We aim to improve the visibility of students and their research projects on a larger scale and celebrate their achievements. Eight PhD students from across the AMREP precinct: Baker IDI, Burnet Institutes, Monash Central Clinical School and the School of Public Health and Preventive Medicine, will showcase their results. These students do much of their research in a clinical context, at the Alfred Hospital.

About us

Central Clinical School (CCS) focuses on ‘laboratory bench to bedside’ translational research. Our Departments (Immunology, Medicine, Surgery and Clinical Haematology) and research affiliates (Alfred Health, BakerIDI and Burnet Institutes) have strong links with health care providers. Our co-location with Alfred Health, BakerIDI, Burnet and Monash’s School of Public Health and Preventive Medicine, enables many of the School's researchers to hold joint research/clinical appointments. Such a nexus ensures that our research can move towards best practice health outcomes as rapidly as possible. Our work underpins the development of new diagnostics and therapies for a wide range of diseases. Research strengths broadly cover allergy, immunology and respiratory medicine; clinical sciences (medicine, surgery, pathology, anaesthesia, neurosciences); infectious diseases; and haematology.

For more detail about the School, see www.med.monash.edu.au/cecs/
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Michael Roche

HIV-1 escape from the small molecule CCR5 antagonist Maraviroc

The CCR5 antagonist maraviroc (MVC) inhibits the entry of human immunodeficiency virus type-1 (HIV-1) into cells of the immune system by altering the CCR5 extracellular loops (ECL), such that the HIV-1 envelope glycoprotein (Env) no longer recognizes CCR5. Viral resistance to MVC occurs through alterations in gp120 subunit of Env enabling recognition of the MVC-CCR5 complex.

To elucidate the molecular mechanisms underlying MVC resistance, we characterised the virus-cell interactions of gp120 from in vitro-generated MVC-resistant HIV-1 (MVC-Res Env), with comparison to gp120 from the parental sensitive virus (MVC-Sens Env). Studies using Env-pseudotyped luciferase reporter viruses and cells expressing CCR5 mutants showed that MVC-Res Env has increased dependence on residues in the N-terminus of CCR5 which become critical in the presence of MVC. There was no difference in reliance on the CCR5 ECL regions between MVC-Res and MVC-Sens Envs in the absence of MVC, but in the presence of drug MVC-Res Env becomes critically reliant on the H88 and H181 residues in the ECL1 and ECL2 regions, respectively.

Quantitative analysis of gp120-receptor interactions using the 293-Affinofile affinity profiling system showed that MVC-Res Env interacts with CCR5 efficiently in the absence of MVC, but in the presence of drug MVC-Res Env becomes more sensitive to alterations in CCR5 expression, indicating a less efficient interaction with CCR5. Analysis of HIV-1 entry into primary T-cells and monocyte-derived macrophages (MDM)

Following an undergraduate degree in science at Deakin University, Michael undertook an honours year in the department of Microbiology under Associate Professor Johnson Mak at the Burnet Institute in 2006. Michael commenced a PhD with Associate Professor Paul R Gorry at the Burnet Institute through the department of Medicine in 2008. Michael’s thesis focuses on the role of the HIV-1 Envelope glycoproteins in HIV-1 drug resistance and viral tropism. Michael has published three first-author papers and won numerous awards during his PhD and hopes to submit his thesis in October of this year.
revealed attenuated macrophage (M)-tropism by MVC-Res Env in the presence of drug. These results show that HIV-1 escapes MVC by becoming heavily reliant on the CCR5 N-terminus to enter cells, whilst maintaining an atypical interaction with charged His residues within the ECL1 and ECL2 regions. This altered CCR5 recognition by gp120 dramatically reduces gp120-CCR5 interaction efficiency, and abolishes M-tropism. Should attenuated M-tropism be a common feature in patients who develop MVC-resistant R5 virus, continuing MVC even after resistance develops could be clinically beneficial by sparing or reducing the macrophage reservoir of HIV-1.

