Research Report 2008

St Vincent's Centre

for Applied Medical Research

St Vincent's Hospital Sydney and
University of New South Wales

St Vincent's Centre
for Applied Medical Research

ST VINCENT'S CENTRE FOR APPLIED MEDICAL RESEARCH

In 1999, the Wills Review recommended the collocation of Australia's research effort into a limited number of large multi-disciplinary centres of excellence. The vision set forth in the Wills Review was of a stronger health and medical research sector characterised by: 1

- *high impact fundamental research, world-class workforce and infrastructure;*
- *priority driven research that contributes directly to population health and evidence based healthcare;*
- *an industry sector that mutually reinforces the research sector, with an emphasis on biotechnology; and*
- *increased public investment in a well-managed research sector.*

The St Vincent's research community responded to the Wills Review by commissioning McKinsey & Company to review the organisation and structure of its research efforts. At the time of the review, the St Vincent's Campus was characterised by separate research institutes each with varying degrees of governance autonomy and identities distinct from St Vincent's Hospital itself.

McKinsey recommended that St Vincent's Hospital provide leadership in promoting greater collaboration amongst the research entities recognising that great medical institutes were based on mutually reinforcing links between hospitals, research centres and universities.2

The approach recommended by McKinsey incorporated a number of elements:

- St Vincent's Hospital itself focusing more closely on research as part of a virtuous healthcare model of research, teaching and clinical care; and
- greater collaboration between the affiliated, but independent research institutes – Garvan Institute of Medical Research, the Victor Chang Cardiac Research Institute and the University of New South Wales, to secure the funding, both operating and capital - required to achieve world-class research outcomes.

The McKinsey Report set out the essential elements required to achieve research excellence which St Vincent's Hospital, in partnership with its affiliated research institutes, has been pursuing principally through two interrelated initiatives:

- the progressive development of the St Vincent's Research Precinct to physically co-locate and operationally integrate the shared infrastructure of the independent research institutes on the St Vincent's Campus. The "prize" to be achieved from this initiative is the critical mass required to support quality research, world class research talent and greater research funding; and
- *Restructuring of the hospital's research interests through a two stage process:*
  - *the creation of the St Vincent's Centre for Applied Medical Research with its own designated Research Director and with an increasing focus on translational research to complement the basic research of Garvan and Victor Chang.3*
  -
  - *the formation of the Institute of Virology, in partnership with the University of New South Wales, to create a research institute of sufficient size to both complement and equal the Garvan and Victor Chang institutes.*

The focus on complementary research effort – rather than duplicative or competitive

[1] Health and Medical Research Strategic Review, The Virtuous Cycle Working together for health and medical research, Commonwealth Department of Health & Aged Care 1999

[2] St Vincent's Research Community, Collaborating to Win, McKinsey & Co, 1999

[3] St Vincents & Mater Health Sydney, Developing a Five-Year Operational Strategy for Health and Medical Research, Proposed Strategic Framework (2003)

research - is an important theme of the research strategy for St Vincent's Hospital in its own right long with the further strengthening of the research efforts of the hospital with that of the Garvan, Victor Chang and the University.

Implementing our Vision

Drawing on the broad strategic vision set out above, the key elements of the research strategy now being implemented includes:

1) The establishment of the St Vincent's Research Precinct and Hub Governance Council (Darlinghurst Hub) to physically collocate and operationally integrate the shared infrastructure of the independent research institutes on the St Vincent's Campus; and

2) A restructuring of St Vincent's Hospital's own research interests through a two stage process:

The creation of the St Vincent's Centre for Applied Medical Research

The creation of the Institute of Virology in partnership with the University of New South Wales

St Vincent's Research Precinct

St Vincent's Hospital Sydney, Garvan Institute of Medical Research, Victor Chang Cardiac Research Institute and the University of New South Wales have long established mechanisms for working together to promote and enable their shared interests in teaching, research and clinical care.

This governance framework, which has now evolved into a formal Hub Governance Council, was evident through:

- *the creation of a company structure in 2001 (St Vincent's Research & Biotechnology Precinct Limited) to progress the development of the Stage 1 Building of the Precinct – the Victor Chang Lowy Packer Building which is now complete;*

- *entering into of a formal "Precinct Management Agreement" in 2008 by St Vincent's Hospital, Garvan and Victor Chang which sets out the formal arrangements between the Precinct Partners for the sharing and payment (on a cost recovery basis) of key infrastructure on the Precinct;*

- *the development of joint Committee structures, including but not limited to, the Human Research Ethics Committee and the Animal Ethics & Experimentation Committee which are utilised by all research entities on the St Vincent's Campus;*

- *other mechanisms, including the conduct of an annual research symposium and the production of the St Vincents & Mater Health Sydney Research Report which captures the research efforts of all the research entities on the Precinct or related to it.*

In March 2008, the Precinct Partners formed a Hub Governance Council, consistent with the requirements of the NSW Office for Science and Medical Research, to provide a formal structure to discuss and progress matters of mutual interest and strategic benefit in the ongoing development of their independent and hared research interests.

The development of a formal affiliation agreement between the Precinct Partners will now be progressed to capture the commitment each has given to working together to contribute to an improvement in health and health outcomes over the longer term.

St Vincent's Centre for Applied Medical Research

SVCAMR will be formally launched in early 2009, the SVCAMR will bring together the research groups of St Vincent's Hospital, including those formerly housed in the Centre for Immunology and on Level 9 of the Garvan Building, under the leadership of Professor David Cooper AO, as the inaugural Director of Research.

Through the development of the SVCAMR the aim is to increase the applied and clinical research focus of St Vincent's Hospital and to complement and leverage the basic research of Garvan and Victor Chang Institutes in establishing a world class reputation in translational research.

SVCAMR is committed to:

- Excellence in biomedical research. The Centre engages in fundamental scientific research in the fields of immunology and cell biology with relevance to allergy, inflammatory disease, cancer and HIV/AIDS. Collaborative projects link these studies to clinical trials, in particular HIV/AIDS
- Disseminating the results of this research widely to the medical and scientific community and to the general public
- Undertaking undergraduate and postgraduate training and teaching
- Providing the highest standards in research, development and translation of ideas to the diagnostic service delivery arena and patient care in accordance with the Mission of St. Vincent's Hospital

The centre conducts its research through 9 research programs:

- Inflammation
- Neuro-immunology
- HIV Immuno-virology
- Clinical research
- Blood, stem cell and cancer
- Gastro-oesophageal cancer
- Structural Biology
- Cancer
- Cancer Cell Biology

FORWARD

Scientific Success

In 2008 St Vincent's Centre for Applied Medical Research continued to build upon past achievements in inflammation, cancer, HIV and neuro-immunology research. The centre's research record continued to develop during the year with 71 peer-reviewed publications in internationally recognised journals. In addition our staff and students were active in disseminating research results through participation in international, national and local conferences.

The Centre has continued to be highly successful in attracting highly competitive peer-reviewed research grants from within Australia and overseas and has consistently produced highly motivated research students. During 2008 the key indicators of this success were:

- *Awarded 7 new NHMRC peer reviewed grants.*
- *Awarded 5 ARC peer reviewed grants.*
- *Awarded 21 new other peer reviewed grants.*
- *Total new funding awarded in 2008 was $5,165,599.*
- *15 post-graduate research students studying.*
- *10 post-graduate research students graduated in 2008.*

Government Support

St Vincent's Centre for Applied Medical Research has enjoyed the continued Infrastructure support from the Office of Science and Medical Research during 2008.

In addition the N.S.W Government in partnership with the Federal Government has awarded $59 million towards the construction of a new 10-storey Lowy-Packer building located on the St Vincent's Hospital Campus.

At the Official Opening of the Lowy-Packer building, which was held in September 2008, the Crown Princess Mary of Denmark together with the Hon Morris Iemma, MP, Premier of NSW, His Eminence George Cardinal Pell, Archbishop of Sydney and congregational leader of the Sisters of Charity Elizabeth Dodds were among those gathered for the official opening of the building.

In opening the nine-story purpose built research building, Princess Mary described the facility as a "state-of-the-art research environment for some of the brightest and best minds in the country. The new building which was blessed by His Eminence, Cardinal George Pell, will house close to 250 AMR and Victor Chang Cardiac Research Institute researchers.

Community Support

In the 2008 end of tax year appeal direct marketing campaign introduced a theme of fast-tracking biomedical research *'from bench top to bedside'* which raised over $144,000. Several significant donors gave exclusively toward furthering research into HIV and related infections. The campaign announced the stage 1 Lowy-Packer building and the St Vincent's Centre for Applied Medical Research.

Professor David Cooper AO

Director of SVCAMR

SV&MH CEO Mr Steven Rubic, Sr Elizabeth Dodds RSC

HRH Princess Mary of Denmark and Professor David Cooper AO

progress

New CEO sees exciting times ahead for St Vincent's

Dear Friends,

I would like to begin this message by acknowledging what an honour it is to have been appointed Chief Executive Officer of this outstanding organisation. I have worked with the Sisters of Charity for 17 years and am very excited to be leading St Vincents & Mater Health Sydney in its next chapter. I am looking forward to tackling the new challenges that lie ahead in public, private and aged care health services. We have some very exciting projects underway and in the pipeline across all our facilities.

I also take this opportunity to welcome the appointment of Mr Jonathan Anderson as Executive Director of St Vincent's Public Health Services .

Jonathan has an extensive and successful career in public healthcare in New South Wales. He has held leadership positions across a broad range of facilities and service types including tertiary referral teaching hospitals, district hospitals, sub-acute and aged care facilities.

In his numerous roles over 25 years, Jonathan has demonstrated impressive leadership based on building strong relationships with all stakeholders, winning support from doctors, nurses and other partners as well as ensuring the Mission is central to all his actions.
I'm sure as supporters of this great Hospital, you join me in congratulating Jonathan on his appointment.

Finally, I would like to draw your attention to another wonderful initiative – Stage 1 of the amazing St Vincent's Research Precinct, the Victor Chang Lowy Packer Building, housing the new St Vincent's Centre for Applied Medical Research. Stage 1 of what will be a world-class research facility will be unveiled early in September (see back page). I'd like to thank those of you who donated to our recent appeal for vitally needed research equipment for use in this new centre… our overall target for the modern equipment we require has not yet been reached, so we have extended this appeal in a bid to make up the $300,000 shortfall. Any assistance you can provide would be greatly appreciated.

I look forward to getting to know as many of our wonderful supporters as possible on a personal basis in the years ahead.

Steven Rubic
Chief Executive Officer, St Vincents & Mater Health Sydney

Fast-tracking research 'from bench top to bedside'

With the advent of the new St Vincent's Centre for Applied Medical Research within the Victor Chang Lowy Packer Building opening in September, opportunities to optimise results of world-class research and use scientific discoveries to provide improved care for our patients will be greater than ever.

However this amazing facility will require the state-of-the-art tools - critical high-end modern equipment – so our researchers can make the vital discoveries that save lives.

By integrating fundamental research with clinical outcomes, scientists at St Vincent's have already been responsible for many major breakthroughs in fields ranging from the treatment of cancer and inflammatory diseases to HIV/AIDS, dementia and heart disease. But to fast track the application of crucial discoveries 'from bench top to bedside', our researchers need your help.

A recent appeal raised money towards the purchase of several pieces of vital equipment urgently required for the new research facility… machines that will expedite the rapid application of research discoveries to patient care. Our thanks to those of you who responded generously to this important appeal.

Unfortunately, we still have a considerable shortfall to make up as this special equipment is expensive… in fact we still need to raise $300,000 and so have extended our appeal through to the end of winter.

The list of hi-tech equipment our researchers need includes:

Ultracentrifuge – a centrifuge that runs at extremely fast speeds that allows scientists to separate particles far smaller even than blood cells - such as viruses, nucleic acids and proteins.

Nucleic acid extractor - a core item to be shared across research programs. It will enable DNA to be isolated from blood and living human tissue so a wide range of experiments can be undertaken to study the genetic makeup of different genes implicated in disease.

Cryogenics freezers – enabling samples to be frozen at incredibly low temperatures so that living tissues can be stored indefinitely in 'suspended animation' then retrieved and studied years later in conjunction with new discoveries.

LUMINEX xMAP - technology that allows our scientists to interrogate multiple applications vital to the drug-discovery and diagnostics fields.

If you are yet to give to this important appeal, please continue your support of St Vincent's Hospital as a matter of urgency. Your gift will fast track the application of the brilliant discoveries our research teams make, so the patients in our care can receive even better treatment. It could even help to save lives.

To give whatever you can afford, simply complete and return the donation form below. Thank you in anticipation.

Your ongoing support is vital

Many people are touched by the work of the dedicated medical, nursing and ancillary staff at St Vincent's Hospital. Both your financial AND non-financial support are wonderful ways of recognising the care they provide.

Ways to donate

- Phone: 1800 800 595
- Fax: (02) 9361 4573
- Complete and mail this form to St Vincent's using the courtesy envelope enclosed

☐ Yes, I want to help purchase vital research equipment

OR

☐ I would like my donation to be used for other services provided by St Vincent's

Your Privacy. St Vincents & Mater Health Sydney (SV&MHS) respects your privacy and complies with the National Privacy Principles. SV&MHS only collects that information needed to provide and communicate services to you. To read the full privacy statement, visit www.stvincents.com.au

☐ Please tick this box if you do not wish to receive any future communications from St Vincent's Hospital.

