Contents

SCHOOL OVERVIEW .................................................................................................................................5

PROJECTS BY DEPARTMENT ......................................................................................................................6

ALLERGY IMMUNOLOGY AND RESPIRATORY MEDICINE ...........................................................................6

Cardiothoracic Surgery ................................................................................................................................6

PROJECT TITLE: Impact of lymph node sampling and lymph node dissection in surgical resection on clinical outcomes in early stage non-small cell lung cancer (NSCLC) .......................................................... 6

Medical Oncology .......................................................................................................................................7

PROJECT TITLE: Impact of mutation analysis and mutation directed therapies on clinical outcomes in non-small cell lung cancer (NSCLC) .............................................................................................................. 7

AUSTRALIAN CENTRE FOR BLOOD DISEASES (ACBD) ............................................................................8

Serpins Biology Group ...................................................................................................................................8

PROJECT TITLE: Disruption of the plasmin-antiplasmin system; a new approach to dissolving blood clots

Vascular Biology Group ................................................................................................................................9

PROJECT TITLE: Interactions of GPIb-IX-V/GPVI in vascular systems: laboratory studies and clinical translation ................................................................. 9

PROJECT TITLE: The radical world of platelets ..........................................................................................11

PROJECT TITLE: Blood flow regulates metalloproteinase activity on the surface of vascular cells ........12

Fibrinolysis Research Unit .............................................................................................................................13

PROJECT TITLE: To determine the role of tissue type plasminogen activator (t-PA) in the progression and severity of multiple sclerosis ......................................................................................................................... 13

Fibrinolysis and Gene Regulation Laboratory ................................................................................................13

PROJECT TITLE: To understand how t-PA, a clot-busting drug given for the treatment of stroke, modulates cell permeability and blood brain barrier integrity .............................................................................................................. 14

Red Cell Research Group ..........................................................................................................................15

PROJECT TITLE: Using forward genetics to understand the regulation of red blood cells ......................15

Stem Cell Research Group ..........................................................................................................................16

PROJECT TITLE: Self-renewal mechanisms in haematopoietic and leukemia stem cells ..........................16

PROJECT TITLE: Poisoning cancer stem cells by treatment with arsenic ................................................17

PROJECT TITLE: Protein arginine methyltransferase 5 – a new target for lymphoid malignancies ... 18

PROJECT TITLE: Polycomb genes in stem cells and myelodysplasia .......................................................19

Malignant Haematology and Stem Cell Transplantation .............................................................................20

PROJECT TITLE: Targeting heat chock response as a potential therapeutic target in multiple myeloma 20

PROJECT TITLE: Investigation of synergistic drug combinations with a novel JAK inhibitor .................21

PROJECT TITLE: Minimal Residual Disease in Multiple Myeloma (LEOPARD study) .........................22

PROJECT TITLE: Evaluation of a novel beta-catenin inhibitor in multiple myeloma ..............................23

PROJECT TITLE: Identification of optimal proteasome inhibitor for multiple myeloma therapy ..........24

PROJECT TITLE: Therapeutic targeting of PI3K in Acute Myeloid Leukaemia .....................................25

Leukemia Research Laboratory ..................................................................................................................25

PROJECT TITLE: Identifying novel synergistic drug combinations in Acute Myeloid Leukaemia .........26

PROJECT TITLE: Investigating the role of inositol polyphosphate phosphatases in Acute Myeloid Leukaemia ..........................................................27

Thrombosis Research Unit ..........................................................................................................................28

PROJECT TITLE: Investigating new approaches to dissolve blood clots ...............................................28

PROJECT TITLE: Defining the function of thrombin receptors on human platelets during thrombosis ... 29
PROJECT TITLE: What turns you on? Determining activation signals for platelets during thrombosis .................. 30
PROJECT TITLE: Investigation of the functional interplay between platelets and Neutrophils ......................... 31
PROJECT TITLE: Investigating platelet hyperactivity in diabetes ................................................................. 32
PROJECT TITLE: Investigating a new anti-clotting approach: Regulation of platelet adhesion and thrombus formation by the GPIb/V/IX adhesion receptor ................................................................. 33
PROJECT TITLE: Mitochondrial dynamics – a matter of platelet ‘life or death’ ........................................... 34

BURNET INSTITUTE ......................................................................................................................................... 35

CENTRE FOR IMMUNOLOGY .......................................................................................................................... 35
PROJECT TITLE: Understanding the targets and mechanisms of human immunity to malaria .................... 35
PROJECT TITLE: Vaccines against malaria .................................................................................................... 36
PROJECT TITLE: How should we manage Mycobacterium abscessus infection in lung transplant recipients? .................................................................................................................................. 37

DEPARTMENT OF INFECTIONOUS DISEASES .............................................................................................. 37
PROJECT TITLE: Investigating a new anti-clotting approach: Regulation of platelet adhesion and thrombus formation by the GPIb/V/IX adhesion receptor ................................................................. 33

DEPARTMENT OF MEDICINE ....................................................................................................................... 41
PROJECT TITLE: Expression profile of skin tumours with high risk of malignant conversion ......................... 41

MONASH ALFRED PSYCHIATRY RESEARCH CENTRE (MAPRc) ................................................................. 42
PROJECT TITLE: A Neuroscience approach to Enhancing Cognitive Functioning: using transcranial Alternating Current Stimulation to enhance the effects of cognitive training ...................................... 42
PROJECT TITLE: Investigating the physiological response to transcranial magnetic stimulation (TMS). ................................................................................................................................................................. 43
PROJECT TITLE: Investigating the human mirror neuron system via transcranial magnetic stimulation (TMS) ................................................................................................................................................................. 43
PROJECT TITLE: Using tDCS to investigate the role of hemispheric laterality in emotional processing. .... 45
PROJECT TITLE: The Women’s Mental Health Clinic Evaluation ................................................................. 46
PROJECT TITLE: Psychosis Symptom Fluctuation Across the Menstrual Cycle ............................................. 47
PROJECT TITLE: The Interaction Between OCP and Cognition ................................................................. 48
PROJECT TITLE: Lung Function in People with Severe Mental Illness ......................................................... 49
PROJECT TITLE: Menopause and Women with Schizophrenia ...................................................................... 50
PROJECT TITLE: Cognition and symptoms of schizophrenia: What we can learn from biological relatives and schizotypy in the healthy population ........................................................................ 51

DEPARTMENT OF SURGERY ......................................................................................................................... 52
PROJECT TITLE: Management of gastro-oesophageal reflux in obese patients ............................................. 52
PROJECT TITLE: Upper GI symptoms, satiety and gastro-intestinal quality of life following adjustable gastric banding .................................................................................................................................................. 53
PROJECT TITLE: Outcomes of major bariatric surgical procedures ............................................................ 54
PROJECT TITLE: Outcomes of gastro-oesophageal cancer in Victoria ............................................................ 55
PROJECT TITLE: Investigation of human adult dermal pericytes and their role in skin tissue regeneration .... 56
PROJECT TITLE: Use of Human-derived Feeders and Nutrients for Cultured Epithelial Autograph .......... 57
PROJECT TITLE: Use of Artificial Extracellular Matrices for Skin Regeneration ........................................ 58

NATIONAL TRAUMA RESEARCH INSTITUTE ............................................................................................ 59
PROJECT TITLE: Characterisation and manipulation of neurogenesis following experimental traumatic brain injury .................................................................................................................................. 59
PROJECT TITLE: Web 2.0 and linked data for healthcare knowledge ....................................................... 60
PROJECT TITLE: Time to haemorrhage control and outcome in severely injured patients ....................... 61
PROJECT TITLE: Measuring patterns of care in the management of spasticity in people with Traumatic Brain Injury (TBI) ............................................................................................................................................ 62
SCHOOL OVERVIEW

Monash University, through the Central Clinical School (CCS), offers a wide range of opportunities for students to continue their studies through the honours and post-graduate pathways.

The Central Clinical School focuses on translational research – incorporating insights developed from the laboratory bench research to therapies applicable at the patient bedside. Our Departments and affiliates have strong links with health care providers, ensuring that our research can move towards health outcomes as rapidly as possible. Our work provides the springboard for the development of new diagnostics and therapies for a wide range of human diseases – “where research makes a difference”.

The Honours program offers a career path into many areas of medical and clinical research. This booklet outlines many opportunities to undertake translational research.

Clinical and medical research areas include:

<table>
<thead>
<tr>
<th>Allergy</th>
<th>Cardiothoracic surgery</th>
<th>Kidney Disease</th>
<th>Psychiatry</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autoimmune diseases</td>
<td>Diabetes</td>
<td>Leukemia</td>
<td>Substance abuse</td>
</tr>
<tr>
<td>Bionic eye</td>
<td>Endocrine surgery</td>
<td>Lung diseases</td>
<td>Surgery</td>
</tr>
<tr>
<td>Bleeding disorders</td>
<td>Heart disease</td>
<td>Malaria</td>
<td>Thrombosis</td>
</tr>
<tr>
<td>Bone marrow &amp; lung transplantation</td>
<td>HIV Immunity</td>
<td>Myeloma</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>Burns</td>
<td>Immunology</td>
<td>Neurosurgery</td>
<td></td>
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<td>Cancer</td>
<td>Inflammation</td>
<td>Pathology</td>
<td></td>
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</tbody>
</table>

CCS is located primarily at The Alfred Hospital campus, Prahran, in the Alfred Medical Research and Education Precinct (AMREP). This precinct houses a number of world renowned research teams from Monash University, The Alfred Hospital, The BakerIDI Research Institute, The Burnet Institute and others. As such, this consortium offers a unique range of research strengths and interests aimed at progressing human health. The site offers research interests that range from the basic sciences to clinical applications.

How to use this booklet

This booklet lists topics and abstracts for research. Research interests have been grouped according to the Monash Departments or institutions. For further information regarding individual research projects, students should approach the laboratory head or nominated person associated with a particular project.

For general information regarding the Honours courses, please contact:

Laisa Tigarea, Student Services Officer  
E: laisa.tigarea@monash.edu or hdr.ccs@monash.edu  
T: +61 3 99030027

How to apply

Applications are completed centrally through Monash University. Prospective applicants should complete an application form, which can be downloaded or obtained from the faculty office. Further information on entry requirements and to download application form visit: http://www.med.monash.edu.au/bmedsci/

AMREP Honours Scholarships – apply for $6,000 scholarships to study at AMREP
PROJECTS BY DEPARTMENT

ALLERGY IMMUNOLOGY AND RESPIRATORY MEDICINE

Cardiothoracic Surgery

PROJECT TITLE: Impact of lymph node sampling and lymph node dissection in surgical resection on clinical outcomes in early stage non-small cell lung cancer (NSCLC)

SUPERVISOR/S: Dr Rob Stirling
Associate Professor Silvana Marasco

CONTACT EMAIL: r.stirling@alfred.org.au

DEPARTMENT: Allergy Immunology and Respiratory Medicine

PROJECT DESCRIPTION:

NSCLC is the fourth most common cancer in Victorians and is the leading cause of cancer mortality in Victoria. Treatment outcomes in NSCLC are largely determined by the adequacy of initial evaluation, diagnosis and staging followed by the application of appropriate treatment. Early stage NSCLC is amenable to surgical resection with very favourable early survival.

Surgical approach and resection in NSCLC may be affected by numerous factors including tumour type, staging, tumour location and comorbidity. Pathological staging achieved by evaluation of resected tissue in combination with lymph node sampling and pathological evaluation helps confirm adequacy of preoperative clinical staging. Lymph node dissection however may improve therapeutic impact of resection and positively impact outcomes including progression free survival and overall survival. A clinical evaluation of surgical approach in NSCLC may help refine surgical strategy in resection of NSCLC and help improve outcomes in this disease.

LABORATORY / PROJECT LOCATION: Allergy Immunology and Respiratory Medicine, Cardiothoracic Surgery, The Alfred Hospital
Medical Oncology

PROJECT TITLE: Impact of mutation analysis and mutation directed therapies on clinical outcomes in non-small cell lung cancer (NSCLC)

SUPERVISOR/S: Dr Rob Stirling
Dr Andrew Haydon

CONTACT EMAIL: r.stirling@alfred.org.au

DEPARTMENT: Allergy, Immunology and Respiratory Medicine

PROJECT DESCRIPTION:

NSCLC is the fourth most common cancer in Victorians and is the leading cause of cancer mortality in Victoria. The identification of specific driver mutations in genes contributing to control of cell cycle events provides an important and novel axis for intervention in NSCLC. The identification of specific mutations helps identify individuals who may benefit from specific mutation directed therapies.

The use of such mutation analysis and mutation directed therapies has potential to significantly impact survival in selected patients with NSCLC although the utility and effectiveness is as yet undescribed in our population. Clinical review of NSCLC patients, mutation testing and clinical impact are needed to help guide treatment selection in NSCLC.