Awards
(only 2011 awards given here)
2011 — Awarded a Keystone Symposia scholarship ($1200) to attend the Keystone meeting on HIV Evolution, Genomics and Pathogenesis in Whistler, Canada
2011 — Awarded international travel scholarship ($5000) to attend the 6th IAS Conference on HIV Pathogenesis, Treatment and Prevention (AIDS 2011) in Rome, Italy
2011 — Awarded two student prizes at the Australian Centre for HIV and Hepatitis Virology conference (ACH2) at Maroochydore, Australia, ($1000)

Publications
First Author Publications
‘Authors contributed equally (50%)
Multiple Myeloma (MM) is an incurable malignancy. The bone marrow microenvironment (BMME) is recognised as having a crucial role in the development and survival of MM. It is known to support MM tumor cells in a complex and dynamic way allowing evasion of apoptosis from anti-MM agents. This facilitates the acquisition of an increasingly drug resistant phenotype culminating in refractory terminal disease, thus mandating the need for new and insightful therapies in the context of the BMME.

Cytokine-mediated drug resistance (CM-DR) can be caused by a variety of soluble factors that may act alone or in concert, for example, IL-6, IGF-1, VEGF, BAFF, APRIL, HGF, SDF-1, and IFN-a. Likewise, cell adhesion-mediated drug resistance (CAM-DR) has also been described in MM. CAM-DR may result from MM cell interactions with VLA-4 and fibronectin and more recently other proteins with a potential role in CAM-DR, including CD138 and CS1, have been implicated. These soluble and contact-mediated stimuli lead to the activation of essential signalling pathways including JAK/STAT, PI3K/AKT, RAS/MAPK, and NFκB that engender an antiapoptotic state. Models of the BMME provide some insight into the mechanisms of BMME-mediated drug resistance but have many practical limitations.

Similarly, while MM cell lines allow for the reproducible evaluation of potential therapeutics they clearly are not representative of MM cells in vivo. Only through the development of re-producible and manageable
coculture models of MM-BMME interactions will investigators be able to identify relevant drug targets that may overcome the survival advantage engendered by the BMME.

Awards
2011 International Myeloma Society Award for Young Investigators.

Publications


Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder caused by a mutation in the dystrophin gene, which results in complete absence of sarcolemmal dystrophin protein expression and progressive muscle wasting. To date no cure or effective treatment is available for DMD. The four-and-a-half LIM (FHL) domain protein FHL1 regulates skeletal muscle mass and promotes myofibre hypertrophy via regulation of NFATc1 transcriptional activity. FHL1 could therefore serve as a novel therapeutic target for muscle wasting in DMD.

To determine whether FHL1 expression has therapeutic benefit for DMD, FHL1 transgenic mice overexpressing HA-tagged FHL1 specifically in skeletal muscle were crossed with a mdx mouse model of human DMD, to generate FHL1-Tg/mdx mice. Transgenic expression of FHL1 normalises the muscle histological features of mdx mice, as FHL1-Tg/mdx mice exhibit improved muscle membrane integrity, reduced skeletal muscle degeneration and inflammation relative to mdx mice.

Several studies have reported that activation of the calcineurin/NFATc1 pathway leads to increased sarcolemmal expression of the dystrophin homolog, utrophin A, and can improve the mdx clinicopathological phenotype. In this study utrophin A expression was analysed in FHL1-Tg/mdx skeletal muscle. Transgenic expression of FHL1 in mdx muscle enhances sarcolemmal utrophin A expression and promotes reassembly of dystrophin-associated-proteins. Therefore, utrophin A expression in FHL1-Tg/mdx muscle can functionally compensate for the absent dystrophin.
In C2C12 cells FHL1 enhances the transactivation of the utrophin A promoter via the calcineurin/NFATc1 pathway.

In conclusion, overexpression of FHL1 in skeletal muscle enhances sarcolemmal utrophin A expression via the calcineurin/NFATc1 pathway, to a level sufficient to improve muscle membrane integrity and prevent the progression of muscular dystrophy in mdx muscle. Therefore this study identifies FHL1 as a regulator utrophin A expression via regulation of the calcineurin/NFATc1 pathway. The findings in this study may lead the way to new therapies for DMD and other human myopathies.

Awards
(only 2011 awards given here)

NHMRC Dora Lush Biomedical Postgraduate Research Scholarship (for PhD) (2008 – 2011)

Monash University Group of Eight Merit and Equity Scholarship (for MBBS) (2004 – present)

Rural Australia Medical Undergraduate Scholarship (for RAMUS) (MBBS) (2004 – present)

Publications


Molecular imaging is a rapidly evolving field, which allows non-invasive detection of vascular pathologies. Activated platelets are key players in thrombosis, atherosclerosis and inflammation. We hypothesised that single-chain antibodies (scFv) directed against activated platelets and conjugated to ultrasound contrast bubbles would provide a unique approach for high sensitivity imaging of thrombus development and facilitate early diagnosis and treatment of thrombosis.