<DonorNumber> <campaign code>
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Phone ( )_____

Please accept my ☐ Single or ☐ Monthly donation of:

<donation amounts>

☐ My cheque/money order is enclosed (payable to St Vincent's Hospital)

OR

☐ Please debit the amount I've indicated above from my:

☐ VISA ☐ MasterCard ☐ Diners Club ☐ Amex

Cardholders Name_____

Card No. ☐☐☐☐ ☐☐☐☐ ☐☐☐☐ ☐☐☐☐

Expiry Date ☐☐/☐☐

Signature _____

☐ Bequests – please send me information.

I authorise St Vincent's Hospital to deduct this amount from my credit card on receipt of this form. If monthly pledge has been ticked please deduct this amount from my credit card accordingly. This authority will remain valid until revoked in writing by me or St Vincent's Hospital. Every donation of $2 or more is tax deductible.

St Vincent's Hospital ABN 77 054 038 872 SV0808D

GOVERNANCE

The St Vincent's Centre for Applied and Clinical Research, has its own Board of Governance. The Board operate under delegation from the St Vincent's & Mater Health Sydney Board, which is the Board of St Vincent's Hospital Sydney Limited. The Board includes an independent Chairman and directors, the majority of whom are independent of the Centre.

The external chairman was formally appointed to the board on June 1, 2006.

Scientific Management Committee

The AMR Research Program Heads Committee reports to the Director of Research, St Vincent's Hospital Sydney, in relation to research activities and operational matters arising on campus. The focus of the Committee is on improving the effectiveness and efficiency of laboratory research activities. In particular, the meetings

- *Identify opportunities for improving laboratory research productivity, particularly the potential for collaboration or more effective networking of laboratory research sectors and service providers;*
- *Review and report on proposed improvements in relation to governance of the research campus*
- *Have regard to matters relating to the research infrastructure funding agreement with NSW Health Department and other funding agencies.*
- *Other issues relevant to campus research as may arise.*

The current organizational structure of AMR has been defined. Seven primary research programs:

Inflammation and cytokine research (Professor Samuel Breit) - commercialization of MIC-1, two sub-groups neuroinflammation (David Brown) and cell biology of inflammation (Lele Jiang)

Neurovirology, neuroimmunology and adult stem cells (Professor Bruce Brew) continuing research in effects of HIV on nervous system and a second group more recently potential applications of stem cells in treatment of neurodegenerative diseases and stroke.

HIV Immunopathogenesis program (A/Prof Anthony Kelleher) largest group involving three main groups cellular immunology, molecular pathogenesis and clinical trials. The new building has a new state of the art PC3 containment laboratory currently undergoing certification by the Gene Technology regulator.

Blood, Stem cell and Cancer program (Professor David Ma) looking at stem cell transplantation, haematological malignancies, and molecular basis to clotting disorders.

Gastro-oesophageal cancer (A/Prof Reg Lord) – new program looking at the pathology and molecular aspects of progression of Barretts's oesophagus to cancer which is increasing in prevalence.

Clinical Research Program (Professor Andrew Carr) to consolidate and provide a support base for clinical research initiatives on campus incorporating clinical services, allied health support units and compliance departments. The new program's objective is to promote excellence in clinical research, support and training, manage risks and to provide advice to Board on ethical and research governance matters and matters of dispute. The group will also continue clinical research in HIV

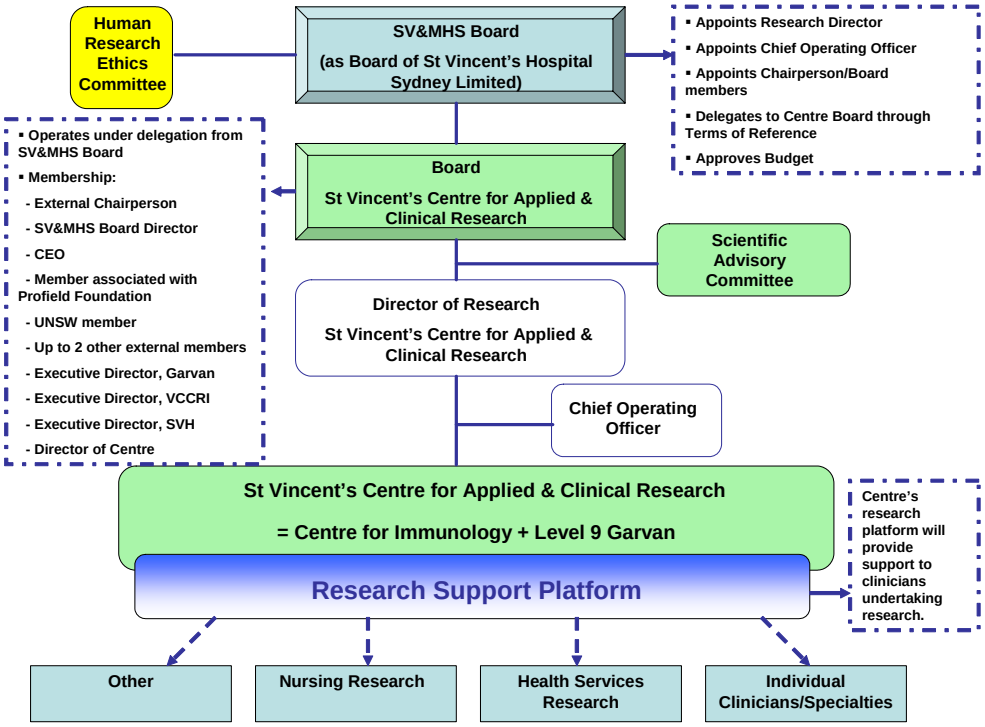
medicine and the metabolic disorders associated with antiretroviral therapy.

Structural biology (Professor Paul Curmi) the only research program located on the University Randwick campus due to the dependence on significant scientific infrastructure housed at the School of Physics. This work is highly collaborative with a number of the AMR programs and allows detailed research into biomolecular structures, receptors and ion channels important in drug development.

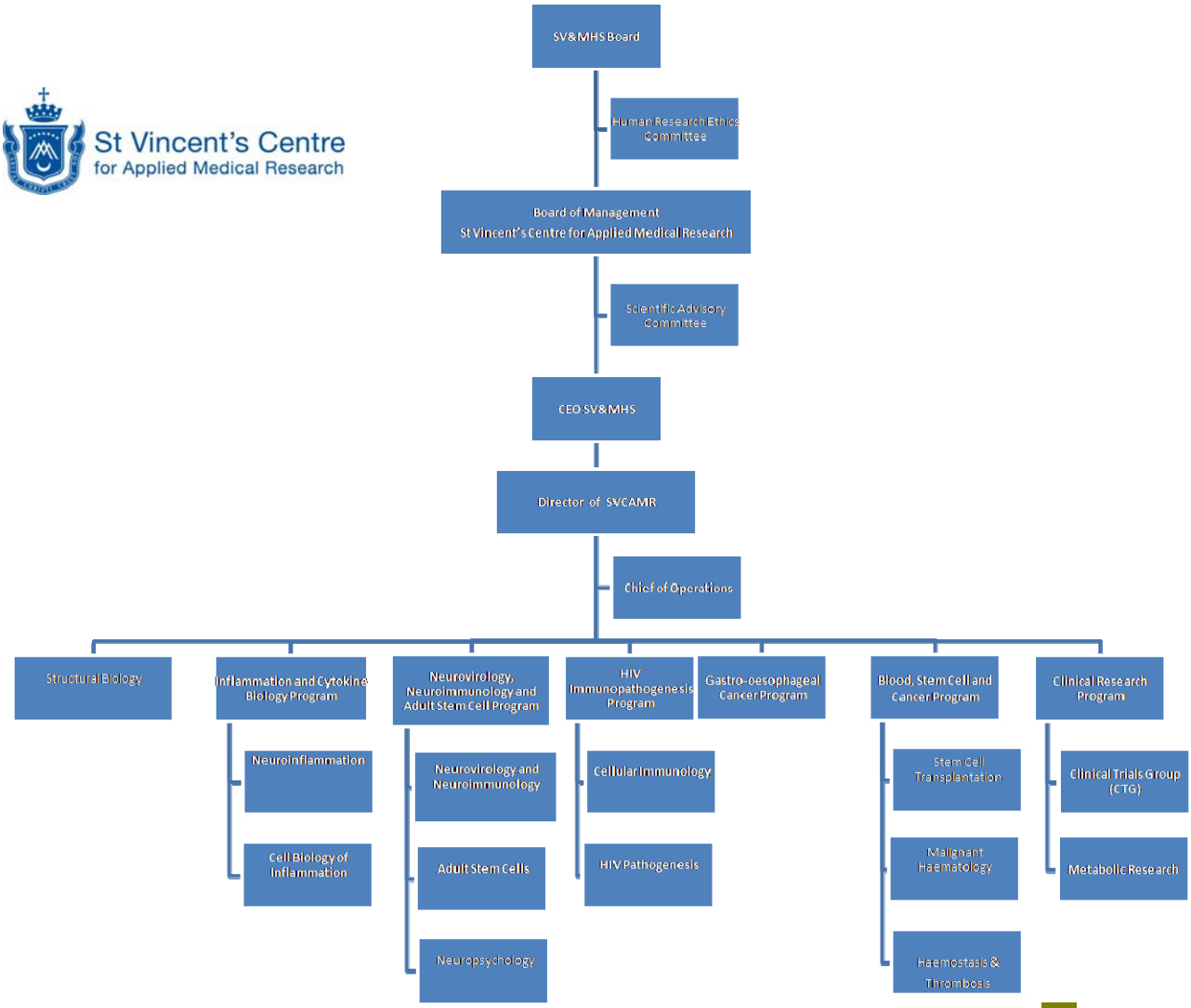
There have been some changes in the AMR structure over the last 12 months which has by default focused the emphasis of research at AMR in the fields of immunology, virology (HIV) and clinical research.

Cancer program (Professor Robyn Ward) is in the process of relocating her research program from the St Vincent's Campus to the soon to be completed Lowy Cancer building at the UNSW Randwick and Prince of Wales Hospital campus. The move is expected to be completed by 2010.

Cancer Cell Biology (Dr Thomas Grewal) has moved to the Sydney University campus to continue collaborative research. He completed his move in April 2008.



St Vincent's Centre for Applied Medical Research



RESEARCH ACTIVITIES

INFLAMMATION

RESEARCH PROGRAM

The work of this group is directed to gaining a better understanding of the pathogenesis of cancer and inflammatory diseases such as atherosclerosis and rheumatoid arthritis. We would then like to utilise this knowledge to improve diagnosis, management and therapy of the conditions in question. We have focussed our studies around 2 proteins, MIC-1 and CLIC1, first identified and characterised in this laboratory in the 1990's, on the basis of increased expression with macrophage activation. We plan to continue and extend our knowledge with observations into the following areas:

MIC-1

- Identify and characterise the MIC-1 receptor and its signalling pathways.
- Further elucidate the role of MIC-1 in the biology of cancer.
- Elucidate the role of MIC-1 in cancer cachexia, weight and appetite control.
- Establish MIC-1 serum level determination and genotyping as a diagnostic test for cancer diagnosis and management and commercialise this technology.
- Undertake a therapeutic trial of monoclonal antibody to MIC-1, to determine if it is effective in treatment of cancer cachexia in humans, as it is in the animal model.
- Further elucidate the role of MIC-1 in regulating immune and inflammatory responses.

CLIC1

- The role of CLIC-1 in regulating platelet function.
- The mechanism of action of CLIC1 in the regulation of the immune and inflammatory responses.
- In collaboration with the groups of Prof Paul Curmi, and Prof Michele Mazzanti, define the structure/function relationship of CLIC1 and obtain the high resoltution structure of the membrane form of this protein
- The role of CLIC-1 in the regulation of immune and inflammatory responses.

BACKGROUND

I. MIC-1 in normal biological processes and disease

Multiple lines of evidence now implicate MIC-1 in several areas of biology and disease pathogenesis including cancer, reproduction, chronic inflammation and immunity, regulation of iron absorption and erythropoiesis, and as is the subject of the application, appetite regulation, as well as disease mediated cachexia.

a. MIC- in immune and inflammatory disorders

MIC-1 is expressed at the site of injury and inflammation such as the brain following thermal injury, sites of atherosclerosis, and rheumatoid synovium. Accompanying synovial expression serum MIC-1 levels are elevated in proportion to rheumatoid arthritis disease activity and return to normal following aggressive therapies such as bone marrow transplantation. Interestingly, MIC-1 is not an acute phase protein and is not modified by therapies such as high dose pulse corticosteroids.

b. MIC-1 and cancer.

MIC-1 is strongly linked to cancer and this subject has recently been reviewed in *Cancer Res* by the applicant. MIC-1 is secreted in large amounts by many cancer cell lines and cancer tissues. We were the first to demonstrate that patients with metastatic cancer of prostate, breast and colon markedly over-expressed MIC-1 protein within tumours and that this resulted in a large increase in serum MIC-1 from normal serum levels of 250-1250pg/ml, to 100,000pg/ml. We have continued studies in this area and have demonstrated diagnostically useful relationships between serum MIC-1 and colon, prostate and pancreatic cancer.