LABORATORY / PROJECT LOCATION: Allergy Immunology and Respiratory Medicine, Medical Oncology, The Alfred Hospital
AUSTRALIAN CENTRE FOR BLOOD DISEASES (ACBD)
Serpins Biology Group

PROJECT TITLE: Disruption of the plasmin-antiplasmin system; a new approach to dissolving blood clots

SUPERVISOR/S: Dr Anita Horvath
Associate Professor Paul Coughlin

CONTACT EMAIL: Anita.Horvath@monash.edu
Paul.coughlin@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

There are many approaches to treating patients with thrombosis but most of these rely on anticoagulation to stop the growth of clots within blood vessels. Some treatments are aimed at dissolving blood clots by using tissue plasminogen activator. This is often successful but comes at a cost of major bleeding in many patients.

We are developing other ways of treating thrombosis patients by manipulating antiplasmin, the natural inhibitor of the clot dissolving enzyme plasmin. The protein antiplasmin possesses domains at its N- and C-termini which are important for the inhibition of plasmin. We have made mutations in antiplasmin and demonstrated that they slow down the inhibition of plasmin. It is hypothesised that the antiplasmin mutations will increase the efficiency of clot lysis by increasing plasmin activity. The aim of this project is to investigate the effects of these mutations in clot dissolution assays. These investigations will be extended into animal thrombosis models to determine if agents that block the antiplasmin-plasmin interaction will enhance fibrinolysis in vivo.

These studies will contribute to the development of small molecule inhibitors of antiplasmin which will be used to improve the clearance of blood clots in patients with thrombosis.

LABORATORY / PROJECT LOCATION: Serpins Biology/ACBD
PROJECT TITLE: **Interactions of GPIb-IX-V/GPVI in vascular systems: laboratory studies and clinical translation**

SUPERVISOR/S: **Associate Professor Robert Andrews**

CONTACT EMAIL: rob.andrews@monash.edu

DEPARTMENT: **Australian Centre for Blood Diseases**

PROJECT DESCRIPTION:

The unique platelet-specific receptor of the leucine-rich repeat (LRR) family, glycoprotein (GP)Ib-IX-V, and the immunoreceptor complex GPVI/FcRγ play a central role in immune/non-immune vascular biology at high shear stress, and control thrombus formation and procoagulant activity on activated platelets. GPIbα (the major ligand-binding subunit of GPIb-IX-V) coordinates interactions of von Willebrand factor (VWF), endothelial P-selectin, leukocyte αMβ2, and coagulation factors thrombin, coagulation factors XI and XII, and kininogen. GPVI/FcRγ binds collagen, and together with GPIb-IX-V mediates adhesion of circulating platelets to subendothelial matrix or activated endothelial cells, and controls thrombotic diseases such as heart attack and stroke, coagulopathy and pathology associated with congenital, non-immune or autoimmune thrombocytopenia. The major ligand-binding domain of GPIbα is the extracellular N-terminal sequence His1-Glu282, consisting of seven LRR (Leu36-Ala200), N- and C-terminal flanking sequences (His1-Ile35 and Phe201-Gly268), and an anionic sulfated sequence Asp269-Glu282. The ligand-binding domain of GPIbα is conformationally-sensitive to shear stress, and not amenable to analysis by short peptides or random scanning-mutagenesis. However, previous studies analysing cross-species human/canine chimeras of GPIbα have mapped binding sites for VWF under shear and inhibitory anti-GPIbα mAbs to specific structural regions. This approach is based on specificity of human VWF and murine mAbs for human (not canine) GPIbα, and identified LRR2-4 spanning an electronegative patch in Leu60-Glu128 as crucial for GPIbα-dependent adhesion to VWF. The aims of this project are to expand these approaches to investigate binding to GPIbα of other ligands including procoagulant factors such as FXI or FXII, localized to platelets via binding to GPIbα, with an ultimate goal of developing new therapeutic and diagnostic clinical tools.

LABORATORY / PROJECT LOCATION: **Vascular Biology Group**, Alfred Hospital Research and Education Precinct, Prahran
PROJECT TITLE: Interactions of GPIb-IX-V/GPVI in vascular systems: laboratory studies and clinical translation

SUPERVISOR/S: Associate Professor Robert Andrews

CONTACT EMAIL: rob.andrews@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

The unique platelet-specific receptor of the leucine-rich repeat (LRR) family, glycoprotein (GP)Ib-IX-V, and the immunoreceptor complex GPVI/FcRg play a central role in immune/non-immune vascular biology at high shear stress, and control thrombus formation and procoagulant activity on activated platelets. GPIba (the major ligand-binding subunit of GPIb-IX-V) coordinates interactions of von Willebrand factor (VWF), endothelial P-selectin, leukocyte αMβ2, and coagulation factors thrombin, coagulation factors XI and XII, and kininogen. GPVI/FcRg binds collagen, and together with GPIb-IX-V mediates adhesion of circulating platelets to subendothelial matrix or activated endothelial cells, and controls thrombotic diseases such as heart attack and stroke, coagulopathy and pathology associated with congenital, non-immune or autoimmune thrombocytopenia.

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The aims of this project are to expand these approaches to investigate binding to GPIba of other ligands including procoagulant factors such as FXI or FXII, localized to platelets via binding to GPIba, with an ultimate goal of developing new therapeutic and diagnostic clinical tools.

LABORATORY / PROJECT LOCATION: Vascular Biology Laboratory, ACBD
PROJECT TITLE: The radical world of platelets

SUPERVISOR/S: Dr Jane Arthur

CONTACT EMAIL: jane.arthur@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Platelets not only play a critical role in prevention of bleeding but have the capacity to regulate immune function. On the flipside, platelets are the cells responsible for thrombus formation leading to heart attack or stroke, and are involved in the metastasis of cancer cells. Understanding the signalling pathways responsible for the physiological versus pathological activities of platelets is critical to improving public health.

In recent years, it has become clear that reactive oxygen species (ROS) play a role in regulating platelet function: increased oxidative stress promotes platelet aggregation, while antioxidants such as quercetin (found in onions, tea and wine) inhibit platelet aggregation. We have found that the platelet collagen receptor, GPVI, which is one of the receptors involved in the initiation of thrombus formation, and the related immunological receptor FcγRIIa, generate a burst of intraplatelet ROS when either receptor is engaged. This ROS is important for downstream signalling pathways. This project will focus on delineating ROS-dependent signalling pathways in human platelets and determining whether targeted treatments can prevent pathological platelet activation.

Experiments will involve measurement of intracellular and extracellular reactive oxygen species production by human platelets, assessment of temporal changes in platelet function following activation, and determining the effect of antiplatelet therapies on platelet activity. Techniques will include human blood fractionation, flow cytometry, SDS-PAGE, western blotting and platelet aggregation.

LABORATORY / PROJECT LOCATION: Vascular Biology Laboratory, AMREP, Australian Centre for Blood Diseases, Level 6, 89 Commercial Rd Melbourne.
PROJECT TITLE: Blood flow regulates metalloproteinase activity on the surface of vascular cells

SUPERVISOR/S: Dr Elizabeth Gardiner

CONTACT EMAIL: elizabeth.gardiner@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Blood cells are at the frontline of any challenge to normal haemostatic balance and are exquisitely sensitive to changing rheological conditions. Damage to the endothelium lining the blood vessels, or a narrowing of the blood vessel lumen is sufficient to change the normal laminar flow conditions, altering the shear forces experienced by blood cells and triggering vascular cell activation.

Metalloproteases catalyse the regulated ectodomain shedding of membrane-anchored growth factors, cytokines and receptors and so have essential roles in fertilization, angiogenesis, neurogenesis, heart development and cancer. The activity of these metalloproteinases needs to be tightly controlled and in conditions of inflammation (arthritis, atherosclerosis) or on a metastasising cancer cell or in haematological diseases such as immune thrombocytopenia, these systems are dramatically upregulated.

We have discovered that by exposing vascular cell membranes such as platelets to changing blood flow conditions, cell surface metalloproteinases can become activated and trigger shedding of ectodomains from receptors that are important for cell adhesion and cellular activation. This has enormous implications for how the cell can then function to adhere to a damaged endothelium, activate and secrete important cytokines and other secondary mediators.

Working mainly with human blood, you will be trained in laboratory techniques including blood fractionation, flow cytometry, SDS-PAGE, western blotting, ELISA and fluorescence-based enzyme activity assays and your project will centre around understanding how these processes are routinely controlled, and what happens under conditions of disease, or inflammation such as seen in thrombosis, arthritis and atherosclerosis.

LABORATORY / PROJECT LOCATION: Vascular Biology Laboratory, AMREP, 6th floor 89 Commercial Rd, Melbourne at the Australian Centre for Blood Diseases
Fibrinolysis Research Unit

PROJECT TITLE: To determine the role of tissue type plasminogen activator (t-PA) in the progression and severity of multiple sclerosis

SUPERVISOR: Associate Professor Robert Medcalf  
Associate Professor Frank Alderuccio

CONTACT EMAIL: Robert.medcalf@monash.edu  
frank.alderuccio@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Multiple sclerosis (MS) is an immune-mediated chronic inflammatory disease that results in demyelination of the central nervous system (CNS). It causes acute focal demyelination and axonal loss and results in the formation of multi-focal sclerotic plaques. The cause of this disease is unknown and there is no cure. Recently, an enzyme system more commonly associated with the removal of blood clots has been implicated in MS. This system is the fibrinolytic enzyme system that controls the generation of the powerful protease plasmin from its precursor, plasminogen. The enzymes responsible for activating plasminogen are tissue type plasminogen activator (t-PA) and urokinase (u-PA). More recent findings have established important roles for this system, particularly t-PA and plasmin, in the CNS including memory and learning, motor function, modulation of the blood brain barrier and neurotoxicity. Some studies have reported impaired fibrinolysis in MS where the build up of fibrin deposits due to reduced t-PA and plasmin may exacerbate the disease. However, clinical studies have revealed that t-PA levels are massively increased in the cerebrospinal fluid of MS patients. Hence it is unclear what the significance and effect of these high levels of endogenous t-PA levels in MS patients. We have available a mouse model of experimental allergic encephalomyelitis (EAE) that recapitulates some features of MS. In this model, mice are immunized against a component of the myelin sheath resulting in the formation of autoreactive T-cells and anti-myelin antibodies and clinical features of MS over a two week period. This project will determine the relationship between levels of endogenous t-PA with the onset and progression of this MS-like disease. EAE will be generated in wild-type mice and changes in endogenous t-PA levels determined. EAE will also be generated in mice deficient in t-PA (t-PA−/− mice) and also in transgenic mice that selectively overexpress t-PA in the brain (T4 mice). These mice contain ~20-fold higher levels of active t-PA in the brain. Hence, this will allow a comparison to be made between the onset of MS-like symptoms in the absence of t-PA and in the presence of very high levels of t-PA. Disease severity will be determined using functional criteria and immunohistochemically. Disease severity will be determined using functional criteria and immunohistochemically. This is a new collaborative project between the ACBD and the Department of Immunology.

LABORATORY / PROJECT LOCATION: Fibrinolysis and Gene Regulation Laboratory  
Monash-Alfred Health
PROJECT TITLE: To understand how t-PA, a clot-busting drug given for the treatment of stroke, modulates cell permeability and blood brain barrier integrity

SUPERVISOR: Associate Professor Robert Medcalf

CONTACT EMAIL: Robert.medcalf@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Stroke is a major cause for death and disability in Australia and the western world. About 80% of stroke cases result from an occlusive blood clot which deprives parts of the brain from oxygen and nutrients, leading to neuronal cell death and severe functional outcomes.

To date, the only acute pharmacological intervention approved for treatment of ischaemic stroke is tissue-type plasminogen activator (t-PA), a blood protease which cleaves the zymogen plasminogen into the potent clot-busting enzyme plasmin. Unfortunately, t-PA treatment is strictly limited to 4.5 hours from stroke onset as later use increases the risk for intra-cerebral bleeding, a complication which outweighs the potential benefit of t-PA.

In recent years t-PA was also found to have a direct weakening effect on the blood vessels of the brain. These unique blood vessels, also termed the Blood-Brain barrier (BBB), are comprised of specialized endothelial cells supported by astrocytes, pericytes and other cells to form a tight barrier which carefully regulates the brain environment. The current hypothesis suggests that t-PA causes changes to cells of the BBB, contributes to loss of BBB integrity and therefore promotes bleeding during t-PA treatment in stroke. There is an urgent need to further understand this process to allow improvement of stroke treatment.