Microbubbles were conjugated to either a scFv specific for activated GPIIb/IIIa (LIBS-MB), or a non-specific scFv (control-MB). Flow experiments over pre-activated platelets demonstrated strong adhesion of LIBS-MB at 50s-1 when compared with control-MB (p<0.001). Detachment assays at increase shear rates of 1000s-1 and 6000s-1 dislodged most control-MB while LIBS-MB remained strongly attached (p<0.001). Platelet-rich thrombi were induced in carotid arteries of mice in vivo by ferric chloride injury (6%, 3 min) and assessed by ultrasound before and 20 minutes after microbubble injection. There was no change in greyscale area for animals injected with control-MB, whilst greyscale area strongly increased after LIBS-MB injection (p<0.001). After thrombolysis, ultrasound imaging observed a reduction in thrombus size (p<0.001).

We could demonstrate that anti-GPIIb/IIIa antibody targeted microbubbles specifically bind to activated platelets in vitro and in vivo, as well as facilitate monitoring of pharmacological thrombolysis on ultrasound imaging. This non-invasive and cost effective method has the potential to reduce the need for other expensive procedures and apply suitable therapeutic action earlier.

Xiaowei commenced her PhD in BakerIDI Heart and Diabetes Institute, under the supervision of Professor Karlheinz Peter in the Atherothrombosis and Vascular Division. Her research focuses on the detection of thrombus in blood vessels with ultrasound imaging. With increasing healthcare costs, the use of the cheaper ultrasound imaging in detection of molecular targets could potentially reduce the need for other expensive procedures and apply suitable therapeutic action earlier. Xiaowei’s research is supported by scholarships from Monash University and Baker Institute.
imaging modality provides a unique opportunity to detect arterial microthrombi at an early stage allowing for early diagnosis and therapy.

**Awards and Scholarships**
(only 2011 awards given here)

**2011:**
- World Molecular Imaging Congress 2011 Travel Grant (San Diego, USA)
- 59th Annual Scientific Meeting of the Cardiac Society of Australia and New Zealand 2011 Ralph Reader Prize Finalist (Perth, Australia)
- XXIII Congress of the International Society on Thrombosis and Haemostasis 2011 Young Investigators Award (Kyoto, Japan)
- European Molecular Imaging Meeting 2011 Travel Grant (Leiden, Netherlands)
- Monash Postgraduate Travel Grant 2011 (Monash University)
- Harold Mitchell Travelling Fellowships (Baker IDI Heart and Diabetes Institute)

**2008 – 2011:**
- Monash International Postgraduate Research Scholarship. (Monash University)
- Monash Graduate Scholarship (Monash University)
- Baker Bright Sparks Top-up Scholarships (Baker IDI Heart and Diabetes Institute)
  - Pierce Armstrong Foundation
  - Snowy Nominees Award

**Publications**

Abstract
Autoimmune diseases are characterized by a chronic adaptive immune response that targets self-antigens and leads to clinical pathology. Treatments of autoimmune diseases are often non-specific and do not address the cause, but aim to reduce symptoms. Multiple sclerosis (MS) and its animal model experimental autoimmune encephalomyelitis (EAE) are autoimmune diseases of the central nervous system. We have previously shown that transplantation of bone marrow (BM) cells transduced with retrovirus encoding the myelin autoantigen myelin oligodendrocyte glycoprotein (MOG), into total body irradiated mice can prevent the induction of EAE. This work has shown the potential of utilising BM gene therapy to cure autoimmune diseases; however the undesirable side effects of total body irradiation remain an obstacle for translation to the clinic. In this study, we have investigated the use of Treosulfan as a less toxic preconditioning regime and assessed the induction of tolerance and disease susceptibility to provide potential clinical feasibility assessment. Transfer of BM expressing MOG into partially myeloablated and non myeloablated mice using Treosulfan resulted in molecular chimerism and robust protection from the EAE. Moreover, in clinically relevant scenario of established EAE we could also promote immune tolerance and long-lasting disease resistance using a combination of corticosteroid treatment to induce initial remission, followed by Treosulfan at non myeloabltive dose and the transfer
of transduced BM to maintain long-term remission. Mice remained resistant to EAE even upon subsequent rechallenge with MOG-peptide. These results suggest that less toxic and more clinically applicable preconditioning regimes can be utilised to promote immune tolerance for the prevention and treatment of established autoimmune diseases.