MIC-1 and colon cancer. We have shown a progressive rise in serum MIC-1 levels accompanying progression from normal to benign colonic polyps to dysplastic colonic polyps and finally to colon cancer. Additionally, MIC-1 level at presentation is an independent predictor of metastasis and survival in this malignancy. As part of this study, we also investigated the MIC-1 H6D polymorphism, which we were the first to describe, and found that the D allele was associated with significantly better patient survival though earlier relapse.
The role MIC-1 plays in colon cancer pathogenesis is not clear, but evidence thus far suggests it is protective. Transgenic mice overexpressing MIC-1 were protected from azoxymethane induced aberrant crypt foci formation. When crossed with APCmin mice, the presence of the MIC-1 transgene was also associated with a reduction in small bowel polyp formation.

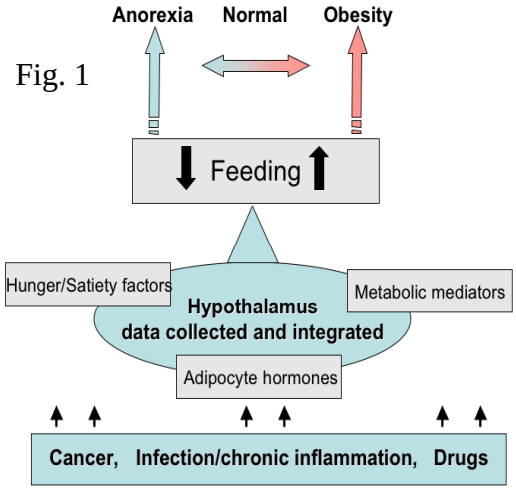
MIC-1 studies in prostate and pancreatic cancers. We have also been able to demonstrate diagnostically useful relationships between serum MIC-1 and both pancreatic cancer and PCa. In collaboration with Rob Sutherland's group at the Garvan Institute, we have examined MIC-1 staining in tissue arrays from about 194 subjects with PCa and shown that MIC-1 is over-expressed as expected and there is a strong association between decreasing MIC-1 immunostaining and extra-prostatic invasion in radical prostatectomy specimens (odds ratios 1.6-3.8, p=0.018).

Serum MIC-1 levels are elevated in advanced PCa and elevated levels are the best predictor of bone metastasis. In early disease, we have demonstrated that an algorithm incorporating MIC-1 serum levels led to significantly increased diagnostic specificity over PSA and/or % free PSA and potentially could reduce unnecessary biopsies as often occurs following abnormal PSA results alone.

c. MIC-1 in appetite regulation and cancer cachexia

Mammals have evolved a complex system to regulate food intake and to maintain energy homeostasis (Fig. 1). Meal size is controlled by short-term hormonal and neural signals that are derived from the gut, such as ghrelin, which initiates meals, and cholecystokinin, GLP-1, PP and PYY(3-36), which act as satiety factors. Insulin and leptin, together with circulating nutrients, regulate long-term energy stores. All these signals act on sites in the brain, which converge on the hypothalamus and influence food intake. Energy deficiencies, as seen in prolonged starvation, activate powerful brain NPY pathways that increase appetite and decrease energy expenditure. At the same time energy deficiency decreases levels of alpha-melanocyte-stimulating hormone (α-MSH) and cocaine-amphetamine-related transcript (CART), neurotransmitters that normally reduce food intake and increase energy expenditure.

Fig. 1



Imbalances in the normal regulation of food intake can lead to obesity or severe weight loss, which are caused by genetic, lifestyle and behavioural factors as well as underlying disease. Obesity is a major global public health concern, with Australia being one of the most affected countries. Obesity-associated cardiovascular disease and diabetes are leading causes of death and are expected to increase as the obesity epidemic worsens. Conversely, severe anorexia and weight loss leading to cachexia are more commonly due to underlying disease processes such as cancer, chronic infection, renal or cardiac failure. Cachexia greatly limits cancer therapy, causes about 25% of cancer deaths, and its treatment has limited efficacy.

We have recently published a major paper in *Nature Medicine* identifying MIC-1 as a major cause of anorexia/cachexia of advanced cancer and chronic renal failure. In this paper we were able to demonstrate a strong and direct correlation between serum MIC-1 levels, which rise dramatically in many advanced cancers, and the degree of patient weight loss over a six month period. Further, mice xenografted with tumours over expressing MIC-1 developed dramatic weight loss and became cachectic. This was directly attributable to MIC-1 as its serum levels in mice correlated with the degree of weight loss and the weight loss could be completely reversed by monoclonal antibodies to MIC-1. Additionally, direct injection of recombinant MIC-1 into mice caused rapid weight loss that was mediated directly by decreased food intake, rather than metabolic effects. Further, we showed that a major site of action of MIC-1 was the arcuate (ARC) nucleus of the hypothalamus, a major brain centre for weight regulation. The ARC ist susceptible to modulation by blood born appetite regulatory molecules. Following systemic administration in mice, a major action of MIC-1 in the ARC was to decrease the expression of NPY, a major brain peptide which mediates appetite stimulation and increase the expression of POMC, a major brain peptide mediating anorexia. These effects occurred via the TGF-b RII receptor and involved activation of both ERK and STAT3 pathways of neuronal cells in the ARC. The above data had several important implications, which indicate that:

- MIC-1 is a previously unrecognised novel appetite control molecule.
- monoclonal antibodies to MIC-1 are potentially useful therapeutics for cancer anorexia/cachexia. They will probably also be effective for any cause of anorexia/cachexia associated failure).
- therapeutics based on recombinant MIC-1 may be a useful treatment of severe obesity.

II. CLIC1 in normal biological processes and disease

Ion channels are expressed on the plasma membrane of all cells and have also been found on the membranes of intracellular organelles. They subserve essential functions in all cells and evidence of their

importance includes their high degree of conservation across species and the rapidly growing list of genetic diseases associated with ion channel defects. Ion channels are also important therapeutically and have been utilised extensively and effectively as drug targets, by the pharmaceutical industry. Early evidence suggests that CLIC1, the subject of this grant, may be a suitable therapeutic target for inflammatory disease therapy and to our knowledge is a subject of interest of both Pfizer and Aventis, who have contacted us about this protein.

Cloning and biology of CLIC1

CLIC1 (formerly NCC27) is a 241 amino acid ion channel protein first cloned by us because of its increased expression with macrophage (MAC) activation. We have subsequently published extensively on this protein, which was the first identified human member of a growing family of intracellular organellar ion channels, whose biological function is still incompletely understood.

a. Biological significance of CLIC1 and the CLIC family. Whilst there is still little know about the biology of CLIC proteins, evolution has provided us with an irrefutable argument as to their importance: remarkably preservation across evolution of this family. The whole CLIC family is highly conserved across a very wide range of species e.g. only three conservative substitutions between human and murine CLIC1 proteins. Clearly defined relatives can be detected in the genomes of all vertebrates sequenced so far, the chordate, *Ciona intestinalis*, and the invertebrates *Anopheles* and *Drosophila* and *C. elegans*. Even *Ciona* CLIC and human CLICs are about 50% identical. CLIC1 itself is located within the major histocompatibility complex (MHC), one of the most conserved and important regions in the genome. It is in close proximity to other stress response proteins including TNF-a, HSP70 proteins and proteins involved in Ag presentation.

b. Other members of the human CLIC Family. The six member mammalian family of CLIC proteins share high similarity (about 60-75%) in the "CLIC domain" but vary in their cellular and sub-cellular distribution. CLICs are associated with various intracellular membranes including the plasma and nuclear membranes and localises to granular cytoplasmic organelles, the ER membrane, large dense-core vesicles, mitochondria, TGN vesicles and secretory vesicles. CLIC4 (mtCLIC) is partly localised to mitochondria, helps maintain mitochondrial membrane potential and participates in the apoptotic response to p53.

Electrophysiology of CLIC1

We have published detailed electrophysiological characterisation of CLIC1. Using a combination of whole cell, single channel and macropatch recording, we have shown that CLIC1 is a Cl^- dependent Cl^- channel and conducts both inward and outward current, with a reversal potential around 0 mV and conductances of about 8.2 pS for inward and 15.8 pS for outward current. Despite CLIC1's unusual characteristics, (small and with only a single putative transmembrane region), we and others have published data that definitively identify it as an ion channel. By selectively tagging either the N- or C-terminus of CLIC1, and varying the side of the membrane from which we record channel activity, we have shown that CLIC1 is a transmembrane protein that forms an integral part of the ion channel. Further, these studies indicate that the N-terminus projects outwardly and the C-terminus inwardly. Additionally, we and others have demonstrated that soluble recombinant *E.coli*-expressed CLIC1 protein forms ion channels in artificial lipid bilayers. Whilst bilayer studies of solubilised membranes may be prone to artifact, the situation with CLIC1 is more clear-cut. Most ion

channels must be incorporated into liposomes, which then fuse with the lipid bilayer. However, with CLIC1 (and CLIC4), soluble aqueous recombinant protein enters the bilayer directly. CLIC1 has similar electrophysiological characteristics, whether transfected into CHO cells or in artificial lipid bilayers, indicating it can function as an ion channel without ancillary proteins.

Structure/Function Studies

An understanding of structure/function is an essential element in understanding molecule function and our group has started to unravel this in the CLIC family. Our collaborators (Prof Paul Curmi's group) have solved the high-resolution crystallographic structure of the soluble form of CLIC1, the first high-resolution study of a member of this family and more recently the structure of CLIC4, drosophila CLIC and EXC-4. CLIC1 is a structural homolog of the glutathione-S-transferases (GST) and contains a glutathione (GSH) binding site motif but does not bind reduced GSH. CLIC1 must undergo significant conformational change from its globular, soluble structure in order to form an ion channel. Its GST-like structure provides a strong argument for the role of oxidation/reduction/GSH in the function of CLIC1 and pursuing this line of reasoning, we have shown that on oxidation, CLIC1 undergoes a reversible transition from a monomeric to a non-covalent dimeric state, due to the formation of an intra-molecular disulphide bond (Cys24-Cys59). We have determined the crystal structure of this oxidised state, and show that a major structural transition has occurred, exposing a large hydrophobic surface, which forms the dimer interface. The oxidised CLIC1 forms Cl^- channels in artificial bilayers and vesicles, while a reducing environment prevents the formation of ion channels. Initial mutational studies suggested that both Cys24 and Cys59 are required for channel activity, but later, as yet unpublished studies indicate that only Cys24 is essential, whilst Cys59 acts by increasing sensitivity to the oxidative modification needed for lipid bilayer binding.

Biological role of mammalian CLIC family proteins

There is limited data on the biological function of vertebrate CLICs in general and CLIC1 specifically: i) A mutation, generating a stop codon in exon five of CLIC5, is the cause of a spontaneous mutation (jitterbug) in mice, causing impaired hearing and vestibular dysfunction associated with dysmorphic stereocilia, progressive hair cell degeneration. CLIC5 is normally localised to stereocilia of cochlear and vestibular hair cells. ii) CLIC4 is up-regulated by TNF-a, stress and p53 and has been strongly linked to *in vitro* control of apoptosis. iii) CLIC1 is up-regulated by activation in MACs and we have shown that PMA and amyloid peptide induce CLIC1 on the plasma membrane of both murine microglial cells and the microglial cell line BV2. In co-cultures with neuronal cells, these activated microglia cause neuronal cell apoptosis due to release of reactive nitrogen species and TNF-a.

Sub-program Neuro-inflammation

David Brown Lab leader

Molecular and cellular mechanisms of CNS immunity

(David Brown, Vicky, Sabina)

T-cells mediate neuroprotective/ neurodegenerative events and can be easily manipulated by systemic therapy. The mode of T-cell regulation of critical events in the CNS is essentially unknown. We are currently investigating the normal state of CNS immunity and the molecular and cellular changes associated with T-cell mediated neurodegeneration/ neuroprotection.

Neurological disease is a leading cause of morbidity and mortality with escalating economic and social consequences. Alzheimer's disease and stroke in the elderly and; spinal cord injury and multiple sclerosis in younger patients, lead to significant disability and economic burden. The core pathological mechanism that dictates disability in these conditions is neurodegeneration. As T-cells may induce neuroprotection or neurodegeneration and can be manipulated outside the CNS, they represent an obvious target for therapeutic intervention. However, the mechanisms by which T-cells mediate these events are poorly understood. Consequently, the systematic assessment of the CNS-immune interface and its relationship to neurodegeneration/neuroprotection holds the promise of delivering therapies to limit and perhaps reverse the devastating effects of neuroinflammatory disease.

The central nervous system (CNS) has been considered to be exempt from many immune mechanisms. However, CNS autoreactive T-cells mediate neuroprotection and neurodegeneration and regulate neurogenesis. To define T-cell characteristics mediating these apparently opposing functions we are determine the distribution of major CNS cellular immune elements and their relationship to neurodegeneration in normal and experimental allergic encephalomyelitis (EAE) affected mice. Additionally, we are characterising CNS antigen processing and its effect on T-cell mediated neurodegeneration. Ultimately, this will identify novel transcripts modulating T-cell mediated neurodegeneration and neuroprotection. This data will be used for the development of novel therapeutic strategies to treat neurodegenerative diseases such as Alzheimer's and Parkins's disease as well as multiple sclerosis.