This honours project will investigate how t-PA and plasmin affect brain endothelial cells (BEC) in culture. We will generate primary BEC cultures from mice brains and expose them to t-PA and plasmin under normal conditions or after deprivation of oxygen and glucose (which mimics stroke in vitro). We will test how t-PA and plasminogen modulate BEC viability, tight-junction structure, signaling pathway and overall morphology. We will then assemble BECs on porous membranes and culture them with or without astrocytes (their natural in vivo counterparts). This will allow us to test if t-PA and plasmin affect BECs directly or via astrocytes, an important question which is currently under debate. Finally, we will grow BECs under flow of culture medium and observe if the cessation of flow sensitizes BECs to the actions of t-PA. During the project we will give special emphasis on cell imaging and gain experience in the use of microscopes.

This project will add further to our understanding of the mechanisms by which t-PA influences integrity of the BBB and may ultimately provide new insights to improve the safety of stroke treatment.

LABORATORY / PROJECT LOCATION: Fibrinolysis and Gene Regulation Laboratory, Monash-Alfred Health
PROJECT TITLE: Using forward genetics to understand the regulation of red blood cells

SUPERVISOR/S: Associate Professor David Curtis
Professor Stephen Jane

CONTACT EMAIL: David.curtis@monash.edu
Stephen.jane@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Chemical mutagenesis has been used to identify genetic pathways in lower organism for more than 20 years. We have recently used ENU mutagenesis in the mouse to generate mouse lines with defects in red blood cells.

This project will characterise one of these mouse mutants - RBC21. Techniques will include SNP arrays and next generation sequencing to identify the gene mutation together with functional assays of erythropoiesis including flow cytometry, cell culture and in vivo animal studies such as bone marrow transplantation.

LABORATORY / PROJECT LOCATION: Red Cell Research Group, Division of Blood Cancers, Australian Centre for Blood Diseases
Level 1, AMREP Centre
Stem Cell Research Group

PROJECT TITLE:  
Self-renewal mechanisms in haematopoietic and leukemia stem cells

SUPERVISOR:  
Dr Stephen Ting

CONTACT EMAIL:  
stephen.ting@monash.edu

DEPARTMENT:  
Australian Centre for Blood Diseases, Division of Blood Cancers

PROJECT DESCRIPTION:

The daily and lifelong regeneration of the blood system is dependent on haematopoietic stem cells (HSCs), which have the unique ability to proliferate and differentiate into all blood cellular elements (multipotency) whilst maintaining (via self-renewal) or preserving (through quiescence) their HSC identity. These unique stem cell properties of self-renewal, quiescence and multipotency may be mechanisms by which normal HSCs and cancer cells are maintained or expand. This project aims to understand the molecular pathways that govern HSC self-renewal with the longer-term goal of applying this knowledge to the clinical settings of ex-vivo HSC expansion for bone marrow transplant and impairing cancer cell growth.

A mechanism by which self-renewal can be achieved is via the segregation of cell fate determinants at the time of HSC division. During this process, the HSC has an intrinsic cell orientation (or polarity). Via a candidate gene approach focusing on genes that are functional in cell polarity and an in vivo HSC expansion assay, we have identified novel genes that are able to alter HSC fate.

Two projects are available, concentrating respectively on the Ap2a2 and Gpsm2 genes, to investigate the molecular details by which these two genes achieve HSC self-renewal in both mouse and human HSCs. Techniques used include isolation of HSCs for cell culture, live cell microscopy, and mouse bone marrow transplantation.

We shall also initiate translational studies to study whether these two genes can expand human HSCs in human to mouse xenografts and/or alter the clinical outcome of various mouse models of blood cancers such as leukemia and lymphoma.

LABORATORY / PROJECT LOCATION:  
Stem Cell Research Group, Division of Blood Cancers/Monash-Alfred Health
PROJECT TITLE: Poisoning cancer stem cells by treatment with arsenic

SUPERVISORS: Dr Cedric Tremblay
Associate Professor David Curtis

CONTACT EMAIL: Cedric.tremblay@monash.edu
David.curtis@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Acute Lymphoblastic Leukemia (ALL), a cancer of primitive lymphoid cells, is the most common cause of cancer-related death in children. Cure by current therapeutic strategies require several years of chemotherapy but death from recurrence (known as relapse) of the leukemia still occurs in 25% of cases. Relapse is most likely due to quiescent cancer stem cells that are resistant to current chemotherapies. Using a mouse model of ALL, this project will test the ability of arsenic trioxide to kill cancer stem cells. The rationale for this study is that arsenic trioxide is able to promote the degradation of PML bodies, small nuclear bodies that contain the homeobox protein Hhex. We have recently shown genetic deletion of Hhex in our model of ALL enhances sensitivity of cancer stem cells to radiation. Therefore, we postulate that Arsenic trioxide will be able to target Hhex, which will sensitize the cancer stem cells to normal chemotherapy.

Cancer stem cells will be isolated from the mouse model of ALL using flow cytometry. Isolated cells will be co-stained with PML and Hhex antibodies for immunofluorescence using confocal microscopy. Leukemia cell lines derived from the ALL mice will be used to examine the effect of arsenic trioxide on PML bodies and expression of Hhex. Finally, ALL mice will be treated with arsenic trioxide and then examined to determine the number of cancer stem cells. The ultimate goal of this project is to generate data necessary for testing of arsenic trioxide in phase I clinical trials.

During this honours project, the student will develop expertise in flow cytometry, confocal microscopy, cell culture and develop an understanding of the use of mouse models for cancer research.

LABORATORY / PROJECT LOCATION: Stem Cell Research group, Division of Blood Cancers, Australian Centre for Blood Diseases
Level 1, AMREP Centre
PROJECT TITLE: Protein arginine methyltransferase 5 – a new target for lymphoid malignancies

SUPERVISORS: Dr Stefan Sonderegger
Dr Tiffany Khong

CONTACT EMAIL: Stefan.Sonderegger@monash.edu
Tiffany.khong@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:
Protein arginine methyltransferase 5 (PRMT5) is an enzyme that symmetrically dimethylates specific arginines on histones (H2AR3, H3R8 and H4R3) and non-histone proteins such as p53. In general, this modification on histones leads to closed chromatin and gene repression whilst its effect on non-histone proteins is unknown. PRMT5 is aberrantly expressed in a number of different cancers of the lymphoid system including chronic lymphocytic leukemia and mantle cell lymphoma. However, increased expression may be a bystander effect with neither relevance to the underlying biology of the disease nor a useful therapeutic target.

This project will use a number of tools developed in the laboratory to determine the relevance of PRMT5 to multiple myeloma (MM), a cancer of mature lymphoid cells known as plasma cells. Tools will include immunofluorescence by confocal microscopy for PRMT5 localisation, short hairpin technology to decrease expression in MM cells, testing of small molecule inhibitors of PRMT5 on MM cells, and the use of genetic deletion or doxycycline knockdown of PRMT5 in animal models. The student will develop expertise in a wide range of molecular (shRNA, qPCR, cloning) and cell biology (cell culture, flow cytometry, microscopy including confocal) techniques as well as develop an understanding of how mouse models can be used for cancer research.

LABORATORY / PROJECT LOCATION:
Stem Cell Research group, Malignant Haematology and Stem Cell Transplantation Group, Australian Centre for Blood Diseases
Level 1, AMREP Centre
PROJECT TITLE: Polycomb genes in stem cells and myelodysplasia

SUPERVISOR/S:  
Dr Christopher Slape  
Associate Professor David Curtis

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Myelodysplasia (also known as myelodysplastic syndromes, or MDS) is a clonal haematopoietic stem cell disorder characterised by ineffective hematopoiesis, leading to reduced blood cell counts in the patient. MDS are among the most common hematological malignancies, and existing therapies are not curative and only effective in a subset of patients. Therefore, research into this disease carries the possibility of making major real world impact.

Recent work has demonstrated that mutations in the \( EZH2 \) and \( ASXL1 \) genes are frequent in MDS. These two genes are the catalytic components of separate polycomb complexes (PRC2 and PR-DUB, respectively), famous for their repressive role of Hox genes in differentiated cells. \( EZH2 \) catalyses the addition of the repressive epigenetic histone mark H3K27me3, and \( ASXL1 \) catalyses the removal of the same mark. The \( EZH2 \) mutations are particularly interesting, as in MDS they are loss-of-function mutations, but in lymphoid leukemia there exist presumed gain-of-function mutations, and there is very recent evidence to support that acute myeloid leukemia is absolutely dependent on the normal function of PRC2. This paradox designates the role of polycomb genes in haematopoietic stem cells, differentiation, and myelodysplasia as a research topic of enormous interest.

Resources at our disposal for investigating these questions include our MDS mouse model (the \( NUP98-HOXD13 \) model), mouse models genetically deficient in \( Ezh2 \) and related genes, short hairpin RNA knockdown of \( Ezh2, Asxl1 \) and other polycomb group genes, and genome-wide epigenetic assays. The student involved will engage these resources to manipulate the expression and function of the polycomb genes and examine the effect on haematopoietic stem cell phenotype using in vitro and in vivo analysis. The student will be instructed in molecular, cellular and animal techniques and apply these to a very significant and actively studied area of clinical haematology research.

LABORATORY / PROJECT LOCATION:  
Stem Cell Research group, Division of Blood Cancers, ACBD
Level 1, AMREP Building
The Alfred Campus
PROJECT TITLE: Targeting heat shock response as a potential therapeutic target in multiple myeloma

SUPERVISOR/S: Professor Andrew Spencer
Dr Tiffany Khong

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Multiple myeloma (MM), the second most prevalent blood cancer (10%) after non-Hodgkin's lymphoma, is a clonal malignancy of plasma cells. MM is characterised by the presence of a monoclonal protein in serum and/or urine, widespread osteolysis, renal failure and anaemia. MM remains incurable despite significant advances in treatment over the past decade with successive relapses manifesting increasing drug resistance, invariably culminating in uncontrollable and fatal disease. New treatments are constantly sought to overcome this disease.

We are interested in the modulation of the master regulator of heat shock response, heat shock transcription factor 1 (HSF-1). HSF-1 controls the induction of heat shock proteins (HSPs) which act as molecular chaperones restoring and maintaining normal folding and intracellular trafficking of their cognate proteins. Under stress conditions, the HSF-1/HSP-controlled program is advantageous for normal cells but activation of this program can also shield malignant cells from oncogene-induced cellular stress or drug induced stress under therapeutic intervention. Inhibition of HSPs by agents such as HSP90 inhibitor (AUY922, HSP990 or geldanamycin) leads to up regulation of HSP70, HSP40 and HSP27 which protects malignant cells from apoptosis and eventual drug resistance. Studies have revealed over-expression of HSF-1 in primary MM samples but not in normal plasma cells or in monoclonal gammopathy of undetermined significance (MGUS); pre MM stage. Eliminating the master regulator by siRNA knockdown or HSF-1 inhibitor may represent an attractive therapeutic strategy in MM. Therefore the aim of this study is to ascertain if HSF-1 plays a significant role in MM pathogenesis and does removal of HSF-1 sensitises malignant cells to conventional and novel chemotherapeutics.

LABORATORY / PROJECT LOCATION: Malignant Haematology and Stem Cell Transplantation Group, ACBD
Level 1, AMREP Building
The Alfred Campus
PROJECT TITLE: Investigation of synergistic drug combinations with a novel JAK inhibitor

SUPERVISOR/S: Professor Andrew Spencer
Dr Tiffany Khong

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Multiple myeloma (MM) is an incurable clonal B cell malignancy localised to the bone marrow. It is a heterogeneous disease characterised by de novo drug resistance. The emergence of novel chemotherapy agents in recent times has greatly increased the overall survival of patients with MM. However drug resistance is still eventually seen in all patients with the disease. It is because of this that novel combination approaches need to be developed. Janus kinases (JAKs) are important signal transduction molecules involved in many pathways that are exploited by MM cells. Here we pre-clinically evaluate a novel JAK inhibitor for the treatment of myeloma.

This project will aim to identify synergy between the JAK inhibitor and other novel agents as well as conventional chemotherapeutic agents using a panel of human myeloma cell lines within the laboratory. It will characterise the impact of drug scheduling with the synergistic combinations. The project will also further determine which types of MM cells are more sensitive to treatment in order to better understand which patients will respond well to this treatment. The project will also endeavour to determine the effect of successful combinations on primary patient myeloma cells. This project will allow the student to learn various interesting laboratory techniques while developing their analytical and independent research skills.

LABORATORY / PROJECT LOCATION: Malignant Haematology and Stem Cell Transplantation Group, ACBD
Level 1, AMREP Building
The Alfred Campus
PROJECT TITLE: Minimal Residual Disease in Multiple Myeloma (LEOPARD study)

SUPERVISOR/S: Professor Andrew Spencer  
Dr Tiffany Khong  
Dr Anna Kalff

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Multiple myeloma (MM) a clonal malignancy of plasma cells is the second most prevalent blood cancer (10%) after non-Hodgkin Lymphoma. Despite recent advancements, MM remains an incurable disease, except for patients who receive allogeneic transplantation who can achieve a prolonged disease free survival and possibly cure.

