and have similar detrimental effects on behaviour and neurocognition and quality of life to those of obesity. While obesity is well recognised as the primary cause of OSA in adults, the relationship between the two disorders is less clear in childhood, with about 50% of obese children also having OSA.

In this study we will specifically recruit a group of obese children to delineate the independent and combined effects of obesity and OSA on sleep, behaviour and neurocognitive outcomes and quality of life. Importantly, we will examine body fat composition and perform detailed imaging of the upper airway and brain structures, which will help reveal the mechanisms involved in these adverse outcomes. These studies will answer important clinical questions so that clinical management of the growing population of obese children can be improved: Does the added burden of OSA worsen the adverse mental health or psychological outcomes of obesity in children? What factors are associated with a higher risk of OSA in obese children? Do the effects of obesity and OSA have significant effects on brain structure?

Index: Children, behaviour, neurocognition, obesity, MRI

Research Group: Cell Therapy and Regenerative Medicine

46. Novel stem cell therapies for the treatment of cystic fibrosis

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Dr Rebecca Lim, Professor Graham Jenkin, Professor Euan Wallace and Courtney McDonald**

Email: *graham.jenkin@monash.edu*
Phone: 03 9902 4736 (Graham)

Project Description: There is a dire need for a cell-type therapy to replace dysfunctional lung epithelial cells in patients with cystic fibrosis. We aim to produce functional lung epithelial cells from placental stem cells. We will utilise a novel method of delivering these cells into the lungs of a transgenic pig model of cystic fibrosis to incorporate the functional lung epithelial cells into the respiratory conducting airway and the lung. We will track placental stem cell-derived lung epithelial cells in the lung using novel imaging techniques and assess their effectiveness in repairing lung function of piglets with cystic fibrosis.

Index: Cystic fibrosis, amnion stem cells

47. Human amnion epithelial cells as therapy for lung inflammation in preterm newborns

Suitability: Honours, PhD

Location: Level 3, MIMR and Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Associate Professor Tim Moss, Professor Graham Jenkin and Professor Euan Wallace**

Email: *graham.jenkin@monash.edu*
Phone: 03 9902 4736 (Graham)

Project Description: Bronchopulmonary dysplasia (BPD) is a life-threatening chronic lung disease that affects many infants born very preterm. Lung inflammation likely underlies the pathogenesis of BPD. Epithelial cells isolated from the amniotic membrane have stem cell-like properties and other characteristics that make them attractive as a potential cell therapy. The aim of this project is to identify the effect of human amnion epithelial cells on inflammatory responses of newborn preterm lambs. The experiments include whole-animal physiology, immunology, microscopy and molecular biology techniques.

Index: Bronchopulmonary dysplasia, newborn lung disease, amnion stem cells

48. Isolation and banking of cord blood stem cells and placental tissues for future clinical therapies

Suitability: Honours

Location: Level 3, MIMR

Project Leaders: **Professor Graham Jenkin and Courtney McDonald**

Email: *graham.jenkin@monash.edu*
Phone: 03 9902 4736 (Graham)

Project Description: Umbilical cord blood and the umbilical cord are a recognised source of mesenchymal stem cells and the cord is lined by amnion epithelial cells, which have the potential to differentiate into a wide range of cell types and are also potently immunomodulatory and anti-inflammatory. The use of these cells is being explored in a number of therapeutic settings. This project, carried out in collaboration with Cell Care, will validate methods for collection, processing and storage of umbilical cord tissue containing these cells, and their retrieval post-thaw, to enable patients to have the option to store umbilical cord tissue at birth, in addition to cord blood.

Index: Stem cell isolation and storage, regenerative medicine

49. Stem cells and tissue scaffolds

Suitability: Honours, PhD

Location: Level 3, MIMR

Project Leaders: **Professor Graham Jenkin and Dr Tony Goldschlager**

Email: *graham.jenkin@monash.edu*
Phone: 03 9902 4736 (Graham)

Project Description: In these studies, we are investigating the suitability of novel new biomimetic matrices to form tissue structures to produce biomimetic spinal discs for repair of discs damaged by trauma or degenerative processes. We will study the characteristics of biomatrices both in vitro and in vivo, in collaboration with the commercial company, Mesoblast. We will determine the appropriateness of our cellular scaffolds for the production of engineered tissues. We will determine the most appropriate polymer compositions and stem cell combinations that can be developed into the most viable scaffold for therapeutic use in clinical trials.

Index: Stem cells, biomimetic scaffolds, spinal disc repair and regeneration

50. Tracking human amnion epithelial cells in vivo in regenerative medicine

Suitability: Honours

Location: Level 3, MIMR

Project Leaders: **Professor Graham Jenkin, Professor Euan Wallace and Dr Tony Goldschlager**

Email: *graham.jenkin@monash.edu*
Phone: 03 9902 4736 (Graham)

Project Description: We are exploring the use of human amnion epithelial cells (hAECs) and mesenchymal progenitor cells (MPCs) as cellular regenerative therapy for a variety of diseases, including bronchopulmonary dysplasia, chronic lung disease of the preterm infant, and spinal disc repair. This project will utilise novel labelling techniques, including MRI, that will allow us to track the migration profile of stem cells in real-time.

Index: Cell tracking, stem cells, regenerative medicine

51. Stem cells and pregnancy: what women want

Suitability: Honours

Location: Level 3, MIMR and Level 5, Block B, Monash Medical Centre, Clayton

Project Leaders: **Professor Graham Jenkin and Professor Euan Wallace**

Email: *graham.jenkin@monash.edu*
Phone: 03 9902 4736 (Graham)

Project Description: As a component of a program of stem cell and cell therapy research, the student will explore women's views about stem cell therapies and their application to their baby's health, using validated surveys The project will be based at Monash Medical Centre, where the student will interview new mums who have just had a baby at either Monash or Jessie McPherson Private Hospital, exploring their attitudes to the collection of cord blood stem cells and placental stem cells. Skills in questionnaire development, data analyses, and bioethics will be gained in this project, as well as participation in stem cell research.

Index: Stem cell survey, pregnancy, baby health

52. Isolation and expansion of umbilical cord blood stem cells for regenerative medicine

Suitability: Honours

Location: Level 3, MIMR

Project Leaders: **Professor Graham Jenkin, Dr Abhilasha Tiwari, Courtney McDonald and Associate Professor Mark Kirkland (Deakin University)**

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Phone: 03 9902 4736 (Graham)

Project Description: Umbilical cord blood (UCB) is one of the richest sources of "young" hematopoietic stem cells. Currently, more than 3000 UCB stem cell transplants are performed each year. However, these are mostly restricted to children, as UCB samples usually do not contain sufficient stem cells to treat adults. Hence, this research project aims to develop and refine methods for expanding the number of stem cells obtained from human UCB under laboratory conditions and translation of this research to the clinic. This stem cell research could help save lives of people suffering from blood disorders, cancers and auto-immune diseases. The experiments will include cell culture and molecular biology techniques and transplantation of UCB stem cells to mice to determine their efficacy.

Index: Stem cell isolation and expansion, regenerative medicine

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