CCAAT/enhancer binding protein-delta (CEBPD) in neuroinflammation

(David Brown, Vicky, Sabina)

T_h17 cells cause organ specific autoimmune diseases, including Multiple Sclerosis (MS). CEBPD modulates the generation of T_h17 cells and disease suppressing T-regulatory cells (Tregs). This project will determine how CEBPD acts and provide the preliminary information required to advance CEBPD to therapeutic studies in humans.

Recruitment of CNS neurotoxic T-cells is a defining feature of MS a disease costing in excess of $2 billion per year. The development of MS with the emergence of neurotoxic T_h17 cells appears to be due to reduced T-cell regulatory cell (Treg) function. Similar mechanisms are operation in experimental autoimmune encephalomyelitis (EAE). CEBPD deficient animals have altered CNS T_h-cell differentiation, reduced numbers of T_h17 cells and increased numbers of Tregs with reduced EAE disease. This indicates CEBPD regulates the differentiation of T_h17 and Tregs. CEBPD is upregulated with inflammation and is not expressed in normal inflammatory cells. Additionally, multiple inflammatory pathways, including those of IL1 and IL6, converge upon CEBPD. Targeting CEBPD in circulating cells leads to

reduction in EAE suggesting circulating inflammatory cell CEBPD expression participates in EAE. As these cells are easily accessible for therapeutic modification, CEBPD represents a credible therapeutic target for EAE and ultimately MS, as well as other T_h17 mediated autoimmune diseases.

Multiple sclerosis (MS) is mediated by T_h17 T-cells, which secrete IL-17. Both IL-17 and a transcription factor CCAAT/enhancer binding protein-delta (CEBPD) are upregulated in human MS plaques. Additionally, IL-17 mediates its effects via CEBPD leading to IL-6 production a key factor in T_h17 cell differentiation, potentially exacerbating disease or leading to relapse. Consequently, CEBPD may be a novel therapeutic target regulating T-cell differentiation in CNS inflammation. We are currently determining the time course and cellular distribution of CEBPD expression in EAE and its relationship to T_h-cell differentiation. Additionally, we are defining the effect of modulating CEBPD expression upon T_h-cell differentiation in EAE. Ultimately this work will determine the molecular mechanisms by which CEBPD modulates T_h-cell differentiation.

Macrophage Inhibitory cytokine in disease

(David Brown, Sam Breit)

MIC-1 is a TGF-ß superfamily member first cloned by us and can be viewed as anti-inflammatory and antitumourogenic. It has a coding single nucleotide polymorphism (SNP) that alters predisposition to, and survival of cancer; and progression of inflammatory diseases. Serum MIC-1 level determination is also a useful clinical tool. Increased tissue expression of MIC-1 is associated with serum levels above the normal range. Elevated serum MIC-1 may be used for diagnosis/management of a number of cancers; and predicts outcomes in atherosclerosis and rheumatoid arthritis. While the role of MIC-1 in inflammation has not been defined, it is likely to be important in the progression of cancer and inflammatory diseases.

Macrophage inhibitory cytokine-1 (MIC-1) participates in the development of cancer and inflammatory diseases. Additionally, elevated serum MIC-1 levels predict adverse events in these diseases. However, the role of MIC-1 in disease pathophysiology is poorly characterised. The major thrust of this Project is to extend the clinical utility of MIC-1 and bridge the gap between clinical and pathological roles of MIC-1 in cancer and inflammation. The focus of this project is defining the role of serum MIC-1 measurement in the diagnosis and management of cancer and inflammatory diseases and the role of MIC-1 in the pathogenesis of inflammatory diseases and cancer immunity.

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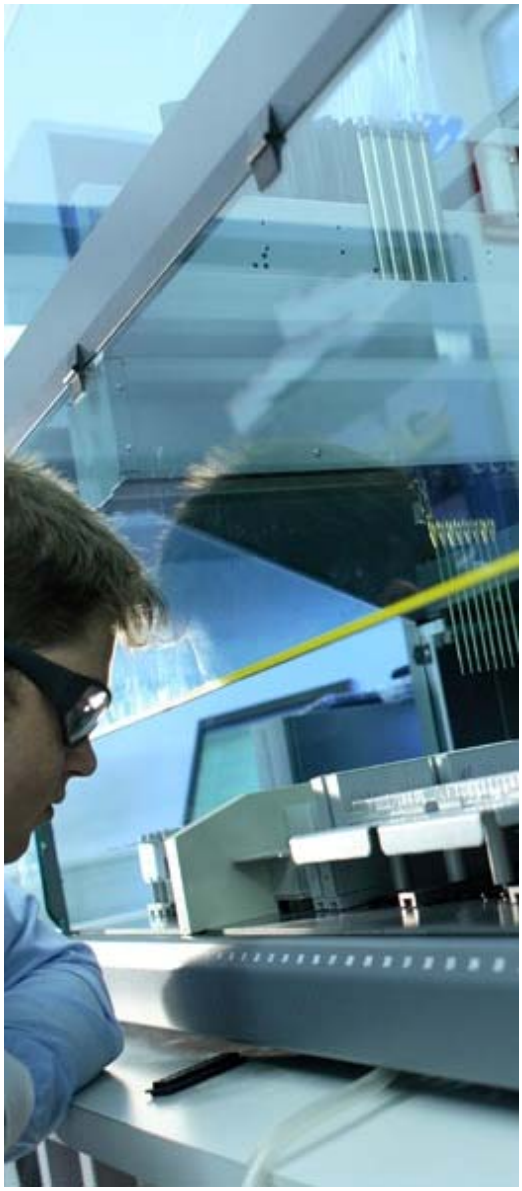
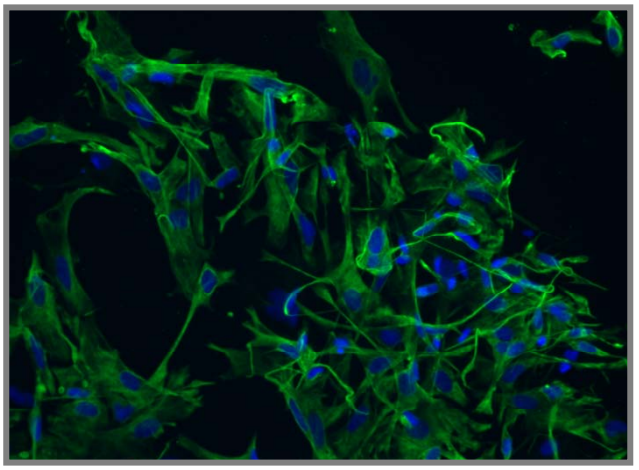


NEURO-IMMUNOLOGY

RESEARCH PROGRAM

The broad research areas of the neuro-immunology research program lead by Professor Bruce Brew is neurology and neuroscience. Specifically these include neurodegenerative disorders, HIV/AIDS dementia complex, kynurenine pathway, multiple sclerosis and adult stem cells. The group's research objective is to extend knowledge into the following areas:

- Molecular and cellular basis AIDS dementia complex – immunological, virological and neurological
- The kynurenine pathway, chemokines in the pathogenesis of AIDS dementia
- Stem cell transplantation to facilitate remyelination in multiple sclerosis and Krabbe disease
- Involvement of quinolinic acid and other tryphophane catabolites in the pathogenesis of Alzheimer's disease
- The kynurenine pathway in the pathogenesis of amyotrophic lateral sclerosis (ALS)



Adult human astrocytes

Sub-program Neuro-stem cell group

Juliana Lamoury group leader

RESEARCH INTERESTS:

Adult stem cells derived from brain and marrow tissues: i) investigation of differentiation of stem cells into neural cells; ii) examination of the potential of bone marrow- and brain-derived cell transplantation as a treatment for multiple sclerosis and genetic disorders that result in demyelination. Collaboration exists with centres in the USA, Germany, Melbourne and University of Sydney.

1. Adult stem cells and their application to neurodegenerative disorders.

The cause of multiple sclerosis is unknown but it is thought most likely to be a consequence of an autoimmune process. The disorder is characterised most often by a relapsing remitting course that over time transforms into a chronic slowly progressive disease without remissions. It is postulated that the remissions are related to the presence of oligodendrocyte precursors that can differentiate into oligodendrocytes and lead to remyelination. Over time

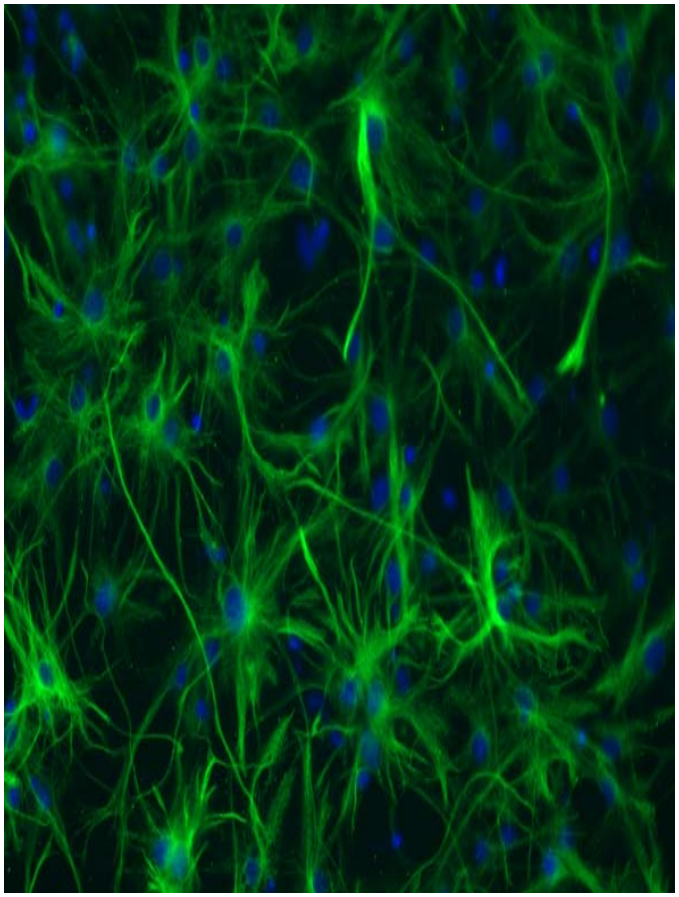
the "pool" of oligodendrocyte precursors becomes exhausted and so the disease becomes progressive. Our group is in the process of differentiating human and mouse brain and marrow derived stem cells into neural cells including oligodendrocytes for transplantation into mouse models of demyelination to determine their efficacy in amelioration of disease.

2. Tryptophan metabolism in stem cell biology.

In relation to the effects of interferon beta and copolymer-1 on MSC neural differentiation, we have shown that both bone marrow- and brain-derived stem cells express the full complement of enzymes in the kynurenine pathway (KP) of tryptophan metabolism. We have shown that the KP in stem cells can be induced by interferon beta. Such induction is known to lead to significant depletion of tryptophan in the cellular milieu, which in turn is now known to compromise rapidly dividing cells with consequent impairment of differentiation. These data are now being prepared for publication. Hence this project has established an essential platform upon which further stem cell transplant studies can be built. Moreover, the KP results provide a unique mechanism whereby stem cell division and differentiation can be significantly enhanced.

3. Role of chemokines in adult stem cell migration.

The use of adult stem cells for therapeutic substitution in neurodegenerative diseases assumes the ability of precursor cells to migrate to lesion sites and provide trophic support and/or functional replacement of damaged neural cells. For such therapeutic strategies to be effective, it is critical to have a thorough understanding of the signals in the stem cell microenvironment that provide cues to control their recruitment and migration. This study should determine which chemokine(s) are optimal in promoting migration to the brain of stem cells. Moreover, it will establish whether commonly used MS therapies may be able to enhance stem cell selection and migration. Finally, it will establish whether such therapies can enhance stem cell migration into damaged areas. The results will have wide applicability to other stem cell therapies.



Mouse neural stem cells

Sub-program Neuro-degenerative diseases

Gilles Guillemin group leader

Introduction:

Dr Guillemin is studying the involvement of the tryptophan catabolism (via the kynurenine pathway) in several human neurodegenerative diseases. He demonstrated the importance of the kynurenine pathway in Alzheimer's disease, which opens numerous very promising research opportunities and has important therapeutic potential. Dr Guillemin has extended his research to other diseases such as amyotrophic lateral sclerosis, multiple sclerosis, Parkinson's disease and brain tumours. These have been the focus of national and international collaborations that have led to several grants.