In patients with MM, achieving a complete remission (CR) is an important prognostic factor. Treatment regimens incorporating novel agents are associated with higher rates of CR compared to previous standard regimens. Data from studies using highly sensitive techniques such as PCR and multiparameter flow cytometry (MPFC) suggest that the more stringent the definition used for CR the greater the prognostic significance of achieving that degree of response: achievement of molecular remission is associated with increased long-term disease-free survival.

Clinical relevance of minimal residual disease (MRD) investigation is well established for several haematologic malignancies, however only preliminary results have been reported in MM.

This project aims to quantify sequential minimal residual disease (MRD) in patients with MM who are post autologous stem cell transplantation and on lenalidomide and alternate day prednisolone maintenance (as part of the LEOPARD study – 60 patients). This will be done using allele specific oligonucleotide real time quantitative PCR (ASO-RQ-PCR) on bone marrow aspirate and trephine (BMAT) samples to compare the yield from both types of samples. The utility of the molecular MRD technique will be compared to MPFC, which will also be performed on the aspirates.

Methods will involve: extraction of genomic DNA from BMATs for amplification of IGH gene rearrangements (VDJH and DJH), sequencing of these rearrangements, patient specific ASO primer design, then RQ-PCR and subsequent quantification of MRD in sequential samples.

This project may be expanded to adapt this method to monitoring MRD in patients with MM who are post allogeneic transplant by PCR on peripheral blood (plasma/serum).

LABORATORY / PROJECT LOCATION: Malignant Haematology and Stem Cell Transplantation Group, ACBD  
Level 1, AMREP Building  
The Alfred Campus
PROJECT TITLE: Evaluation of a novel beta-catenin inhibitor in multiple myeloma

SUPERVISOR/S: Professor Andrew Spencer
Dr Tiffany Khong

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Multiple myeloma (MM) is a plasma cell malignancy and despite advances in the treatment of this disease, MM remains incurable. Beta-catenin is over expressed in various human tumours including MM and is known to play a critical role in cell survival. It is a 92kD protein and is usually found in the cytoplasm of the cell but nuclear accumulation of the protein is observed in cancers. This protein is the downstream effector of the Wnt signaling pathway and is important for cell proliferation, cellular adhesion and signal conduction.

The aims of this project are to elucidate the potential of a beta-catenin inhibitor, BC2059, as a single agent and in combination with immunodulators in MM. We will also seek to identify biomarkers by microarray to aid the development of associated treatments for MM, patient screening and prognosis. Experimentally we will utilise a panel of human myeloma cell lines and primary myeloma samples from consented patients to assess the anti-MM effect of the inhibitor alone and in combination with novel and conventional chemotherapies. The relative effects of cell to cell contact versus soluble factor mediated interactions will be evaluated via co-culture assays, a system optimised in our laboratory. Finally we plan to examine the anti-MM activity in the 5T33 murine model of systemic myelomatosis. The model is a highly reproducible tumour implant model of MM that manifests bone marrow infiltration, paraprotein production and osteolysis thus closely resembling human MM. The primary end-point in the murine model is time to euthanasia, usually mandated by hind-limb paralysis. A promising efficacy of the novel compound may lead to a Phase 1 clinical trial.

LABORATORY / PROJECT LOCATION: Malignant Haematology and Stem Cell Transplantation Group, ACBD
Level 1, AMREP Building
The Alfred Campus
PROJECT TITLE: Identification of optimal proteasome inhibitor for multiple myeloma therapy

SUPERVISOR/S: Professor Andrew Spencer
Dr Sridurga Mithraprabhu

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Multiple myeloma (MM) is a malignant plasma cell disorder characterised by the production of monoclonal proteins (paraprotein), osteolytic lesions, renal failure and anaemia. It is the second most prevalent blood cancer and remains incurable owing in large due to the development of drug resistance to chemotherapies currently available in clinic. Adoption of high-dose chemotherapeutic strategies and the emergence of novel therapeutics (thalidomide, lenalidomide, bortezomib) over the past 15 years have improved the duration of survival for patients, however, the median survival remains less than 10 years irrespective of the prognostic characteristics or age at diagnosis.

Targeting the ubiquitin-proteasome pathways through utilisation of proteasome inhibitor, bortezomib, has shown to be an effective anti-MM agent. Second generation proteasome inhibitors with novel properties such as NPI-0052 and carfilzomib are currently being evaluated for approval as anti-MM agents for relapsed and refractory MM. This project will examine two unique proteasome inhibitors, oprozomib and ONX0914, in comparison with bortezomib and carfilzomib to identify the optimal proteasome inhibitor for MM therapy. The impact of these inhibitors on cell proliferation and apoptosis, and the mechanism of action will be evaluated utilising a panel of human myeloma cell lines and consented primary MM patient samples. Determination of the most favourable proteasome inhibitor will help to further optimise anti-MM therapy.

LABORATORY / PROJECT LOCATION: Malignant Haematology and Stem Cell Transplantation Group, ACBD
Level 1, AMREP Building
The Alfred Campus
Leukemia Research Laboratory

PROJECT TITLE: Therapeutic targeting of PI3K in Acute Myeloid Leukaemia

SUPERVISOR/S: Dr Mark A Guthridge (Monash University)  
Dr Andrew Wei (Alfred Hospital)

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Cancer cells arise because of a loss of regulation between cell survival and proliferation. PI3K is a pivotal regulator of both cell survival and proliferation and constitutive activation of the PI3K pathway represents one of the most common oncogenic events in cancer. By comparing the cell survival pathways in normal non-transformed cells to those in leukemic cells, we have identified a “PI3K cell survival network” that is deregulated in human AML. Biochemical and functional mapping of this network has led to the identification of key targets that govern cell survival in AML cells. We now have a drug development program to block key components of this survival network in order to induce apoptosis (programmed cell death) in AML cells but not normal bone marrow cells. These studies have the potential to lead to novel therapeutics for the treatment of AML in the future.

LABORATORY / PROJECT LOCATION: Leukaemia Research Laboratory, Australian Centre for Blood Diseases, Monash University and Alfred Hospital
PROJECT TITLE: Identifying novel synergistic drug combinations in Acute Myeloid Leukaemia

SUPERVISOR/S: Dr Mark A Guthridge (Monash University)
Dr Andrew Wei (Alfred Hospital)

CONTACT EMAIL: Mark.guthridge@monash.edu
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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:
Chemotherapy fails to discriminate between normal and malignant cells. Leukaemic stem cells may evade chemotherapy induced cell death by activating oncogenic signalling pathways causing chemoresistance. Identification of kinase inhibitors which target key mechanisms regulating leukaemic stem cell survival represents an important goal for improving clinical outcomes. Our group has novel strategies to systematically identify synergistic drug combinations with clinical potential in AML. This project will utilize inducible lentiviral vectors expressed in a variety of primary AML cell lines to neutralise complementary Bcl-2 pro-survival members in leukaemia. These “sensitised” lines will then be screened for synergy using a drug discovery chemical library enriched for compounds known to target oncogenic kinases. This “synthetic lethal” screen will unravel cooperating pathways regulating canonical survival pathways in leukaemia that will provide new leads for drug development and clinical trials.

LABORATORY / PROJECT LOCATION: Leukaemia Research Laboratory, Australian Centre for Blood Diseases, Monash University and Alfred Hospital
PROJECT TITLE: Investigating the role of inositol polyphosphate phosphatases in Acute Myeloid Leukaemia

SUPervisor/S: Dr Mark A Guthridge (Monash University)  
                   Dr Andrew Wei (Alfred Hospital)

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Department: Australian Centre for Blood Diseases

Project Description:
AML is dominated by molecular lesions affecting pathways governing differentiation, proliferation and survival. These include activating mutations of tyrosine kinases such as FLT3 (25% AML), c-KIT (30% of core-binding factor AML) and RAS (9-14% AML). These kinases activate the downstream PI3K-Akt-mTOR signalling axis, with several studies showing that the PI3K/Akt pathway is deregulated in the majority of AML. Remarkably, the molecular basis for PI3K-Akt activation in AML remains largely unknown. In contrast to many solid cancers, acquired mutations affecting PI3K and AKT have not been identified in AML. AKT activity is regulated by a family of 3-, 4- and 5- inositol polyphosphate phosphatases (INPPs), with hypofunction of INPPs causing AKT activation an emerging theme in human malignancy. The role of INPPs in human AML has not been systematically studied to date and will be the focus of this honours project. A variety of molecular biology and animal models will be used with an emphasis on deciphering pathology identified in primary human AML samples.

Laboratory / Project Location: Leukaemia Research Laboratory, Australian Centre for Blood Diseases, Monash University and Alfred Hospital
Thrombosis Research Unit

PROJECT TITLE: Investigating new approaches to dissolve blood clots

SUPERVISOR/S: Dr Simone Schoenwaelder
Professor Shaun Jackson

CONTACT EMAIL: Simone.schoenwaelder@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Blood platelets play a critical role in the development of occlusive arterial blood clots (thrombi), precipitating diseases such as heart attack and ischaemic stroke. The rapid reperfusion of occluded blood vessels to minimise tissue death is a key treatment goal in patients suffering heart attack and stroke, with the administration of thrombolytic therapy an important means of establishing reperfusion. This is usually achieved through administration of fibrinolytic agents modelled on tissue-type plasminogen activator (tPA). However, thrombolytic therapy is not without its limitations, with lysis resistant blood clots, as well as hemorrhage presenting as major complications.

One of the main factors delaying reperfusion and increasing the risk of reocclusion of cerebral vessels is the presence of platelets in arterial thrombi. Platelets inhibit thrombolysis through multiple mechanisms and numerous preclinical and clinical studies have demonstrated the benefits of adjunctive anti-platelet therapy to enhance cerebral reperfusion and reduce reocclusion following thrombolysis. Unfortunately in stroke patients, the benefits of combined antiplatelet and thrombolytic therapy are partially offset by the increased risk of life-threatening intracerebral bleeding, limiting the widespread use of this approach.

Our laboratory has recently demonstrated that inhibitors of PI 3-kinase (PI3Kβ), when administered alone or with tPA, are highly effective at promoting thrombus dissolution, without markedly increasing tail bleeding times. These results raise the possibility that PI3Kβ inhibitors may represent a safe and effective adjuvant therapy for the treatment of stroke. This project will examine the potential use of PI3Kβ inhibitors as adjuvant therapy for stroke and compare their safety and efficacy with that of currently used anti-platelet agents. Studies will involve the use of in vivo models of thrombosis and thrombolysis, in vitro flow-based assays, genetic mouse models and state-of-the-art imaging systems (confocal microscopy, intravital microscopy), complemented with in vitro analysis of platelet function. These studies will not only provide important insight into our understanding of blood clot formation, but may also lead to new approaches to regulate the size and stability of blood clots forming in the body, providing major clinical benefit in the delivery of thrombolytic therapy (blood clot removal).

LABORATORY / PROJECT LOCATION:
Thrombosis Research Unit
Australian Centre for Blood Diseases
AMREP, Alfred Hospital
PROJECT TITLE:  Defining the function of thrombin receptors on human platelets during thrombosis

SUPERVISOR/S:  Dr Justin Hamilton

CONTACT EMAIL:  justin.hamilton@monash.edu

DEPARTMENT:  Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

This project will investigate the role of the platelet thrombin receptors in thrombosis. Over the past decade, we have shown that thrombin activates platelets via protease-activated receptors (PARs) and that PAR-deficient mice are protected against thrombosis but do not exhibit spontaneous bleeding. Our work indicates the potential of PARs as targets for antithrombotic therapy in humans and has led to the development of PAR antagonists – two of which are currently in Phase 3 clinical trials for the prevention of arterial thrombosis. There are two thrombin receptors on human platelets, PAR1 and PAR4, yet current antagonists target only PAR1. The function of PAR4 during platelet activation and thrombus formation is poorly understood, in large part due to the lack of effective antagonists against this receptor. To address this, we have recently developed an effective and highly specific PAR4 antagonist. This project will use this newly developed reagent to determine the contribution of PAR4 to human platelet activation and subsequent thrombus formation and to determine whether PAR4 antagonists will have utility in the prevention of arterial thrombosis in humans.