**Publications**

Eight publications and two posters (details see below)


This thesis examined two of the most commonly occurring musculoskeletal conditions; osteoporosis and osteoarthritis. These musculoskeletal diseases are both leading causes of long-term pain and disability, and musculoskeletal disease is a major public health burden in developed countries worldwide, with significant attributable morbidity. It has been suggested that osteoporosis and osteoarthritis share common modifiable risk factors that are associated with socioeconomic status (SES); a construct that considers the level of social disadvantage, and usually measured by income, education, occupation, marital status, or by area-based aggregate scores. However to date, little is known of the relationship between SES and osteoporosis, and osteoarthritis. The results of this thesis provide a better understanding of the distribution of risk factors for both osteoporosis and osteoarthritis across SES; the relationship between SES and BMD; and the relationship between SES and fracture. Factors that affect the progression of osteoarthritis disease, as well as those that have adverse effects on cartilage and bone in asymptomatic clinically healthy individuals were identified. Structural changes in the knee associated with the development of osteoarthritis such as loss of articular cartilage, presence of cartilage defects, and BMLs were explored, and potentially modifiable risk factors for these changes were identified. Finally, the associations between SES and endpoints of both osteoporosis and osteoarthritis were examined; fracture as the endpoint of osteoporosis, and joint replacement in osteoarthritis. Sharon Brennan undertook her PhD with the DEPM under the supervision of Dr Anita Wluka, and with external supervision from Associate Professor Julie Pasco, The University of Melbourne. During her PhD she was supported by a NHMRC PhD Scholarship, completed her PhD in November 2010 and was conferred in May 2011. Her thesis was by publication, and included 14 publications. She has presented her work both nationally and internationally, and has received media attention in newspaper, radio and television formats. Sharon received a NHMRC Early Career Fellowship immediately following submission of her thesis, and has subsequently moved/defected to Department of Medicine, University of Melbourne to pursue her fellowship research program in the area of socioeconomic and psychosocial determinants of osteoporosis. However, she continues to work closely with Monash University on various research projects.
osteoarthritis. Overall, fourteen publications were included within the body of this thesis, and three further publications included as appendices.

**Awards**
(only 2011 awards given here)

National Health and Medical Research Council of Australia (NHMRC) Public Health Early Career Fellowship (1012472); 2011–14

School of Business Scholarship to undertake Graduate Certificate of Advanced Learning and Leadership, The University of Melbourne; 2011–12

Australia and New Zealand Bone and Mineral Society Travel Award, Gold Coast 2011. Endogenous parathyroid hormone is associated with reduced cartilage volume in vivo in a population-based sample of adult women.

Barwon Health Research in Progress Seminar; Best Presentation, June 21, 2011, Geelong. Does an increase in body mass index influence knee structure in healthy, non-asymptomatic adult females?

**Publications**
(only 2011 publications given here, see all at: www.findanexpert.unimelb.edu.au/researcher/person125267.html)

Pasco JA, Williams LJ, Jack FN, **Brennan SL**, Berk M. Don’t worry, be active: positive affect and habitual physical activity. *ANZ J Psychiatry*, Accepted 28 August 2011


Heart failure (HF) typically represents the end result of myocardial damage and myocyte loss, an inability to sufficiently regenerate the heart following injury. With the recognition that cardiac progenitor cells exist in the heart, there has been considerable interest in the development of strategies for cardiac regeneration in HF. Recently, the cardiac surgical resection model in zebrafish has been successfully exploited to study myocardial regeneration. However, the relevance of these studies to HF is limited given that they do not recapitulate HF and may therefore not account for the influence of potentially important changes in the local environment that could alter the regenerative response. Nerve growth factor (NGF) is a protein expressed in cardiac myocytes (CMs), and our lab has previously identified a significant decrease of NGF levels in the failing heart. Therefore, we hypothesised that NGF may play an important role in regenerating the heart, and the aim of this thesis was to examine if NGF can enhance cardiac regeneration by using a heart failure chemical injury model in zebrafish.