List projects:

1. The involvement of the kynurenine pathway and the neurotoxin quinolinic acid in the pathogenesis of Alzheimer's disease
(Post-doc: Wei WU)

The kynurenine pathway (KP) of tryptophan (TRP) metabolism is one of the major regulatory mechanisms of the immune response. We have shown that this pathway is switched on in the neuroinflammatory process of Alzheimer's disease (AD) and is likely to be involved in the progression of AD pathogenesis. We have carefully characterised the KP in neurons. We now have strong preliminary and published evidence that prolonged KP activation leads to accumulation of the by-product quinolinic acid (QUIN) in neurons, an excitatory neurotoxin that we believe is subsequently involved in neurodegenerative processes. KP inhibitors or analogues are already in clinical trials for neuroinflammatory brain diseases (i.e. multiple sclerosis) and one is already on the market for use in treating inflammatory arthritis. We believe there is real promise that this type of drugs represents a novel and clinically viable therapeutic target for AD patients. We have also developed a new monoclonal antibody targeting QUIN with potential for neutralizing the effects of the neurotoxin in our culture and animal model systems. We propose to investigate KP mechanisms in human brain cell culture and animal models of AD and to test whether KP inhibitors/analogues, QUIN antibodies or NMDA receptor antagonists can reduce neuroinflammation and subsequent neurodegeneration.

2. Involvement of the kynurenine pathway in the persistence of childhood and adult brain tumours.
(PhD student: Seray Adams)

Tryptophan depletion leads to inactivation of the anti-tumoral immune response. Tryptophan is depleted in body fluids and brain through the kynurenine pathway. A common feature of many cancers is an increase in kynurenine pathway activity. We will characterize kynurenine pathway metabolism within human brain tumours and normal brain cells. We will test whether changes in this pathway play a role in the tumour persistence and immune evasion. A successful outcome of this project could lead to the identification of a new therapeutic target for the treatment of brain tumours.

3. The involvement of quinolinic acid and other tryptophan catabolites in the neuropathology of amyotrophic lateral sclerosis.
(PhD Student: Yiquan CHEN.)

We have identified a new neurotoxic mechanism involved in the neuroinflammatory disease. We propose to demonstrate that the tryptophan metabolism plays an important role in the pathogenesis of amyotrophic lateral sclerosis (ALS). Our main hypothesis is that a downstream tryptophan product, the neurotoxin quinolinic acid (QUIN), produced by activated microglia

induces motor neuron dysfunction and astrocyte activation. The results from this study will open a new and important therapeutic door for ALS using specific inhibitors already available from drug companies for other inflammatory diseases.

4. Development of a new treatment for multiple sclerosis based on the alteration of Tryptophan metabolism

(PhD Students: Edwin LIM & Gayathri SUNDARAM)

Activation of the essential amino acid tryptophan degradation (through the kynurenine pathway) leads to a decrease of both tryptophan and NAD+, which are essential for brain cell repair and survival. The kynurenine pathway is also an essential regulator of immune system and is involved in autoimmune disease, especially MS. By investigating and identifying the components of the kynurenine pathway involved in MS, we sole to open a novel therapeutic door for MS using some compounds already available from drug companies for other brain diseases able to interfere with the kynurenine pathway.

5. Involvement of the kynurenine pathway in Parkinson's disease

(PhD Student: Anna ZINGER)

The kynurenine pathway (KP) of tryptophan metabolism is one of the major regulatory mechanisms of the immune response. We have shown that this pathway is switched on in the neuroinflammatory process of Alzheimer disease and amyotrophic lateral sclerosis, and is likely to be also involved in Parkinson's disease (PD) pathogenesis. We have strong evidence that prolonged activation of the KP leads to accumulation of the by-product quinolinic acid (QUIN), an excitatory neurotoxin, which subsequently is involved in neurodegenerative processes. We propose to investigate KP mechanisms in brain cell cultures and animal models of PD as well as in brain tissue from PD patients, and to test KP inhibitors in reducing neuroinflammation and subsequent dopaminergic neurodegeneration in culture and animal models.

6. NAD^+ Metabolism in Aging and Degenerative Diseases

(PhD Student: Nady BRAIDY)

Accumulating evidence has suggested that NAD^+ could be a fundamental mediator of several biological processes, including energy metabolism, gene expression, immunological functions, aging, DNA repair and cell death. Investigation into the metabolism and biological functions of NAD^+ may expose fundamental properties of life, and suggest new strategies for treating diseases of aging, including cancer and neurodegenerative disease, and perhaps in slowing down the aging process itself.

Sub program Neuro-pathology
Michael Buckland group leader

This newly formed group is interested in the molecular underpinnings of a variety of neuropathological diseases such as brain tumours and neuropsychiatric disorders. Established with funding from the St Vincent's Clinic Foundation, Cure for Life Foundation, and Pfizer corporation, the group currently has two main research projects.

1. Epigenetic changes in human brain tumours
(Michael Buckland, Bjorn Espedido)

This project is examining DNA changes associated with gene silencing (DNA methylation) in specific chromosomal regions of human brain tumours (oligodendrogliomas). Using DNA microarray technology we have produced a comprehensive 'map' of the regions commonly affected in oligodendrogliomas, identifying genes which have been consistently 'switched off', and hence are likely important in tumour formation.

2. Epigenetic profiling in schizophrenia
(Michael Buckland, Bjorn Espedido)

Schizophrenia is a common and devastating disease with an inherited component, but which has so far eluded attempts to identify common molecular aberrations associated with its onset. We are interested in the possible contribution of disordered small regulatory RNAs in this disease. Small regulatory RNAs influence gene expression at both the DNA and RNA level, are highly expressed in the brain, and their role in numerous disease processes is only now being elucidated.

Sub program HIV Neuro-Immunology
Lucette Cysique group leader

Current research projects include:

1. Investigating the neuro-cognitive complications in older HIV-infected individuals using neuropsychological and MR-based and PET imaging methodologies.
This project is mainly based at St. Vincent's hospital (Neurology, Infectious Diseases and Medical Imaging department). It also involves the collaboration of Prof. Brew (Head of Neurology Department at St. Vincent's Hospital), Prof. Sachdev (Director of Neuropsychiatric Institute at Prince of Wales Hospital) members of Brain Science UNSW, Prof. Rowe (Director of Austin Health Centre for PET) and Dr. Chaganti (Head of Medical Imaging Department at St. Vincent's Hospital). This project has been successfully funded by a NHMRC project grant.

2. Strategic Timing of AntiRetroviral Treatment (START) study as part of the International Network for Strategic Initiatives in Global HIV Trials (INSIGHT).
Lucette Cysique is providing neuropsychological expertise. She also is part of the International NeuroAIDS consortium which is a body of leading experts which aim is to foster standardized neuropsychological research and clinical practices across the world.

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Specker, Elisa
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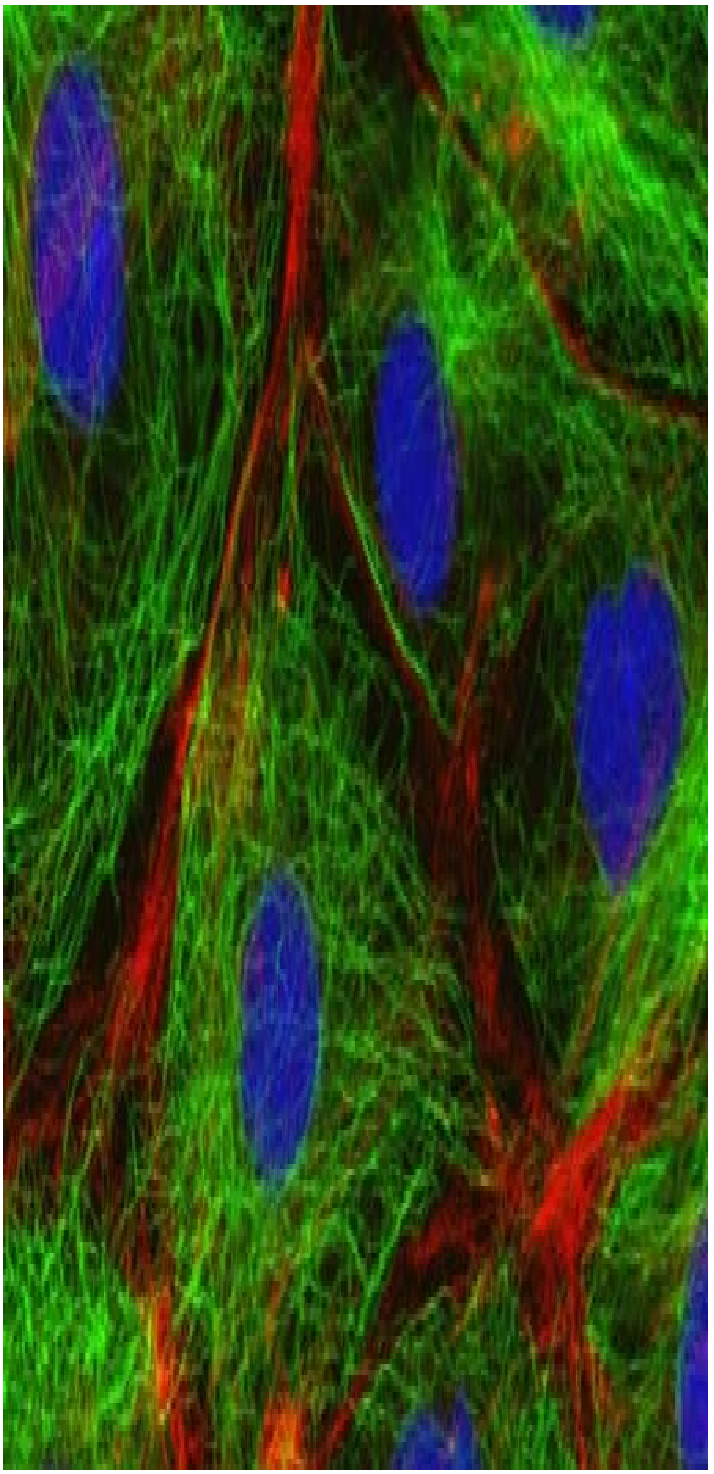
To December 2008



HIV IMMUNOVIROLOGY

RESEARCH PROGRAM

The Immunovirology research program can be divided into two categories. Some of the laboratory's activities are directed towards providing routine and semi-routine procedures essential for the successful conduct of clinical trials and epidemiological studies conducted in collaboration with the National Centre in HIV Epidemiology and Clinical Research. In addition senior staff are responsible for research projects on pathogenesis.

The laboratory continued to act as the Australian coordinating laboratory for the natural history studies conducted in collaboration with the National Centre for HIV Epidemiology and Clinical Research. The laboratory's expertise was further recognised by an invitation to join the laboratory advisory committee for the newly created INSIGHT network. The laboratory continued to perform well in the external QA program for PBMC storage run by Immunovirology Research Network PBMC quality assurance program.

Pathogenesis work relating to antigen-specific CD4 T-cell function continued to bear fruit with new methodologies established in the laboratory resulting in the lodging a further provisional patent, and the lodgement of separate application for a full patent. Both patents are based on novel assay strategies for the enumeration and evaluation of antigen specific CD4+ T cells. These assays were employed by one of our partners in the NHMRC program grant, Professor Stephen Kent to monitor immunogenicity of therapeutic vaccines in SIV infected macaques. The previously patented methodology for identifying human Treg was developed into a commercial kit under a licensing arrangement with Becton Dickinson. Flow cytometric analysis capacity was further expanded with up grades of machinery. The combination of novel assay techniques, advanced technology and expertise allowed a complex analysis of the effects of a novel CCR5 inhibitor, P04112, on lymphocyte function and trafficking as a formal sub-study to phase 1 trial run by the TVRP. The quality of this work in T cell immunology was recognised by the awarding of several oral presentations at international conferences to Nabila Seddiki and John Zaunders to speak at the *IL-7 Nobel Mini-Symposium* in, Stockholm, Sweden. A large contract was awarded to the laboratory for the conduct of immunogenicity assays for a large phase II trial of a novel flu vaccine. This effort is being led by Mee-ling Munier.

The laboratory's ability to perform molecular techniques was enhanced with the acquisition of a state of the art real time PCR machine and spectrophotometer. This equipment will aid the development of siRNA technology which was progressed further during the year by Heidi Lim with successful identification of targets for transcriptional gene silencing within the SIV promoter regions and further elucidation of the mechanism of action of these potentially powerful therapeutic strategies. Sanjay Swaminathan exploring the mechanism of action of these siRNAs in SIV and HIV infection was awarded the Kanematsu / Kitamura Memorial Award 2008 - Trainee Award by the Royal College of Pathologists of Australasia for his proposed studies on the mechanisms of actions of theses siRNAs. Techniques for the characterisation of neutralising antibodies were established in the laboratory by Chris Weatherall. in collaboration with another partner in the Program Grant, Dr Damian Purcell. The quality of Chris's work was recognised by him receiving the KI Scientific Award for Research Excellence at the St

Vincent's Campus Research Symposium.

An NHMRC project grant entitled "Delineation of establishment and maintenance of the T cell reservoirs of HIV-1 infection" was awarded to John Zaunders and John Murray which commence in 2008. This grant will allow exploration and understanding of the establishment of the viral reservoirs early in HIV infection.

Projects

Anthony Kelleher, Head of the Immuno-virology and Pathogenesis Program, has a supervisory role for all projects that fall within the Program, but is only named under the project summaries in this section for those projects that he takes specific responsibility for as a named Principal Investigator or externally recognised leading investigator.

Sub program Clinical trial laboratory service and support

1. Specimen receipt and processing for clinical trials and natural history studies

The laboratory provides a service to other NCHECR Programs encompassing the separation of blood components; cryopreservation of serum, plasma and PMBC; and archiving and onshipping of samples. This allows for the smooth running of clinical trials and natural history studies.