LABORATORY / PROJECT LOCATION:  Thrombosis Research Unit
Australian Centre for Blood Diseases
AMREP
Alfred Hospital
PROJECT TITLE:  What turns you on? Determining activation signals for platelets during thrombosis

SUPERVISOR/S:  Dr Justin Hamilton

CONTACT EMAIL:  justin.hamilton@monash.edu

DEPARTMENT:  Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Thrombosis is the pathological formation of blood clots leading to heart attack and stroke. Platelets are the blood cells responsible for forming these blood clots, but they must be activated before they will do so. Therefore we are interested in determining what controls the activation of platelets during the formation of blood clots. This project will involve the first studies of the role of a family of intracellular signalling enzymes, the Class II phosphoinositide 3-kinases (PI3K-C2s), in regulating platelet function.

We have previously shown that a Class I PI3K is important for platelet activation during thrombosis. We developed selective inhibitors of this enzyme and showed them to be highly effective at preventing arterial thrombosis in rodents and in human models. These inhibitors are currently undergoing Phase II clinical trials, indicating the potential of this family of platelet signalling enzymes as targets for novel antithrombotic therapy. In an extension of our earlier studies on the Class I PI3Ks, we have recently discovered that two isoforms of the Class II PI3Ks, PI3K-C2α and PI3K-C2β, are also important for normal platelet function. Specifically, we have produced a series of PI3K-C2-deficient mice and observed that they have dysregulated platelet function in vitro and in vivo (e.g. see figure). These promising findings will be further examined in this project in which we aim to define the contribution of PI3K-C2s to platelet function in order to determine whether inhibition of PI3K-C2s is likely to be an effective strategy for the prevention of arterial thrombosis in humans. The specific aim of this project is to determine which platelet activation signals are responsible for stimulating this important activity of the PI3K-C2s.

LABORATORY / PROJECT LOCATION:  Thrombosis Research Unit
Australian Centre for Blood Diseases
AMREP
Alfred Hospital
PROJECT TITLE: Investigation of the functional interplay between platelets and Neutrophils

SUPERVISOR/S: Dr Yuping Yuan

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

The adhesion of platelets and leukocytes to sites of vascular injury or inflammation represents one of the fundamental defence mechanisms. These adhesive interactions are critical for the arrest of bleeding, vascular repair mechanisms, wound healing and for innate immune responses. In addition to these physiological functions, dysregulated platelet-leukocyte adhesive interactions have also been implicated in disease, including atherosclerosis, ischaemia-reperfusion injury and a number of inflammatory disorders. However, the mechanisms behind platelet-mediated leukocyte recruitment have yet to be fully defined.

Studies from our laboratory have identified a novel proinflammatory function for platelets, leading to enhanced neutrophil adhesion and activation.

We have demonstrated that a specific form of platelet cell death, termed programmed platelet necrosis, leads to a selective increase in platelet proinflammatory function. Using mice that are resistant to apoptotic cell death (Bak:Bax knock-out mice) or necrosis (Cyclophilin D knock-out mice), in combination with in vivo models of inflammation and ischaemia-reperfusion injury, we will investigate the role of specific platelet cell death pathways in platelet proinflammatory function. This project utilises a wide range of techniques including in vitro perfusion assays, flow cytometry, confocal microscopy and in vitro models of thrombosis and ischaemia reperfusion.

LABORATORY / PROJECT LOCATION:

Thrombosis Research Unit
Australian Centre for Blood Diseases
AMREP
Alfred Hospital
PROJECT TITLE: Investigating platelet hyperactivity in diabetes

SUPERVISOR/S: Professor Shaun Jackson

CONTACT EMAIL: shaun.jackson@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Diabetes, with impaired glucose tolerance and associated dyslipidaemia, is an important disease affecting up to 5% of the Australian community, and is recognised as a major risk factor for cardiovascular disease. Acute cardiovascular events in diabetic patients are typically caused by the development of an arterial thrombosis at sites of atherosclerotic plaque rupture. For reasons that have not been clearly defined, there is often an exaggerated accumulation of platelets and fibrin at sites of vessel injury in diabetic patients, leading to the development of pathological thrombi and the occlusion of blood vessels.

We have recently defined a new pathway that is dysregulated in diabetes, leading to increased platelet reactivity. This project aims to define the mechanisms by which this pathway controls platelet function and examine new approaches to reduce the enhanced reactivity of diabetic platelets. These studies will utilise a combination of techniques including characterisation of the platelets from mouse models of hyperlipidemia and diabetes, platelet functional assays, flow cytometry, confocal microscopy and in vitro models of thrombosis.

LABORATORY / PROJECT LOCATION:

Thrombosis Research Unit
Australian Centre for Blood Diseases
AMREP
Alfred Hospital
PROJECT TITLE: Investigating a new anti-clotting approach: Regulation of platelet adhesion and thrombus formation by the GPIb/V/IX adhesion receptor

SUPERVISOR/S: Professor Shaun Jackson

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DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Adhesion of circulating blood platelets to an injured blood vessel results in the formation of a blood clot. When this occurs in diseased vessels (eg. atherosclerosis), this normally protective cascade of events results in arterial thrombosis, which is responsible for heart attack and ischaemic stroke, which together, are the biggest cause of death in industrialised societies. One platelet receptor, the glycoprotein (GP) Ib/V/IX complex plays a major role in promoting both haemostasis and thrombosis. GPIb/V/IX has unique binding characteristics, allowing efficient platelet capture from the bloodstream, even under the most rapid blood flow conditions. This initial step in the haemostatic process is important in mediating subsequent platelet activation required for blood clot formation. Factors controlling the function of this receptor are therefore critical to the regulation of the normal clotting function of platelets as well as being potentially important in the development of thrombosis.

The GPIb/V/IX receptor is composed of 4 subunits; GPIbα, GPIbβ, GPIX and GPV. Current evidence demonstrates that the cytoplasmic tail of GPIbα plays an important role in platelet adhesion and thrombus formation through its interaction with cytoskeletal and signalling proteins. In recent studies we have developed a transgenic mouse expressing mutant forms of the GPIbα protein which no longer interact with filamin A. This project will involve characterisation of the platelets from these mice using a wide range of techniques including platelet functional assays, flow cytometry, confocal microscopy and in vitro models of thrombosis. These studies will establish the role of the GPIbα-filamin A interaction in platelet adhesion and thrombus formation which may represent a novel target for the development of new antithrombotic drugs.

LABORATORY / PROJECT LOCATION:
Thrombosis Research Unit
Australian Centre for Blood Diseases
AMREP
Alfred Hospital
PROJECT TITLE: Mitochondrial dynamics – a matter of platelet ‘life or death’

SUPERVISOR/S: Dr Simone Schoenwaelder

CONTACT EMAIL: simone.schoenwaelder@monash.edu

DEPARTMENT: Australian Centre for Blood Diseases

PROJECT DESCRIPTION:

Mitochondria represent the powerhouse of the cell, critical for energy production, calcium homeostasis, redox control and certain metabolic pathways. Mitochondrial viability is therefore fundamental to cell survival, with perturbations in the integrity of the outer or inner mitochondrial membrane a key trigger leading to apoptotic or necrotic cell death, respectively. Although platelets represent anucleate fragments of megakaryocytes, they possess a high energy requirement and are thus mitochondria-rich, acquiring 80% of their resting energy (ATP) requirements via oxidative phosphorylation. Increasing evidence supports an important role for mitochondrial function in regulating platelet survival and function, through the initiation of apoptotic and necrotic cell death pathways. First, mitochondrial viability determines the lifespan of platelets in the bloodstream, with the clearance of aging platelets initiated by a Bak/Bax-mediated intrinsic apoptosis. Second, a key component of the inner mitochondrial membrane - cyclophilin D (CypD), which is essential to the formation of the mitochondrial permeability transition pore (MPTP) and the initiation of the necrotic cell death pathway, has been implicated in the platelet activation process. Third, platelets stored ex vivo for transfusion purposes undergo functional deterioration associated with cellular features of both apoptosis and necrosis, a phenomena known as the Platelet Storage Lesion (PSL). Taken together, these studies raise the possibility that multiple mitochondrial cell death pathways may function in platelets to regulate distinct aspects of platelet function and survival.

Despite the importance of mitochondria for platelet viability and function, and the potential for mitochondrial cell death pathways to impact upon haemostasis and thrombosis, the existence of mitochondrial regulators in platelets and their contribution to platelet function remain ill-defined. We have generated novel mouse models that have a selective defect in apoptosis, necrosis, or both apoptosis and necrosis, restricted to the megakaryocyte and platelet lineage. Utilising these mice, in combination with pharmacological agents that induce apoptosis in human and mouse platelets, we will examine for the first time the relative contribution(s) of apoptotic and necrotic cell death pathways on platelet survival and procoagulant function.
BURNET INSTITUTE

CENTRE FOR IMMUNOLOGY

PROJECT TITLE: Understanding the targets and mechanisms of human immunity to malaria

SUPERVISOR/S: Professor James Beeson
Dr Jack Richards

CONTACT EMAIL: richards@burnet.edu.au

DEPARTMENT: Burnet Institute

PROJECT DESCRIPTION:

This project will focus on identifying the key antigens that are targets of protective immunity against malaria and understanding the mechanisms mediating immunity, which includes antibodies and cell-mediated responses. This knowledge is crucial for the development of effective vaccines against malaria. The project may combine detailed studies of immune responses with clinical and population studies in Africa, Asia, and Papua New Guinea. It will examine how immune responses protect children from malaria, or protect pregnant women and their developing babies from the devastating consequences of malaria in pregnancy. The studies would particularly focus on understanding how antibodies neutralize and clear malaria parasites in the blood, and examine interactions with monocytes/macrophages and dendritic cells, and understanding the nature and specificity of antibody responses.

LABORATORY / PROJECT LOCATION: Malaria Research Laboratory, Centre for Immunology, Burnet Institute
PROJECT TITLE: Vaccines against malaria

SUPERVISOR/S: Professor James Beeson  
Dr Jack Richards  
Dr Damien Drew

CONTACT EMAIL: richards@burnet.edu.au

DEPARTMENT: Burnet Institute

PROJECT DESCRIPTION:

The aim of this project is to evaluate candidate antigens as potential malaria vaccines, understand what combinations of antigens could be use to generate the most effective immune responses, and understand the protective activity of vaccine-induced immune responses. These studies will focus on several leading candidate antigens (AMA1, EBAs, PfRh, MSP2), and other promising antigens. They will use novel approaches in molecular biology, cell biology and immunology to address these aims. In addition, the project could include working on optimising vaccine approaches to induce potent protective immune responses (e.g. improving antigen presentation). The project could focus on vaccines for P. falciparum and P. vivax, which are the two main causes of human malaria.

LABORATORY / PROJECT LOCATION: Malaria Research Laboratory, Centre for Immunology, Burnet Institute
DEPARTMENT OF INFECTIOUS DISEASES

PROJECT TITLE: How should we manage *Mycobacterium abscessus* infection in lung transplant recipients?

SUPERVISOR/S: Dr Orla Morrissey  
A/Prof Bronwyn Levvey  
Professor Greg Snell

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DEPARTMENT: Infectious Diseases, Monash University and Infectious Diseases Unit, The Alfred Hospital

PROJECT DESCRIPTION:

*Mycobacterium abscessus*, whilst an uncommon organism complicating lung transplantation, is associated with significant morbidity and mortality. *M. abscessus* is resistant to many antimicrobial agents and has a high propensity to disseminate to the skin and brain. It appears to be on the increase.

A number of small studies have been performed looking at the incidence and outcomes and have attempted to provide guidelines for the management of *M. abscessus* infections. However, there were a number of problems with these studies including:

1. Failure to examine the relative benefits of different drug regimens  
2. Inclusion of only the most severe cases  
3. Failure to examine the relationship between *M. abscessus* and the timing of other infections  
4. Lack of data on chronic allograft rejection  
5. The reporting of single centre experiences only

Given the current increase in the infection and the dearth of good quality data on which to base the management of *M. abscessus* infection; it is timely to perform an international survey of *M. abscessus* infection in lung transplant recipients, world-wide looking at outcomes, therapies and relationship to other infections and chronic allograft rejection.

A web-based cross-sectional survey will be developed and sent to lung transplant centres worldwide. Relevant clinical and microbiological data will be collected. The data will be analysed using Stata statistical package and used to develop improved guidelines for the management of *M. abscessus* infection and thus, has the potential to improve patient outcomes.

A wide range of clinical research skills will be used in this project. The project is ideal for a medical student or a B Med Sci (Hons) student.

LABORATORY / PROJECT LOCATION: Infectious Diseases Unit, Alfred Medical Research and Education Precinct (AMREP), Level 2 Burnet Institute, Commercial Rd, Melbourne 3004.
PROJECT TITLE: What is the role of thoracic high resolution computed tomographic scan changes in the diagnosis of invasive aspergillosis in high-risk haematology patients?