This thesis developed a chemical injury model, using Aristolochic acid (AA), a known agent to cause HF in larval zebrafish. HF was induced in 72 hours post fertilization (hpf) zebrafish larvae, by exposure to aristolochic acid (AA) for 3 hours. By 168hpf, AA induced a HF phenotype and death in 38% and 21% of larvae respectively (p<0.001 vs control). However, zebrafish exposed to AA and supplemented with NGF (50ng/ml) reduced the incidence of HF by 50% (p<0.001) and death by 65% (p<0.01). Hearts of cmlc2:GFP zebrafish were also studied.
isolated under fluorescence microscopy for real time PCR. AA exposure caused a 1.62 fold increase in caspase3 mRNA expression (p<0.05), consistent with induction of apoptosis. The addition of NGF did not alter caspase expression but increased Islet-1 mRNA levels by 2.7 fold (p<0.05), whilst expression of GATA4 was not altered. In association, in zebrafish incubated in BrdU, whole mount immunohistochemistry revealed that AA reduced the number of BrdU+ cardiac myocytes by 6.4 fold (p<0.01). In contrast, the addition of NGF post AA treatment increased the abundance of BrdU+ CMs in the heart by 4.8 fold (p<0.05), demonstrating that NGF increases proliferation of cardiac myocytes in the heart.

In summary, this thesis discovered that in a zebrafish model of cardiotoxic injury, NGF reduces the incidence of HF and mortality. The effect of NGF is mediated via a regenerative response rather than by a reduction in apoptosis, and this response is accompanied by proliferation of CMs.

Awards
Finalist – Three Minute Thesis competition, (Central Clinical School, Faculty of Medicine, Monash University).
Alfred Hospital Week Poster Prize – ‘Baker IDI Heart and Diabetes Institute Prize for Cardiovascular Research’ Baker IDI Rod Andrew Prize.
Finalist – International Society for Heart Research (ISHR) Student Investigator Award (Australasian Section). Oral Presentation.
Harold Mitchell Foundation Travelling Fellowship.
Australian Regenerative Medicine Institute Post-graduate Scholarship.
Nanotechnology is a rapidly developing field with increasing biomedical applications, although there is concern about potential adverse health effects. In humans, inhalation of ambient and anthropogenic nanoparticles (NPs) promotes lung inflammation and allergic asthma, although a significant component of these adverse effects are due to particle contaminants and induction of oxidative stress. However, little is known of the effects of inert non-inflammatory NPs on lung immunobiology and asthma. Previous studies from our group have shown that inert polystyrene 50nm nanoparticles are not inflammatory and are taken up preferentially by dendritic cells (DC) in the periphery. Here we tested the long-term effect of such inert nanoparticles on pulmonary DC function and induction of allergic asthma. Instillation of inert polystyrene NPs did not induce lung oxidative stress, and inhibited key features of allergic asthma including airway eosinophilia and allergen-specific Th2 cytokine production, using both experimental (OVA) and clinically-relevant allergens (Bermuda-grass pollen). Inert NPs did not impair peripheral allergen sensitisation, but exerted their effect locally at the lung allergen challenge phase by inhibiting the expansion of CD11c+MHCIihi dendritic cell (DCs) in the lung and draining lymph nodes, and allergen-laden CD11bhi DCs in the lung following allergen challenge. NPs further suppressed the ability of CD11bhi DCs to induce proliferation of OVA-specific CD4+ T cells in the draining lymph node following acute allergen challenge. The discovery that a defined type of NP can inhibit, rather than promote, lung inflammation via
modulation of DC function opens the door for nanotechnology to benefit other lung inflammatory diseases.

**Awards**

Jeanne was awarded the Cooperative Research Centre for Asthma and Airways (CRC-AA) top-up scholarship and travel scholarships. Jeanne is currently writing her PhD thesis and is preparing publication manuscripts of her results.
Acknowledgement

We would like to thank the students for their impressive work, dedication and achievements.

Our appreciation to Supervisors for their continued support and contribution to these outcomes.

To all our Q&A chairs

And to the audience who are interested in and supportive of medical research and its ultimate translation for the benefit of the entire community.