Status: Ongoing

Personnel: Mee-Ling Munier (PhD student), Michelle Bailey, Kate Merlin, Julie Yeung, Maria Piperias, Bertha Fasdni.

2. Immuno-phenotyping of T-cell subsets

Many NCHECR clinical trial and natural history protocols involve immunological substudies. The laboratory supports these substudies as a semi-routine service. Intensive assays were performed as part of the phase 1 trial of P04112

Status: Routine use of 6-10 colour multiparameter flow cytometry.

Personnel: Nabila Seddiki, Mee-Ling Munier (PhD student), David van Bockel (PhD student), Michelle Bailey, Anthony Kelleher, John Zaunders

Sub program Cellular immunology

1. Assays of T-cell function, proliferation, cytotoxicity and identification of antigen- specific T-cells, and assays of dendritic cell number and function

A range of assays for assessing CD4+ and CD8+ T-cell function are worked up in the laboratory. These include measures of T-cell proliferation, activation, cytokine secretion, identification of antigen-specific T-cells and enumeration of dendritic cell subpopulations and the cytokines they produce. Such assays are included in the protocols of clinical trials and natural history studies carried out by NCHECR. Intensive assays were performed as part of the phase 1 trial of P04112 and a large contract to assess the immunogenicity of a Flu vaccine was commenced.

Status: Continued analysis of samples from PULSE, CORE01, PHAEDRA and the Long-term nonprogressor cohorts.

Personnel: Nabila Seddiki, Mee-Ling Munier (PhD student), David van Bockel (PhD student), Chansavath Phetsouphanh , Celine Yan, Yin Xu, Anthony Kelleher, John Zaunders

2. Evolution of immune responses in primary infection and long-term non progressors

This study furthers mechanisms of viral escape from cytotoxic T-lymphocyte responses, and particularly the events leading up to

escape from the HLA-B27 mediated T-cell response at the level of T-cell receptor usage. It employs samples and data gathered during the follow-up of the Long-term nonprogressor (LTNP) cohort (see *HIV Epidemiology and Prevention Program*), and samples collected from the PHAEDRA cohort.

Status: TCR repertoire defined on a range of HLA-B27+ LTNP, analysis ongoing.

Personnel: Anthony Kelleher, David van Bockel (PhD student), Nabila Seddiki.

Collaborators: Peter Doherty, Stephen Turner, Department of Microbiology and Immunology, The University of Melbourne; Daniel Douek, David Price, Vaccine Research Centre, US National Institutes of Health; Miles Davenport, Centre for Vascular Research, UNSW

3. Characterisation of CD4+ CCR5+ T-cells in primary HIV and other primary viral infections

This project involves investigations of the role CD4+ CCR5+ T-cells in the outcome of disease in the long-term nonprogessor (see *HIV Epidemiology and Prevention Program*) and the PHAEDRA/CORE01 cohorts.

Status: Preferential infection of virus-specific CD4+ CCR5+ T-cells identified at primary infection. Role of CTLA-4 in regulation of hIV specific immune response defined.

Personnel: Anthony Kelleher, Mee-Ling Munier (PhD student), John Zaunders

Collaborators: Daniel Kaufmann, Partners AIDS Research Center (Massachusetts General Hospital), Harvard University

4. IL-7 receptor modulation

The impact of IL-7 and the expression of its receptor on T-cell subsets, T-cell homeostasis, CD4 T-cell recovery post HAART and developing lymphoma are being explored using both *in vitro* and *ex vivo* techniques. These studies have been extended to include the cell biology of the IL-7 receptor modulation.

Status: Studies of IL-7 receptor on malignant B cells in lymphomas and leukemias continued. The cellular processing of IL-7 receptor after binding its ligand was explored using molecular techniques.

Personnel: Anthony Kelleher, Sarah Sasson (PhD student) John Zaunders,

Collaborators: Sandy Smith, Sam Milliken, John Moore, Keith Stanley, Natasha Foster, St Vincent's Hospital, Sydney

5. Definition of T regulatory subsets

Studies carried out to define a novel and more rigorous way of defining human T regulatory cells.

Status: Novel assay developed and submitted as provisional patent. Assay development was completed, and was used for the sorting of functional subsets for *in vitro* suppression assays and epigenetic studies of the granzyme B gene. A licencing agreement was negotiated with Becton Dickinson for the use of the original patented assay. The use of the assay was extended to non-human primates in therapeutic vaccine trials.

Personnel: Nabila Seddiki, Anthony Kelleher, Sarah Sasson, (PhD student), Kai Brown (Hons Student), Chansavath Phetsouphanh, John Zaunders

Collaborators: Barbara Fasekas, Centenary Institute of Cancer Medicine and Cell Biology, The University of Sydney; Alan Landay, Rush Medical School; Stephen Kent, Department of Microbiology and Immunology, The University of Melbourne; Sudha Rao, Australian National University

6. Novel assays for assessing T-cell function

Assays designed to amplify small "primed" responses, and also

simplified methodologies that may be applicable in the field in developing countries where large scale vaccine trials are likely to be run.

Status: Priming assays were conducted on the primary infection patients who control virus and those who do not. A provisional patent was lodged for a methodology for a simplified T-cell assay and negotiations for development of the assay were commenced with biotech companies.

Personnel: Mee-Ling Munier (PhD student), Michelle Bailey, Nabila Seddiki Anthony Kelleher, John Zaunders

Collaborators: Stephen Kent, Department of Microbiology and Immunology, The University of Melbourne

7. B-cell subsets, neutralising antibodies and auto-antibodies at primary HIV-1 Infection

Studies of overlap between neutralising antibodies and auto-antibodies at primary infection and the subsets of B cells producing these responses.

Status: Characterisation of the B cell subsets responding HIV-1 during primary infection was commenced. Assays determining the carriage of neutralizing assays for hIV-1 and anticariolipin antibodies in over 300 primary infection patients were completed

Personnel: Chris Weatherall (PhD student), Anthony Kelleher, John Zaunders

Collaborators: Damian Purcell, Department of Microbiology and Immunology, The University of Melbourne; Stuart Tangye, Immunology and Inflammation Program, Garvan Institute of Medical Research

8. Immuno-pathogenesis of immune reconstitution disease

Studies of the immunopathogenesis of immune reconstitution disease (IRD) based on the samples studied *ex vivo* from patients suffering this disease.

Status: A study exploring the causes of this dysregulation commenced in 2006.

Personnel: Nabila Seddiki, Anthony Kelleher, David van Bockel (PhD student), Chansavath Phetsouphanh,

Collaborator: Sarah Pett and Debbie Marriott, St Vincent's Hospital, Sydney

Sub program Pathogenesis research

1. iRNA inducing viral latency

This project is established to determine the optimal design of dsRNAs for the induction of transcriptional gene silencing (TGS) of viral genes in HIV-1 infected cells; and to define the pathways by which dsRNAs targeting the promoter regions of HIV-1 induce TGS.

Status: Constructs applicable for use in SIV-infection were developed and transferred into plasmid delivery vehicles . Epigenetic changes induced by dsRNAs targeting HIV-LTR were defined.

Personnel: Anthony Kelleher, Heidi Lim (PhD student), Sanjay Swaminathan PhD student), Kazuo Suzuki.

2. HIV drug resistance

This project involves the development of expertise in the application of a number of methods of detecting antiretroviral drug resistance through genotypic testing of HIV isolates.

Status: Over 200 HIV-1 resistance genotypes were performed.

Personnel: Anthony Kelleher, Philip Cunningham, Kazuo Suzuki,

Collaborators: Leon McNally, Alexander Carrera. Sydpath St Vincent's Hospital Sydney.

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Hospital Scientist

Bailey, Michelle BSc
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Fsadni, Bertha BSc
Technical Officer

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Maternity leave to December 2008

Leas, Leakhena BSc
Hospital Scientist
Maternity leave

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PhD candidate

Lim Heidi BSc
PhD candidate

Munier, Mee Ling BSc
PhD candidate

McBride, Kristin
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Swaminathan, Sanjay
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Seddiki, Nabila PhD
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PhD candidate

Weatherall, Sajay
PhD candidate

Yan, Celine
Research Officer

Yeung, Julie BSc
Hospital Scientist

Yin, Xu
Research Officer

Clinical Research

RESEARCH PROGRAM

The Clinical Research Program (CRP) is a recently formed clinical research program, incorporating the previous St Vincent's Hospital's Clinical Trials Centre, HIV Clinical Trials Unit and Antiretroviral Toxicity Research Group. The aim of the CRP is to provide high quality clinical trials service across the St Vincent's Campus for the clinical implementation of pharmaceutical and investigator-initiated clinical studies. The CRP has clinical trials expertise in multi-centred, investigator-driven research projects, the major focus of the CRP into the future.

The CRP currently has 75 research projects across the following clinical specialties:

HIV infection – treatment and observational cohort studies of antiretroviral therapy, treatment complications (particularly metabolic complications), immunopathogenesis, and vaccines;

Viral Hepatitis - treatment and observational cohort studies in patients with and without HIV infection, including new oral treatments for hepatitis C;

Anal Intraepitheal Neoplasia - observational cohort studies of the relationship between AIN and human papillomavirus in men. The CRP recently joined the US AIDS Malignancy Clinical Trials Consortium and will participate in planned treatment studies;

Palliative Care - randomized trials aimed at controlling symptoms in patients with advanced, terminal disease, having recently joined the Australian Palliative Care Clinical Studies Collaborative.

Cardiology - cardiac device and stent studies in collaboration with cardiologists and cardiothoracic surgeons, including of new prosthetic cardiac valves that can be inserted without surgery.

Neurology - treatment studies of acute stroke, Alzheimer's disease and Parkinson's disease.

Innovation and research leadership continue as central themes for the program. The program continues to grow as an effective advocate and collaborator with established research networks, encompassing public-sector, industry and investigator-initiated research. The program commenced participation in a clinical trial of a new class of antiretroviral drugs for the treatment of HIV-1-infection. This investigator driven study is considering the metabolic abnormalities of HIV treatments.

The program continues with a broad range of novel and interesting research of different clinical strategies encompassing therapeutic vaccines studies, gene technology, immunotherapies and clinical evaluation of promising new drug candidates in Phases 1, 2 and 3 of development. The program is gaining specialisation capacity in undertaking pharmacokinetics sub studies. The program also provides clinical research opportunities for PhD, Master and undergraduate students.

Research staff

Andrew Carr MD
Clinical research program Head

Richard Norris, RN MBA
Clinical research manager

Robyn Richardson, RN
Clinical Trial Coordinator

Kate Sinn RN
Clinical Trial Coordinator
From July 2008

Robert Fielden, CNS
Clinical Trial Coordinator
To November 2008

Karen MacRae, CNS
Clinical Trial Coordinator

Martina Rafferty, CNS
Clinical Trial Coordinator

Mark Rollason, RN
Clinical Trial Coordinator

Gary Keogh, RN
Clinical Trial Coordinator

Zoe Potgieter, CNS
Clinical Trial Coordinator

Rebecca Hickey, CNS
Clinical Trial Coordinator

Dianne How-Chow CNS
Clinical Trial coordinator

Blood, Stem cell and Cancer

RESEARCH PROGRAM

Introduction

The Blood, Stem Cell and Cancer Research Group focuses on clinical application of translational research into bone marrow derived stem cell and blood diseases. The group applies 'the state of art' molecular, biochemical and cell culture techniques on clinical samples to dissect out the complex mechanisms controlling normal stem cell and conditions leading to the formation of cancer stem cell. Knowledge gained from these laboratory results is then applied to improve patient outcomes. Our group has three research strands: stem cell transplantation, malignant haematology and haemostasis.

1. Stem Cell Transplantation Projects:

1.1 Multi-potent differentiation potential of human BM-derived mesenchymal stem cells
(H Tao, J Hsu, M Khoo, A Herbert, J Moore and DD Ma)

The aim of this project is to evaluate the ability of bone marrow (BM) derived mesenchymal stem cells (MSCs) to produce mature functioning cells of non-bone marrow tissues. We have taken a multi-disciplinary approach to enhance our ability to success by collaborating with researchers in other scientific areas. We have established a culture system and a panel of bio-markers for studying differentiation of BM MSCs into cells of mesodermal and ectodermal lineages. Using specific stimuli, we have shown BM MSCs can differentiate into intervertebral disc-like cells or with a different culture system to early neuronal cells. The BMP pathway has been identified to be critical in the discogenic differentiation of BM MSC. We are now examining the differentiation fate of BM MSC in normal and degenerative intervertebral discs in *in vivo* animal models in collaboration with Dr A Diwan's research team at St George Hospital Sydney. The success of driving BM MSCs to early neuronal fate has led us to transplanting these cells into the 6-OHDA unilaterally lesioned Parkinsonian rat model. The *in vivo* studies were conducted in collaboration with the research team of Professor Alan Mackay-Sim, Griffith University, QLD. So far, we found short-term survival of grafted cells and the presence of an inflammatory response at the graft site. The absence of early neuronal markers at the graft site also suggests that the transplanted human MSCs did not elicit endogenous neuronal differentiation in the host brain. Studies are underway to examine the nature of the immune response at the graft site.