SUPERVISOR/S: Dr Orla Morrissey
Professor Monica Slavin

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DEPARTMENT: Infectious Diseases Department, Monash University and Infectious Diseases Unit, The Alfred Hospital

PROJECT DESCRIPTION:
Invasive Aspergillosis (IA) is a significant cause of mortality in patients undergoing allogeneic stem cell transplantation (SCT) or chemotherapy for acute leukaemia, due mainly, to the inability of culture and biopsy to make an early and accurate diagnosis. As a result much research has been performed to develop new diagnostic tests. Three main tests have been developed and include thoracic high resolution computed tomographic scan, Aspergillus galactomannan enzyme-linked immunosorbent assay (ELISA) and Aspergillus PCR assays. A number of lesions on thoracic high resolution computed tomographic (HRCT) scan have been identified as consistent with IA and include a nodule (≥1 cm in diameter) with or without halo-sign (a perimeter of ground-glass opacification), an air-crescent sign and a cavity in an area of consolidation. The sensitivity of a nodule with a halo sign is 72-89%.

However, many patients have non-characteristic changes on thoracic HRCT scan including micronodules (< 1 cm in diameter) and consolidation without cavity formation. The utility of these findings in the early diagnosis of IA has not been extensively evaluated.

Thus, we will correlate these findings to the diagnosis of IA (using other standardised diagnostic criteria) from the results of a large randomised controlled trial known as the ASPID trial (ClinicalTrials.gov number, NCT00163722). We have a database of 240 patients enrolled into the ASPID trial containing all their culture, biopsy, Aspergillus galactomannan ELISA, Aspergillus PCR and thoracic HRCT scan results. In this study the sensitivity, specificity, positive and negative predictive values (including confidence intervals) of non-characteristic thoracic HRCT scan changes will be calculated. In addition, the time-differential to development of non-characteristic lesions and the diagnosis of IA by other diagnostic tests will be determined.

The project will help the student to develop skills in clinical research methodology. The project is ideal for a medical student or a B Med Sci (Hons) student.

LABORATORY / PROJECT LOCATION: Infectious Diseases Unit, Level 2 Burnet Institute, Commercial Rd., Melbourne 3004.
DEPARTMENT OF IMMUNOLOGY

PROJECT TITLE: Investigating the role of natural killer (NK) cells in peanut-allergy

SUPERVISOR/S: Dr Sara Prickett
Professor Jennifer Rolland
Professor Robyn O’Hehir

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DEPARTMENT: Immunology, Monash University Central Clinical School

PROJECT DESCRIPTION:

Peanut allergy is the leading cause of food-induced anaphylactic fatalities worldwide. There is no cure. Why peanut allergens are so potent is not clear. Much research has focused on the roles of T cells, B cells, dendritic cells and basophils in peanut allergy, but nothing is known regarding the role of NK cells. We have preliminary data to suggest NK cells may play a role in shaping the immune response to peanut allergens.

NK cells represent a distinct subset of lymphocytes of the innate immune system, that also play important roles in shaping adaptive immune responses. Their major functions are cytotoxicity, cytokine production and stimulation of other cells. Recent developments in the discovery of distinct NK cell subsets (NK1, NK2, N22 and NKreg) suggest key roles in allergic disease by influencing allergen-specific immune suppression, allergen-specific T cell generation and antibody production.

This project will assess the effects of peanut stimulation on the response of NK cells using human peripheral blood samples, and how NK cells influence, and are influenced by, activation of other cell types. We will compare blood samples taken from peanut-allergic donors with those from non-peanut allergic donors. Techniques include cell isolation, cell culture, flow cytometry, cytokine analysis (ELISA) and allergen extract preparation and analysis (SDS-PAGE and immunoblotting). Blocking experiments will be used to assess the roles of different cytokines and/or cell interactions.

Since it is thought that commercial processing of peanuts may play a role in determining the ensuing immune response in peanut-allergic subjects, this project will also compare the effects of stimulation with raw, boiled and roasted peanut extracts.

This project will generate new insight into factors that contribute to the symptoms of peanut allergy and provide important information for the clinical management of peanut allergic individuals.


LABORATORY / PROJECT LOCATION: Allergy Research Group, Departments of Immunology and Allergy, Immunology & Respiratory Medicine (AIRMEd), Central Clinical School, The Alfred Hospital, Commercial Road, Melbourne.
PROJECT TITLE: The role of Toll-Like Receptors (TLRs) in Retinopathy of Prematurity

SUPERVISOR/S: Dr Alex Agrotis
Professor Jennifer Wilkinson-Berka

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DEPARTMENT: Immunology

PROJECT DESCRIPTION:

Retinopathy of prematurity (ROP) is a major cause of long-term visual impairment in children born prematurely. The current view of ROP etiology is that low birth weight, low gestational age, and supplemental oxygen therapy following delivery are major risk factors, and although significant improvements have occurred in the clinical care of neonates, the incidence of ROP has not shown a concomitant decline. In fact, there is evidence to suggest that the incidence of ROP has increased in the last decade compared with the previous one, perhaps because of the increasing survival of smaller and younger premature infants. From a clinical perspective, ROP is considered a vascular disease that develops in two phases. In phase I, when the premature newborn is exposed to the high levels of oxygen needed to support their immature respiratory system, the normal processes that govern vascular maturation in the retina are interrupted, leaving the peripheral retina avascular. In phase II, when the newborn is returned to normal air, retinal hypoxia develops in the peripheral avascular retina and is the stimulus for aberrant growth of blood vessels on the surface of the retina.

It is becoming increasingly recognized that inflammatory mechanisms are likely to contribute significantly to the aberrant growth of retinal blood vessels that occurs in ROP. Critical molecules that can influence the state of retinal inflammation are the Toll-like Receptors (TLRs) which can be activated not only by bacteria and viruses, but also by “self-ligands” such as cellular DNA and High Mobility Group Box Protein-1 (HMGB1). This project will focus on elucidating the roles of TLR2, TLR4, and TLR9 in ROP in a mouse model of the human disease, known as Oxygen-Induced Retinopathy (OIR), using mice genetically ablated of each of these TLRs. Experiments will involve the assessment of neovascularization, vascular permeability, and inflammation in retinas of these mice using the techniques of lectin immunohistochemistry, ELISA, leukostasis, real-time PCR, and cytokine arrays.

LABORATORY / PROJECT LOCATION: Diabetic Retinopathy Laboratory
Department of Immunology
Central Clinical School
The Alfred Hospital
Commercial Road, Melbourne
PROJECT TITLE: Expression profile of skin tumours with high risk of malignant conversion

SUPERVISOR/S: Dr Charbel Darido
Professor Stephen Jane

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stephen.jane@monash.edu

DEPARTMENT: Department of Medicine, Central Clinical School

PROJECT DESCRIPTION:

We have recently shown that the transcription factor Grainy-head like 3 (Grhl3) functions as a tumour suppressor in a mouse model of chemically induced squamous cell carcinoma (SCC) of the skin. Loss of Grhl3 in the epidermis provides a potent stimulus for development of aggressive SCC (Darido et al. Cancer Cell, 2011). We have also shown that a highly related gene, Grhl1 also confers protection against chemical-induced skin damage, with mice lacking this gene developing multiple benign skin tumors. However, these tumors never progress on to SCC establishing a critical point of difference between the two Grhl genes in the development of SCC. These results classify skin tumors from Grhl1 and Grhl3 KO mice as low and high cancer risk, respectively. The molecular signatures that distinguish pre-malignant and malignant skin tumors are currently unknown, and our mouse models provide a unique vehicle to address this critical question. The project will involve identification of differential Grhl1 and Grhl3 direct target genes from different malignant stages. The Honours student is expected to compare gene expression patterns of Grhl1 benign tumours to Grhl3 malignant SCC as well as determine genetic signature from benign and malignant Grhl3 tumours. Identification of Grhl3-specific target genes could provide diagnostic biomarkers to discriminate benign lesions with differing risk for malignant progression as well as novel therapeutic targets for high-risk lesions.

Skills: A wide range of skills will be taught including biochemistry, molecular biology, knockout mice, and bioinformatics approaches (phylogenetic, microarray and ChIP-Seq analysis). This is an ideal project for a student who wishes to pursue higher studies in the future.

LABORATORY / PROJECT LOCATION: Skin group / Grainyhead-like genes in cancer
Level 1, AMREP building, The Alfred Hospital
PROJECT TITLE: A Neuroscience approach to Enhancing Cognitive Functioning: using transcranial Alternating Current Stimulation to enhance the effects of cognitive training

SUPERVISOR/S: Dr Kate Hoy  
Professor Paul Fitzgerald

CONTACT EMAIL: Kate.hoy@monash.edu

DEPARTMENT: Monash Alfred Psychiatry Research Centre (MAPrc)

PROJECT DESCRIPTION:

The overall intention of this world first research is to explore a truly novel approach to the enhancement of cognition by combining two complementary methods of enhancing brain function. Cognitive training is a commonly used technique to improve cognitive performance. Recently, a number of studies have shown that these behavioural techniques, when provided within a certain theoretical paradigm, are actually capable of inducing neurophysiological changes which are associated with improved performances. In addition, brain based techniques such as non invasive brain stimulation, (i.e. transcranial Alternating Current Stimulation (tACS)), have also been shown to induce brain changes and result in improve cognitive performances. To date, these approaches have not been combined.

Combining these behavioural and brain based approaches, i.e. cognitive training with tACS, could therefore generate a cumulative response subsequently leading to greater, more generalized and longer lasting improvements in cognitive function. This would have considerable implications for the treatment of cognitive dysfunction in a range of psychiatric and neurological disorders.

This project will use a combination of neurophysiological (EEG) and cognitive assessments to investigate the effects of combined tACS and cognitive training in healthy controls.

LABORATORY / PROJECT LOCATION: Monash Alfred Psychiatry Research Centre (MAPrc)  
607 St Kilda Rd, Melbourne
PROJECT TITLE: Investigating the physiological response to transcranial magnetic stimulation (TMS)

SUPERVISOR/S: Dr Richard Thomson
Professor Paul Fitzgerald

CONTACT EMAIL: richard.thomson@monash.edu

DEPARTMENT: Monash Alfred Psychiatry Research Centre

PROJECT DESCRIPTION:

Transcranial magnetic stimulation (TMS) is increasingly being investigated in clinical settings for the treatment of neurological and psychiatric disorders such as dystonia, schizophrenia, and major depressive disorder (MDD). Parameters in the application of TMS such as the intensity of stimulation, and the frequency of pulses have variable effects on neural stimulation at motor cortex. Using neuroimaging techniques, changes in blood oxygenation and the electrophysiological response resulting from TMS can be observed in other cortical regions.

This project will seek to use neuroimaging techniques such as EEG and near infra-red spectroscopy (NIRS) to investigate the physiological effects of applying TMS. The use of these tools aids in our understanding of the mechanisms involved in the physiological changes evoked by TMS and efficacious clinical application of TMS in disorders such as MDD.

LABORATORY / PROJECT LOCATION: Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne
PROJECT TITLE: Investigating the human mirror neuron system via transcranial magnetic stimulation (TMS)

SUPERVISOR/S: Dr Peter Enticott
Professor Paul Fitzgerald

CONTACT EMAIL: peter.enticott@monash.edu

DEPARTMENT: Monash Alfred Psychiatry Research Centre

PROJECT DESCRIPTION:

Mirror neurons are cortical cells that fire during both the performance and observation of behaviour. They were originally discovered in macaques, but an analogous mechanism has since been established in humans and can be probed via non-invasive electrophysiological and neuroimaging techniques.

It has been suggested that mirror neurons provide an ‘embodied simulation’ that facilitates empathy and an understanding of others’ mental and emotional states. There is also evidence to suggest that dysfunction within the mirror neuron system (MNS) contributes to the pathophysiology of autism. Nevertheless, it remains largely unclear as to the precise function of mirror neurons, and the conditions under which they are most active.

This project will use a combination of transcranial magnetic stimulation (TMS), electromyography (EMG), and neurocognitive assessment to investigate aspects of the MNS among healthy adults. Possible areas of investigation include attentional or emotional influences on mirror neuron activity, the relationship between mirror neurons and social cognition, and the role of the MNS in action understanding.

LABORATORY / PROJECT LOCATION: Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne
PROJECT TITLE: Using tDCS to investigate the role of hemispheric laterality in emotional processing

SUPERVISOR(S): Dr Rebecca Segrave
Dr Kate Hoy
Professor Paul Fitzgerald

CONTACT EMAIL: Rebecca.segrave@monash.edu

DEPARTMENT: Monash Alfred Psychiatry Research Centre

PROJECT DESCRIPTION:

We know that the left and the right cerebral hemispheres possess degree of specialisation for the processing of language and spatial information, respectively. It has also been suggested that the cerebral hemispheres are specialised for the processing of emotional information; with the left hemisphere dominant for processing positive/approached related information and the right hemisphere dominant for processing negative/withdrawal related information.