1.2 Improving donor CD34+ stem cells to reconstitute T cell compartment in adult haematopoietic stem cell transplants
(S Carlin, J Kwan, B Herrmann, K Fay, S Milliken, A Dodds, J Moore and DD Ma)

Haematopoietic Stem cell transplantation (SCT) from allogeneic (non-self) donors is a well-recognised and effective treatment for malignant and non-malignant haematological diseases. Impaired immune reconstitution, graft versus host disease (GVHD) and graft versus tumour effect (GVT) are the major hurdles to improving patient survival. We hypothesise that stem cell quality and thymic function are key factors in the effective immune reconstitution post SCT. The intended clinical application of this research is to identify therapies, which can selectively enhance immune reconstitution in individual BM transplants. We have used a stromal cell co-culture system to study the generation of T cells from

haematopoietic stem cells. Our work has shown that the Delta/Notch signalling system initiates T cell differentiation but this signalling pathway needs to be switched off to allow further T cell differentiation. Further, we have shown that CD7 signalling is important in T cell differentiation in both early and late stages. We are currently characterizing gene expression in Delta/Notch and CD7 signallings. Running in parallel to the laboratory research, we are tracking these early T lymphoid progenitors, T cell subsets and their correlations with immune reconstitution, GVHD and GVT in patients undergoing allogeneic SCT in the pioneering program at St Vincent's Hospital, which has performed well over 1000 stem cell transplants since its inception in 1975.

2. Malignant Haematology Projects:

2.1 Identification of drug resistance genes by microarray profiling of leukaemic cells treated with tyrosine kinase inhibitors in Philadelphia positive acute lymphoblastic leukaemia (Ph+ ALL)

(T Loi, P Dai, S Carlin and DD Ma)

The cure rate of Ph+ALL remains low in spite of recent advances in the treatment of leukaemia. Imatinib and dasatinib, tyrosine kinase inhibitors, is highly successful in treating Ph+ chronic myeloid leukaemia but is ineffective against Ph+ ALL. This project comprises of gene expression profiling of leukaemic cells from patients receiving imatinib by microarray with downstream protein function validation and aims to dissect novel processes involved in imatinib resistance which may enable the design of new drugs to combat this cancer. Of > 400 genes with altered expression identified, six candidate genes were selected for further analysis. The expression changes of four of the six candidate genes were also observed in Ph+ cell lines treated with dasatinib, a second-generation tyrosine kinase inhibitor. We identified one of these six genes, Protein Kinase C epsilon (PKCε), a positive regulator of survival, proliferation, as the potential gene responsible for drug resistance. We are examining if this kinase also participates in drug resistance in dasatinib, a second generation tyrosine kinase inhibitor. Thus, inhibition of PKCε in Ph+ ALL may represent a novel way to improve the effectiveness of these tyrosine kinase inhibitors.

2.2 Role of microRNAs in the pathogenesis of acute myeloid leukaemia

(M Lutherborrow, A Bryant, D Agapiou and DD Ma)

In the last 10 years, microRNAs have been shown to be important in gene regulation and in 2004, the loss of microRNAs was shown to contribute to the development of chronic lymphocytic leukaemia. We have hypothesised that microRNA abnormalities may be involved in the pathogenesis of acute myeloid leukaemia with normal karyotype (NK-AML). Data obtained from microRNA microarray analysis of samples from patients with NK-AML were correlated with clinical information. Bioinformatic analysis was done in collaboration with researchers at the Department of Mathematics, University of Sydney. A number of microRNAs that targets against known oncogenes or tumour suppressor genes were identified. We are currently performing experiments to verify if the targets of these microRNAs and the role of these differentially expressed microRNAs in *in vitro* AML models with respect to proliferation, apoptosis and differentiation.

3. Haemostasis and Thrombosis Projects:

3.1 Evaluation of the procoagulant properties of platelets and microparticles in malignant and non-malignant states
(D Connor, DD Ma and J Joseph)

Microparticles (MP) are vesicular fragments of the plasma membrane released upon cellular activation and/or apoptosis. These microparticles possess negatively charged phospholipids such as phosphatidylserine on their outer surface, allowing for the binding of activated coagulation factors X and V and the subsequent activation of the clotting pathway. The investigation of the role of microparticles in the pathogenesis of diseases including cancer and their complications is an emerging field. Our group has demonstrated the procoagulant property of MP using a newly developed clotting assay and MP functional assay based on flow cytometry. Recently we have also identified a sub-population of MP that do not bind Annexin V and possess little procoagulant activity. The focus of our research is aimed at discovering clinical significance of MP in cancer and bleeding disorders.

3.2 In vitro and in vivo study of the procoagulant and anticoagulant effects of detergent sclerosants.
(K Parsi, T Exner, DD Ma and J Joseph)

Modern sclerotherapy used for the treatment of varicose veins is performed using detergent sclerosants, to destroy the endothelium of the target veins leading to complete vessel fibrosis. Little is known however about the effects of these sclerosants on haemostasis. A significant, albeit uncommon morbidity associated with sclerotherapy is deep vein thrombosis and pulmonary embolism. The aim of this project is to assess the effects of these sclerosants on the coagulation and fibrinolytic pathways of the haemostatic system. Data generated to date has provided new knowledge on haemostatic effects of sclerosants routinely used in sclerotherapy

Research Staff

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Joseph, Joanne MBBS
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Khoo, Melissa PhD
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Loi, To Ha PhD
Research Officer

Lutherborrow, Mark PhD
Research Officer

Moore, John MD
Research Fellow

Parsi, Kurosh MBBS
PhD candidate

Shen, Bojian BSc
Research Officer

Tao, Helen PhD
Senior Hospital Scientist

Gastro-oesophageal

RESEARCH PROGRAM

The St. Vincent's Centre for Applied Medical Research Gastroesophageal Cancer Research Laboratory is investigating the following subjects:

- gene expression and DNA methylation in Barrett's oesophagus and oesophageal adenocarcinoma,
- immune regulation and stem cells in this disease,
- pharmacogenetics of response to chemotherapy for esophageal adenocarcinoma,
- genetic profile of the neosquamous oesophagus after Barrett's ablation,
- Mechanisms of metabolic benefits incurred with surgical weight loss,
- aetiology of achalasia.

1. The gene expression and DNA methylation tissue studies have resulted in validation of more than 20 genes that are likely to important in this disease. This study validates our methods, previous findings including our microarray results, and analyses the different software programs. We have identified novel pathways to oesophageal adenocarcinoma including the netrin/netrin receptor pathway and tetraspanin family of genes. We completed our study on HSV-tk/GCV suicide gene therapy with the Grp-78 stress-inducible promoter. This reported the most successful gene therapy strategy, with complete abolition of tumours *in vivo* in nude mice.

2. The studies on immune activation and inflammation in this disease resulted in the first identification of the presence, and possible importance aetiologically, of dendritic cells. We believe that we have identified the first stem cell (and likely cell of origin) for Barrett's oesophagus with dysplasia and perhaps oesophageal adenocarcinoma.

3. In vitro studies using knock-down methods are underway. We are submitting an NHMRC project grant application to study the genetic determinants of response to conventional chemotherapy agents for patients with oesophageal adenocarcinoma using the pre-treatment tissues for patients who were in the TROG/AGITG 9401 randomised controlled trial of neoadjuvant therapy versus surgery alone.

4. We introduced radiofrequency ablation of Barrett's oesophagus technology to Australia, performing the first treatments and establishing that, in the 12 patients treated so far, this treatment is effective. Two patients were spared oesophagectomy by RF ablation treatment. A 40 gene mRNA expression study of selected progression-related genes in 10 patients who underwent this new therapy showed that the neosquamous mucosa which replaces the Barrett's premalignant mucosa is similar to normal oesophageal mucosa and dissimilar to Barrett's oesophagus. A project grant application to NHMRC with Flinders University and University of Melbourne will be submitted this year on Barrett's ablation, genetic studies, and prevention of oesophageal adenocarcinoma.

5. Studies on surgical weight loss and its effect on obesity co-morbid conditions are in progress with A/Prof. K. Samaras from the Garvan Institute Diabetes and Obesity Research Group. These studies have demonstrated the importance of visceral fat expression of multiple genes in diabetes improvement, the rapid attenuation of arterial stiffness, and other findings.

6. Achalasia is the commonest named motility disorder of the oesophagus but its aetiology is entirely unknown. It is characterised by absence of peristalsis in the oesophageal body

and a hypertensive, poorly relaxing, lower oesophageal sphincter. We have demonstrated that interstitial cells of Cajal, the “pacemaker cells” of the gut, are present in normal numbers in this disease. We are investigating the function of these cells in achalasia and normal oesophagus in an effort to discover the cause of this mysterious disease.

Research staff

Reginald V Lord MD
HIV Immuno-virology Program Head

Botelho, Natalia BSc
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From May 2008

Scheiders, Fiona BSc
Research Assistant
To February 2008

A/Prof. Yuri Bobryshev
Research fellow

Angelique Levert
Research Assistant

STRUCTURAL BIOLOGY

RESEARCH PROGRAM

The structural biology laboratory's research program is aimed at understanding life processes at a molecular level. Our main focus is on the structure and function of proteins, in particular, those that act as molecular machines.

The group uses an array of techniques, especially:

- X-ray crystallography,
- Recombinant DNA technology,
- Protein chemistry,
- Biophysics and bioinformatics.

The laboratory has several themes including:

- Membrane proteins,
- Proteins that undergo dramatic structural changes,
- Light harvesting proteins and molecular machines.

Current projects include: the CLIC chloride ion channels, RNPs, integron/gene cassette proteins, light-harvesting proteins, serpins, tumour suppressors, archaeal evolution and protein structural transitions.

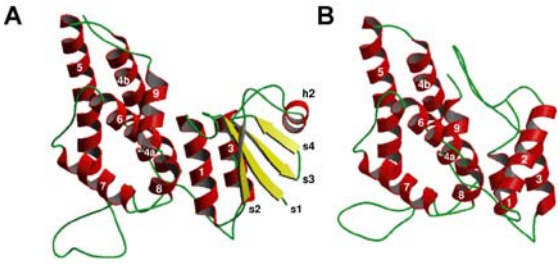
1. CLIC ion channel

CLIC proteins are unusual in that they exist in both globular and integral membrane states. The CLICs are highly conserved in vertebrates with homologues in invertebrates. CLICs can form anion channels (chloride) in vitro and in vivo

Our goal is to gain a comprehensive understanding of the CLIC proteins. CLIC proteins are unusual in that they exist in both globular and integral membrane states. The CLIC protiens are highly conserved in vertebrates with homologues in invertebrates. CLIC proteins can form chloride channels in vitro and in vivo.

We have determined several crystal structures of CLIC proteins in the soluble form. In addition, we have discovered a dramatic structural change in CLIC1 which is stabilised by oxidation. We believe that this transition represents part of the functional cycle, as CLIC1 goes from a soluble form to a membrane bound form, prior to forming a channel

Our current goal is to determine the structure of the integral membrane form of a CLIC protein



Structural change of CLIC-1

2. Molecular chaperones.

Molecular chaperones Protein folding is a key biological problem. The environment in the cell is crowded and the conditions not necessarily conducive to spontaneous folding. Several families of proteins are involved in assisting proteins to fold correctly or preventing aggregation and inappropriate interactions. These proteins are known as molecular chaperones. We are focusing on several types of molecular chaperone, including the chaperonin, Cpn10. Cpn10 also acts as an immuno-modulatory protein.

3. Cryptophyte light harvesting proteins.
Cryptophytes are an unusual type of single-celled algae that have resulted from the endosymbiosis of a red algal cell inside a eukaryotic host. Like cyanobacteria and red algae, the cryptophytes have preserved a light harvesting system based on phycobiliproteins that are members of the globin fold superfamily. Unlike cyanobacteria and red algae, the cryptophyte phycobiliproteins are soluble and reside in the lumen on the thylakoid. We are using crystallography to unravel the mechanism by which these proteins trap light photons and transfer the energy to the membrane bound photosystem. We are collaborating with Greg Scholes, University of Toronto who's group is probing the light harvesting system via ultrafast laser spectroscopy. Our crystals of the light harvesting proteins diffract to ultra high resolution

4. Integron/gene cassette proteins.
Lateral Gene transfer is a major phenomenon in bacteria and archaea. The integron/gene cassette system interconnects bacterial communities via a metagenome of cassette encoded genes which can be acquired, rearranged and discarded as a result of environmental pressure. The integron/gene cassette system is the major mechanism by which pathogens gain antibiotic resistance. Most of the proteins encoded by the gene cassettes are unrelated to proteins in the databases. We are exploring the function of these cassette proteins from environmental samples as well as *Vibrio*, where many species contain large cassette arrays (>100 genes).

5. Archaea and cold adaptation.
Most of the biosphere (>80%) is cold (permanently below 5°C), thus, a large proportion of organisms have evolved to thrive in cold environments. We are collaborating with Rick Cavicchioli, UNSW, who has established a comprehensive program to determine the mechanisms by which archaea adapt to cold environments. We are looking at factors that allow proteins to function at low temperature as well as molecular chaperones and protein folding in psychrophiles.