This lateralised model of emotional processing has been used to explain aspects of major depression. It has also influenced how brain stimulation techniques, such as transcranial magnetic stimulation, are used to treat depression. However, there is a large body of evidence that does not support lateralised models of emotional processing and this area of research remains a contentious one.

Transcranial direct current stimulation (tDCS) is a mild form of non-invasive brain stimulation. It can be applied to such a way that is produces a transient increase or decrease in cortical brain activity. Evidence from our own lab and others has shown that tDCS can be used to enhance cognitive processing in healthy individuals.

This project will use tDCS to probe the role of the left and right hemispheres in emotional processing. It will involve the administration of tDCS to healthy volunteers during completion of a cognitive task that involves processing of positive and negative stimuli. A student undertaking this project will develop an understanding of models of hemispheric laterality and emotional processing, the application of transcranial direct current stimulation and its use in modulating cognition, and some of the ways in which our emotional and our cognitive processes interact with one another.

LABORATORY / PROJECT LOCATION: Monash Alfred Psychiatry Research Centre (MAPrc)
607 St Kilda Rd, Melbourne
PROJECT TITLE: The Women’s Mental Health Clinic Evaluation

SUPERVISOR/S: Professor Jayashri Kulkarni

CONTACT EMAIL: j.kulkarni@alfred.org.au

DEPARTMENT: Monash Alfred Psychiatry Research Centre

PROJECT DESCRIPTION:
Women’s mental health has been overlooked as a special area of mental health requiring specifically tailored understanding and treatment for women suffering with a variety of mental illnesses.

The women’s mental health clinic provides tertiary consultation and adopts a biopsychosocial or holistic approach to assess each woman in the form of second opinions by expert psychiatrists and endocrine specialists for women with a variety of psychiatric disorders. In particular the impact of hormonal changes and other reproductive factors are carefully considered in the management of mental illnesses.

This project will review the number and reasons for referral, diagnoses and management outcomes plus describing what the different features of the clinic operation are, plus exportability of the clinic to other places.

LABORATORY / PROJECT LOCATION: Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne
PROJECT TITLE: Psychosis Symptom Fluctuation Across the Menstrual Cycle

SUPERVISOR/S: Professor Jayashri Kulkarni

CONTACT EMAIL: j.kulkarni@alfred.org.au

DEPARTMENT: Monash Alfred Psychiatry Research Centre

PROJECT DESCRIPTION:

It has been suggested that women are more susceptible to a first episode or relapse of illness at two major periods of hormonal change, both characterised by a decrease in estrogen levels: postpartum and menopause. Fluctuations in estrogen levels during the menstrual cycle are also associated with changes in psychopathology, with exacerbation or recurrence of psychosis observed during low-estrogen phases of the menstrual cycle and improvement in symptoms during high-estrogen phases.

This project will investigate the effects of the menstrual cycle on psychosis symptoms in women with mental illness.

LABORATORY / PROJECT LOCATION: Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne
PROJECT TITLE:  The Interaction Between OCP and Cognition

SUPERVISOR/S:  Dr Sarah Metcalfe
                Professor Jayashri Kulkarni

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DEPARTMENT:  Monash Alfred Psychiatry Research Centre

PROJECT DESCRIPTION:

Oral contraceptives are medications containing either a progestin (progesterone) or a combination of both progestin and estrogen, taken by mouth to inhibit female fertility. Oral contraceptives have also been investigated in terms of their effect on mood in women.

It is suggested that women predisposed to experience changes in mood due to estrogen may potentially show changes in cognition, emotional processing and memory.

The interaction between the oral contraceptive pill (OCP) and cognition will be investigated in this project to determine whether the OCP has any effect on memory and attention in women who are taking it.

LABORATORY / PROJECT LOCATION:  Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne
PROJECT TITLE: Lung Function in People with Severe Mental Illness

SUPERVISOR/S: Professor Jayashri Kulkarni (MAPRC)
Professor Christine McDonald (IBAS)
Dr Chris Worsnop (IBAS)

CONTACT EMAIL: j.kulkarni@alfred.org.au

DEPARTMENT: Monash Alfred Psychiatry Research Centre (MAPrc)

PROJECT DESCRIPTION:

In this project, respiratory function and sleep disturbances will be assessed in people with schizophrenia and bipolar disorder along with their smoking habits. Following a specifically tailored smoking cessation program, which includes cognitive therapy plus nicotine replacement, their lung function will be reassessed.

We expect to collect data from 20 participants over an 8 month testing period.

LABORATORY / PROJECT LOCATION:

Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne.

This project will be jointly run by MAPrc and The Institute for Breathing & Sleep (IBAS) based at Austin Health.
PROJECT TITLE:  
Menopause and Women with Schizophrenia

SUPERVISOR/S:  
Dr Rosie Worsley  
Professor Jayashri Kulkarni

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DEPARTMENT:  
Monash Alfred Psychiatry Research Centre

PROJECT DESCRIPTION:

There has been noted deterioration in the mental state of women with schizophrenia as they enter the menopause. A new ‘brain estrogen’ has been developed (Selective Estrogen Receptor Modulator, SERM) which has fewer side effects than estrogen and has a mechanism of action specifically designed to improve memory and osteoporosis. SERMs are non-feminising as they do not act on reproductive organs.

We are currently conducting a study using SERM (Raloxifene) and as part of this study we would like to explore the relationship between perimenopause/menopause and schizophrenia relapse.

LABORATORY / PROJECT LOCATION:  
Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne
PROJECT TITLE: Cognition and symptoms of schizophrenia: What we can learn from biological relatives and schizotypy in the healthy population

SUPERVISOR/S: Dr Caroline Gurvich
Professor Susan Rossell

CONTACT EMAIL: Caroline.gurvich@monash.edu

DEPARTMENT: Monash Alfred Psychiatry Research Centre (MAPrc)

PROJECT DESCRIPTION:
Mental illnesses, such as schizophrenia, can be viewed on a continuum of severity. At one end of the spectrum are unaffected individuals who may exhibit mild features of the disorder such as unusual thoughts (schizotypy) or unaffected individuals who share genetic risk factors (a first degree biological relative of a person with schizophrenia). At the other end of the spectrum are individuals who have severe forms of the disorder. Schizotypal personality, first degree biological relatives and schizophrenia have been suggested to share common genetic, neurophysiological and neurocognitive abnormalities.

This project will focus on the assessment of cognitive processes that are commonly impaired in schizophrenia, including working memory, inhibitory control and other ‘executive functions’. A combination of neuropsychological assessments including eye movement measurements will be utilised. The broad research project explores the relationship between genetic risk factors, cognition and the symptoms of schizophrenia across the spectrum of phenotypic severity (i.e. differing degrees of affection). Potential areas of investigation for honours projects includes the relationship between symptoms and cognition in healthy individuals who have an increased vulnerability (i.e. genetic - first degree biological relative or phenotypic – high levels of schizotypy).

LABORATORY / PROJECT LOCATION: Monash Alfred Psychiatry Research Centre (MAPrc), 607 St Kilda Rd, Melbourne
PROJECT TITLE: Management of gastro-oesophageal reflux in obese patients

SUPERVISOR/S: Mr Paul Burton
Associate Professor Wendy Brown

CONTACT EMAIL: paul.burton@monash.edu

DEPARTMENT: Surgery (Alfred hospital)

PROJECT DESCRIPTION:

Background: Obesity and gastro-oesophageal reflux disease (GORD) are two of the most significant health care problems facing our community – they are linked physiologically and epidemiologically. Laparoscopic adjustable gastric banding (LAGB) has rapidly emerged as a safe and effective procedure (for obesity) that significantly improves GORD symptoms. There is very limited understanding of the mechanism by which LAGB reduces GORD. This lack of understanding is significantly constraining use of LAGB as an anti-reflux procedure and surgeons urgently need better data to guide the choice of surgical interventions for obese patients with GORD. This need is compounded by a far higher complication and failure rate of fundoplication (the gold standard anti-reflux procedure) in obese patients.

Goal: To better understand the anti-reflux mechanism of LAGB and its impact on gastro-intestinal quality of life, thereby better informing clinicians of the optimal surgical management of obese patients with GORD.

Aims:

1) To determine the association of oesophageal reflux events with transient lower oesophageal sphincter relaxations in LAGB patients
2) To determine the effect of LAGB on oesophageal reflux events in response to reflux provoking stimuli
3) To compare the effects of LAGB and surgical fundoplication on GORD symptoms and gastro-intestinal quality of life

Methods:

Study 1: Eight LAGB patients with a stable weight loss and volume within the LAGB will undergo a study using a combined high resolution manometry and pH recorder. Transient lower oesophageal sphincter relaxations will be recorded and correlated with oesophageal reflux events. A reflux provoking high caloric intra-gastric infusion will be administered. As a comparison group 8 patients who have undergone surgical fundoplication will undergo the same evaluation as will 8 obese controls with GORD.

Study 2: Twenty pre-op LAGB patients and twenty surgical fundoplication patients will be evaluated pre-operatively and six months post-operatively. Reflux scores and gastro-intestinal quality of life scores will be recorded.

LABORATORY / PROJECT LOCATION: Alfred hospital campus
PROJECT TITLE:  Upper GI symptoms, satiety and gastro-intestinal quality of life following adjustable gastric banding

SUPERVISOR/S:  Mr Paul Burton  
Associate Professor Wendy Brown

CONTACT EMAIL:  paul.burton@monash.edu

DEPARTMENT:  Surgery (Alfred hospital)

PROJECT DESCRIPTION:
Follow-up is critical to the success of laparoscopic adjustable gastric banding (LAGB). Few data are available to guide this and expected norms of satiety, adverse symptoms, and outcomes have not been defined – limiting the capacity of clinicians to specify expected long term outcomes and effects. Additionally, the effects of the procedure on gastro-intestinal (GI) quality of life have not been evaluated. Although conventional measures of quality of life improve; whether these change are truly inclusive of the adverse gastro-intestinal effects of LAGB are unknown.

Overall, there are few intermediate (>5 year) data on outcomes other than weight loss, following LAGB.

Methods:  In a cohort of 400 LAGB patients, Baseline data (2007) is available on assessed satiety, adverse upper gastrointestinal (dysphagia, reflux, and epigastric pain), and outcomes (overall satisfaction, weight loss, and quality of life (SF-36)). This project will:
1) Evaluate different measures of gastro-intestinal quality of life in patients who have undergone gastric band surgery
2) Follow up changes over >5 years in terms of satiety, outcomes and quality of life and determine the effects of the procedure on these measures and how they change over time.

Significance:  Patients are generally highly satisfied with the outcome of LAGB and achieve substantial weight loss. Data from this study will significantly improve clinicians’ ability to care for patients by defining expected normal ranges at different time points. In addition far more detailed knowledge on the gastro-intestinal effects of the procedure will be provided. Correlation of different measures to weight loss and complication will be available, allowing determination of the predictors of these important end points.

LABORATORY / PROJECT LOCATION:  Alfred hospital campus
PROJECT TITLE: Outcomes of major bariatric surgical procedures

SUPERVISOR/S: Associate Professor Peter Nottle
Mr Paul Burton
Associate Professor Wendy Brown

CONTACT EMAIL: paul.burton@monash.edu

DEPARTMENT: Surgery (Alfred hospital)

PROJECT DESCRIPTION:

Bariatric surgery has been a defined surgical speciality for nearly fifty years. However, the number of weight loss procedures performed over the last 15 years has continued to increase exponentially. This is not surprising given the worldwide obesity pandemic.

Whilst surgery is the only effective and durable therapy for obesity different procedures carry different risk/benefit profiles. An important sub-group of patients are those undergoing a second line bariatric procedure. Mostly, these are patients who have had an adjustable gastric band or gastroplasty and require Roux-en-Y gastric bypass, sleeve gastrectomy or bilio-pancreatic diversion. These second line surgeries are high risk, however, the precise risks and effects on quality of life and weight loss have not been determined in this setting.

This project will evaluate a cohort of 300 patients who have undergone second line procedures. Data collected will include: preoperative details, operative approach, peri-operative complications (including mortality) and weight loss. All patients will be followed up using gastro-intestinal quality of life instruments.

LABORATORY / PROJECT LOCATION: Alfred hospital campus
PROJECT TITLE: Outcomes of gastro-oesophageal cancer in Victoria

SUPERVISOR/S: 
Associate Professor Peter Nottle  
Mr Paul Burton  
Associate Professor Wendy Brown

CONTACT EMAIL: paul.burton@monash.edu

DEPARTMENT: Surgery (Alfred hospital)

PROJECT DESCRIPTION:

Cancers of the oesophagus and stomach are common malignancies. Adenocarcinoma of the oesophagus and oesophago-gastric junction is one of the most rapidly increasing diseases in the Western world (400% over the past 30 years). Improved staging, multi-disciplinary care and neo-adjuvant therapy should have resulted in measurable improvements in the care delivered to these patients. Additionally, there are a number of newly defined markers of quality of care in the treatment of these malignancies.

There is no recent Victorian data available at a population level relating to the incidence, treatment or outcomes of gastro-oesophageal malignancy.

This project will evaluate those measures on a Victorian population level using cancer registry and databases.

The past 5 years of patients treated at The Alfred hospital have been maintained in a prospective database and will be used as a comparator; particularly concerning markers of quality of care. Comparisons will also be drawn to interstate and international data.

This study will provide important information relating to the management of these malignancies in Victoria.

LABORATORY / PROJECT LOCATION: Alfred hospital campus
PROJECT TITLE: Investigation of human adult dermal pericytes and their role in skin tissue regeneration

SUPERVISOR/S: Dr Heather Cleland
Dr Shiva Akbarzadeh
Dr Pritinder Kaur (external)

CONTACT EMAIL: Shiva.akbarzadeh@monash.edu

DEPARTMENT: Department of Surgery, Central Clinical School, Monash University

PROJECT DESCRIPTION:
The Skin Tissue Culture Laboratory is focused on translational research into adult skin cell biology and its application in developing new techniques for managing and treating burn wounds. Skin basically consists of 2 layers: the dermis which provides structural integrity and acts as a scaffold or matrix for cells, and the epidermis which forms the protective outer surface layer of the skin. Signals from dermis are essential for epithelial proliferation, skin morphogenesis, homeostasis and differentiation.

Conventionally, growth-arrested murine 3T3-J2 fibroblasts are used to secrete extracellular matrix proteins to support keratinocyte growth in vitro (CEA method) [1]. The main limitation of this technique is that secreted undefined murine factors make these cultures unsuitable for clinical application.

We have some preliminary data (in collaboration with Dr. Pritinder Kaur, Peter MacCallum Cancer Centre) in vitro that pericytes (found in lining of blood vessels and in dermis underlying basal epidermal cells) have the capacity to promote skin regeneration from neonatal early differentiating cells [2] and from adult proliferating cells. This is a novel role for pericytes, suggesting they are not only important structurally but that they may also contribute substantially to epidermal tissue renewal.

This project is aimed to develop methods for adult human pericytes isolation and culture and to investigate the ability of human pericytes with human fibroblasts to promote adult keratinocyte growth in 3 dimensional skin models. The project involves primary cell culture and flow cytometry/cell sorting as the main techniques.

References:

Aims
1) Identify, isolate and culture adult pericytes from skin.
2) Study the effect of adult pericytes in adult keratinocyte growth in a 3D-culture system.

Methodology
- Isolation of primary dermal cells from adult skin
- Isolation of primary keratinocytes from adult skin
- Labelling primary dermal cells with specific antibodies and FACS analysis to identify pericytes/fibroblasts subpopulations
- Sorting primary dermal cells to isolate pericytes.
- Confirming the identity of the sorted population using immunofluorescence and Real Time PCR
- Co-culture of Pericytes with fibroblasts to support adult keratinocyte growth

Laboratory / project location: Skin Culture Laboratory, AMREP building, Alfred Hospital
PROJECT TITLE: Use of Human-derived Feeders and Nutrients for Cultured Epithelial Autograft

SUPERVISOR/S: Dr Heather Cleland  
Dr Shiva Akbarzadeh  
Dr Marisa Hersen

CONTACT EMAIL: Shiva.akbarzadeh@monash.edu

DEPARTMENT: Department of Surgery, Central Clinical School, Monash University

PROJECT DESCRIPTION:
The Skin Tissue Culture Laboratory is focused on translational research into adult skin cell biology and its application in developing new techniques for managing and treating burn wounds. Patients with extensive burns lack sufficient skin graft donor sites to facilitate early wound closure, which minimizes risks of complications and promotes recovery from injury. Cultured Epithelial Autograft (CEA) is an effective adjunct in the treatment of patients with life-threatening burn injury. The Skin culture laboratory is committed to manufacturing CEA under strict conditions from patients own keratinocytes (skin cells) during 2-3 weeks culture period. There are however, a number of limitations with CEA. Firstly, CEA uses animal derived feeder cells and products during expansion of keratinocytes which carry intrinsic risks when grafted. Secondly, CEA only replaces the upper layer of the skin (epidermis) and requires healthy dermis to make functional skin. This project is aimed to investigate replacement of animal derived material in production of CEA with human derived or synthetic material. The long term aim of this project is to manufacture animal-free CEA to treat severe burns.

Aims
1. To compare 3T3-J2 and human fibroblasts in their ability to support adult keratinocyte attachment and expansion in vitro.
2. To compare bovine serum with human serum in their ability to support adult keratinocyte expansion in vitro.

Methodology
This project utilises primary cell isolation, cell culture and cell biology techniques.

Laboratory / project location: Skin Culture Laboratory, AMREP building, Alfred Hospital
PROJECT TITLE: Use of Artificial Extracellular Matrices for Skin Regeneration

SUPERVISOR/S: Dr Heather Cleland  
Dr Shiva Akbarzadeh  
Dr Marisa Hersen

CONTACT EMAIL: Shiva.akbarzadeh@monash.edu

DEPARTMENT: Department of Surgery, Central Clinical School, Monash University

PROJECT DESCRIPTION:
Currently, the gold standard practice for treating extensive deep burns is a two-stage procedure skin-graft. Damaged dermis (deep layer of the skin) is replaced by either allograft (transplant of skin from one person to another) or synthetic (animal derived) dermal substitutes, followed by replacing the epidermis (upper layer of the skin) with grafts from a healthy donor site of the same patient. Although damaged dermis can be replaced by dermis from other sources, the grafted epidermis has to be patients's own to avoid rejection. Some of the challenges with the existing practice are the limitation of available healthy donor skin in patients who are extensively burned. Donor sites in these patients are slow to heal, prone to infection, and incapable of ensuring rapid closure of the burn wound. Also, the patient has to go through two procedures, often weeks apart, to replace damaged dermis and then epidermis.

We have generated artificial double layer skin in culture in our laboratory by using human epidermal cells seeded on a dermal substitute, Integra®, and cultured for up to 14 days. The cultured skin has been analysed histologically and showed that Integra is capable of supporting epidermal cell expansion, although the generated epidermis has somewhat irregular appearance.

This project is aimed to optimise neo-epidermis architecture and examine the graftability and the regeneration capabilities of cultured human artificial skin in whole animals.

The long term aim of this project is to facilitate a one-stage procedure to replace damaged skin in treating burn wounds and thus improve healing rates for patients with severe burns.

Aim
• To optimise composite skin architecture
• To measure graftability of artificial human skin to replace both dermis and epidermis in a whole animal model in a one-stage procedure.

Methodology
• Cell culture
• Animal skin grafting
• Histology

Laboratory / project location: Skin Culture Laboratory, AMREP building, Alfred Hospital  
PROJECT TITLE: Characterisation and manipulation of neurogenesis following experimental traumatic brain injury

SUPERVISOR/S: Dr Nicole Bye

CONTACT EMAIL: nicole.bye@monash.edu

DEPARTMENT: National Trauma Research Institute

PROJECT DESCRIPTION:

Traumatic brain injury (TBI) is a global health burden. In Australia TBI is estimated to cost $8.6 billion for life-long care. There are no therapies to reverse the devastating consequences. Traumatic injury to the brain results in a progressive loss of neuronal cells causing secondary tissue damage and consequent neurological deficit. In recent years, various studies, including our own, have shown that, although in a limited fashion, post-traumatic regenerative responses can take place in the adult brain after trauma. One potentially important regenerative process is neurogenesis: the production of new neurons from stem cells that reside in specific regions of the adult brain. It has been proposed that strategies to enhance neurogenesis by administering neurotrophic growth factors known to promote the proliferation, differentiation and survival of neural progenitor cells, may improve neurological outcome. Based on this premise, we will explore whether treatment with specific growth factors will increase neurogenesis and improve neurological outcome in mice subjected to traumatic brain injury (TBI).

Significance: The comprehension of the molecular mechanisms underlying neurogenesis triggered by TBI is of fundamental importance. This study aims at characterising the multiple stages of progenitor cell proliferation and differentiation after TBI, and exploring new methods for the improvement of regenerative processes ultimately of benefit for the treatment of head trauma patients.

LABORATORY / PROJECT LOCATION: National Trauma Research Institute (NTRI), Level 4 Burnet Tower, 89 Commercial Road, Melbourne
PROJECT TITLE:  Web 2.0 and linked data for healthcare knowledge

SUPERVISOR/S:  Professor Russell Gruen  
Dr Julian Elliott

CONTACT EMAIL:  r.gruen@alfred.org.au

DEPARTMENT:  National Trauma Research Institute

PROJECT DESCRIPTION:

Healthcare decision making is dependent on access to accurate and up-to-date evidence. Current approaches to transforming the deluge of research findings into meaningful knowledge are constrained by resource intensive methods and the limitations of current software tools and platforms. This limits the ability of healthcare decision makers to make decisions based on the latest research and contributes to the gap between what is known and what is practiced.

A Monash-based team has been working for several years on the development of new approaches to healthcare knowledge management, including the development of new evidence review methods and supporting software tools. Our aim is to develop and evaluate ‘living’ systematic reviews in which online, high quality evidence summaries are updated whenever new data become available.

The next phase of this work will investigate the use of web 2.0 approaches, including crowd sourcing, and linked open data to the ability of authors to create and maintain living systematic reviews.

This research project will enable the candidate to investigate the use of these novel evidence resources and how this compares to traditional sources of evidence, to become expert at systematic reviews and critical appraisal, and to undertake important evaluative research about how communities of clinicians, researchers and other stakeholders can be developed and sustained to promote evidence-based practice on a global scale.

LABORATORY / PROJECT LOCATION:  National Trauma Research Institute (NTRI), Level 4 Burnet Tower, 89 Commercial Road, Melbourne
PROJECT TITLE: Time to haemorrhage control and outcome in severely injured patients

SUPERVISOR/S: Professor Russell Gruen
Dr Dev Mitra

CONTACT EMAIL: r.gruen@alfred.org.au

DEPARTMENT: National Trauma Research Institute

PROJECT DESCRIPTION:

Background: It is increasingly apparent that earlier control of bleeding may lead to better outcomes in severely injured patients, through a variety of mechanisms, ranging from less resuscitation fluid, to less activation of inflammation at a genomic level. This understanding is leading to a paradigm shift from focus on resuscitation with fluid, to prehospital and hospital systems that prioritise bleeding cessation.

Project Aim: We aim to assess the relationship between time to bleeding control and outcome in patients with haemorrhagic shock. We will do so using the Alfred trauma registry, and outcome data through the Victorian State Trauma Registry.

The candidate will learn to use these valuable data systems, learn multivariate statistical modelling, and be able to participate in Australia’s leading trauma service.

LABORATORY / PROJECT LOCATION: National Trauma Research Institute (NTRI), Level 4 Burnet Tower, 89 Commercial Road, Melbourne
PROJECT TITLE: Measuring patterns of care in the management of spasticity in people with Traumatic Brain Injury (TBI)

SUPERVISOR/S:
Professor Russell Gruen
Dr Denise O’Connor

CONTACT EMAIL: r.gruen@alfred.com.au

DEPARTMENT: National Trauma Research Institute

PROJECT DESCRIPTION:

Background: Some evidence exists to guide the management of spasticity and against which to benchmark current practice. Seven RCTs (including one ongoing), two crossover studies, one cohort study (retrospective), six interrupted time series with no control group, 29 case series and 18 case reports have been identified (www.evidencemap.org). Over half of these studies investigated pharmacological therapies for managing spasticity. The next most common intervention under investigation was casting/splinting. Only eight of the 64 studies investigated therapies other than pharmacological agents or casting/splinting.

The specific aim of this project is to identify and document patterns of care in the management of muscle spasticity, generating a map of current practice to parallel the existing evidence map. From this we will identify important evidence practice gaps and guide future implementation strategies.

To achieve this they will:

1. Develop and pilot test a survey instrument, containing clinical vignettes relevant to TBI spasticity, which aims to document self reported practice and clinician intention in the management of muscle spasticity in people with TBI; and
2. To implement the survey nationally, sampling from the relevant multidisciplinary group/s, so determining indicative current practice.

The candidate will gain an understanding in knowledge translation, learn survey methods, and be able to participate as part of a greater study in knowledge translation in neurotrauma.

LABORATORY / PROJECT LOCATION:
National Trauma Research Institute (NTRI), Level 4 Burnet Tower, 89 Commercial Road, Melbourne