5. RNPs.
Ribonucleoprotein complexes form some of the most ancient, central machines in extant organisms. The Sm/Lsm proteins from a core ring structure that appears in many RNPs in all three domains of life. In collaboration with Bridget Mabbutt, Macquarie University, we are using x-ray crystallography to gain a better understanding of these ring complexes in both archaea and eukarya.

Research staff

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Jormakka, Mika PhD
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Donadini, Roberta
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Mynott, Andrew BSc
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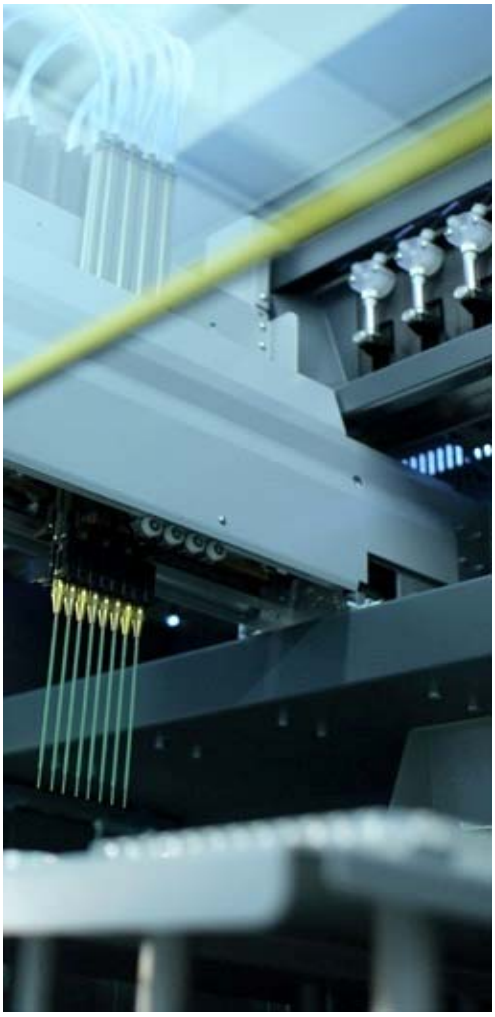
Phang, Juanata
PhD candidate



CANCER

RESEARCH PROGRAM

The Cancer Research Program focuses on clinically relevant research into cancer, to identify abnormal genes and develop gene-directed therapies. A close link with patient care makes the group different to many other research groups. The group is at the forefront of worldwide discoveries in its field and the application of these finds to patients referred to our clinics.

Sub program Epigenetics

The laboratory pursues the goal of better understanding the biological significance of DNA methylation in cancer development and progression. The group does this by drawing on the clinical expertise in the group to identify informative examples of this phenomenon in the real world, and to apply leading edge molecular and biochemical techniques to explore these cases in the laboratory. The ultimate goal is to better understand the factors that lead to cancer, with the ambitious but clear view of early detection, and ultimately prevention, in a significant proportion of individuals at risk of this disease.

1. Epigenetic inheritance in humans.

Familial cancer susceptibility syndromes, including hereditary non-polyposis colorectal cancer (HNPCC), are usually caused by sequence mutations (or spelling mistakes) within the genetic code of particular cancer prevention genes. Our group and others have identified 'germline epimutations' of the MLH1 gene as the cause of HNPCC in some cases. In these cases, promoter hypermethylation and transcriptional inactivation of one allele of the MLH1 gene is found in all somatic cells, in the absence of an explicable sequence change within the gene itself. In 2007 we reported in the New England Journal of Medicine the transmission a germline MLH1 epimutation from a HNPCC-affected mother to one of three sons carrying the affected allele, indicating that this defect is heritable in a non-Mendelian fashion. This has revealed an entirely new pattern of inheritance of cancer susceptibility. We have now identified more families and individuals with early onset cancer syndromes caused by epimutations. This information is being used to guide genetic counselling, clinical surveillance and treatment of affected individuals and their families.

2. Investigate the cause of hMLH1 epimutations.

The group has recently shown that at least 1.35Mb around the MLH1 gene is hypermethylated. This region spans five CpG islands, of which three are associated with known genes; IRPP-21 (CpG 92), STAC (CpG 55), and EMP2A/MLH1 (CpG 93). EMP2A gene encodes a hypothetical laforin-interacting protein, while the STAC gene is thought to be involved in signal transduction. STAC is normally expressed at high levels in the colon, but is absent in colorectal cancer. ARPP-21, the most distal gene within this hypermethylated region encodes an AMP-regulated phosphatase with nucleic acid binding capacity. The largest CpG island, containing 141 CpG

sites, is located just 50kb upstream of the MLH1 promoter. “CpG 141” is not associated with any known genes, but data mining of the UCSC human genome site suggests that two transcripts may initiate within this CpG island, with transcription occurring in the antisense direction.

3. Incorporate molecular information into clinical practice.

In partnership with the NSW Cancer Council our group has developed and tested better systems for the identification, integration and dissemination of clinically relevant molecular information about colorectal cancers. We have used the existing processes for the pathological assessment and reporting of colorectal cancers, as we believe that these are in practical terms the most important pathway for the translation of basic scientific information into clinical practice. As a first step, we have introduced tests to look for mismatch repair deficiency in the cancer. This feature is seen in 15% of all bowel cancers, and can be quite important in determining how the person should be treated. In addition, it can also identify people who are likely to pass on the risk of cancer to their children. Where this is identified, death from cancer in the relatives can be prevented. While our group has world experts in the identification of MMRD, to date this test is not done routinely in hospitals. We have now implemented this test routinely in one an Area Health Service in NSW (which looks after the health of 1.2 million people). We believe that doing this will make a difference to those people. This is just one example. Once we get systems in place to get the latest research into practice, we hope to be able to bring about more and more practical examples of this process. Our research has also developed processes to help consumers and their doctors to better understand molecular reports.

Research staff

Ward, Robyn MBBS PhD
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Kwok, Chau To
Research Assistant

Packham, Deborah BSc
Research Assistant

Lin, Vita Ap
Research Assistant

CANCER CELL BIOLOGY

RESEARCH PROGRAM

The group is interested in the regulation of the localisation and targeting of the Ras/Raf/MAPK signaling pathway. The Ras signaling pathway has attracted considerable attention since in 30% of human cancers, the Ras family of proteins is activated by oncogenic mutations. Ras signaling has been thought to occur exclusively at the plasma membrane, but recently Ras activity has also been identified in intracellular compartments. The localisation of the Ras pathway is regulated by targeting proteins.

One of these targeting proteins, Annexin 6, belongs to a family member of Ca2+-dependent membrane binding proteins, and regulates membrane traffic at the plasma membrane, endosomes and in caveolae/lipid rafts. Annexin 6 interacts with Ras regulators (GAP) and Ras effectors (Raf-1) and is involved in the regulation of the localisation and activity of the Ras pathway. We want to identify the molecular mechanism, how Annexin 6 affects Ras/Raf/MAPK localisation and activity. A better understanding of the mechanisms that regulate the localisation of the Ras pathway will add to a better understanding in human cancer.

1. Regulation of Ras inactivation in cancers with de-regulated ErbB receptors

Enhanced Ras signalling contributes to tumour development in cancer with de-regulated ErbB1/2 receptors. Ras inactivation requires its association with GTPase activating proteins (GAPs). Little is known about the proteins that mediate GAP recruitment and confer Ras-isoform specific targeting of GAPs. The group have shown that assembly of a GAP family member, p120GAP, with H-Ras, is mediated by Annexin A6.

This study will aim to identify the factors and conditions that stimulate Ca^{2+}-dependent GAPs in cancer cells with de-regulated ErbB1/2. The Ras isoforms that are targeted by the various GAPs will be identified and contribute to understand how cells create Ras-isoform specificity. A better understanding of the recruitment of GAPs to Ras will contribute to reveal the regulation of spatio-temporal Ras signalling and offer new approaches for Ras inhibition in ErbB1/2-related cancers.

2. Role of Annexin A6 in the formation of membrane domains and lipid rafts

Annexin A6 –mediated Ras inactivation is closely linked to its role in membrane traffic. The group has shown that Annexin A6 is a very dynamic protein which is found in the cytosol, at the plasma membrane and in endosomes. Annexin A6 stimulates endocytosis, lysosomal targeting and is involved in the formation of lipid rafts. In these compartments Annexin 6 interacts with p120GAP, PKC¤, but also with H-Ras, caveolin and TPD-52. Overexpression of Annexin A6 alters the lipid composition at the plasma membrane and affects the stability of lipid rafts.

This project aims to identify how Annexin A6 contributes to the formation of membrane microdomains and how this regulates/affects the localization and trafficking of its interaction partners. This studies will contribute to a better understanding of Ras signalling and EGF receptor down-regulation, but also address caveolin trafficking and lipid raft formation.

3. Role of annexins in lipid raft – dependent T cell receptor activation

Activation of the T cell receptor (TCR) is accompanied by lipid raft formation. In collaboration with K. Gaus (UNSW) we identified translocation of Annexins (2 and 6) to TCR-containing lipid rafts. TCR activation in rafts require a direct interaction with the cytoskeleton but the regulation of these interactions are poorly understood. This project investigates how Annexins bind to actin and phospholipids to link the cytoskeleton to TCR-rafts. These studies are important to understand T cell activation and the dependence of raft formation on the actin cytoskeleton

4. HDL-induced activation of the Ras/Raf/MAPK pathway in atherosclerosis

High density lipoproteins (HDL) stimulate removal of cellular cholesterol and NO production, thereby protecting against atherosclerosis. This requires a direct interaction of HDL with cells to trigger signalling events. The group has shown that HDL is a potent inducer of the Ras/MAP Kinase pathway. We now have evidence that HDL-induced activation of Ras and MAPK is involved in the regulation of cholesterol transport and NO production. HDL components that mediate Ras activation will be identified and the effect on cholesterol efflux, NO production and eNOS activation/localization will be studied. Gene arrays will identify HDL-inducible genes that are activated through this pathway. Understanding HDL-induced signalling events may have significant impact on the understanding and treatment of atherosclerosis.

Research staff

Grewal, Thomas PhD
Program Head

Wood, Peta BSc
Research Assistant

Core Facilities & Support

The St Vincent's Centre for Applied Medical Research's core research facilities contain state of the art equipment that enables staff and students to undertake research. This includes:

- A PC3 biological containment facility
- Two PC2 biological containment facilities for viral transduction
- A biologically contained cell sorter. This is the only one of its type in NSW and only one of two in Australia. This facility will allow the isolation of cell populations from tissues of individuals with various infectious diseases.
- PCR facility.
- Cytogenetic storage facility.
- Digital imaging facility
- Flow Cytometry laboratory

The Centre's support staff provide a range of services to researchers. These include administration, finance, cleaning, central sterilisation, media preparation, equipment maintenance and purchasing.

Staff

Cunningham, Philip BSc(Med) Hons
Chief Operating Officer

Dimovski, Bill MCom
Research administration and finance

Li Kuet MBA
Scientific Services
From March 2008

Nield, Blair PhD
Scientific Services
To January 2008

Irvine, Anna
Administration Officer

Jones, Nathan
Administration Officer
To August 2008

Peebles, Lyne
Administration Officer

Field, Sarah
Administration Officer
To March 2008

Richwood, Lee
Administration Officer
From January to July 2008

Watchirs-Smith, Lucy
Administration Officer
From April 2008

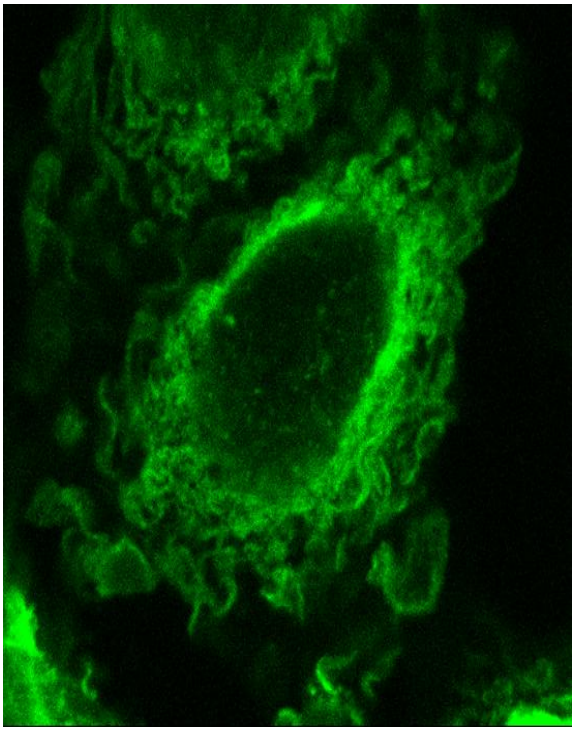
Jauncey, Lydia
Administration Officer
From October 2008

Van Bockel, David
Laboratory aid
To July 2008

Chen, Yiguan
Laboratory aid
From August 2008

Olim, Delinda
Auxiliary services

Dainezi, Assis
Auxiliary services



Post graduate research students enrolled in 2008

Inflammation
Candidate: Luo, Wei
Award: PhD
Title: The study of the biological role of MIC-1
Supervisor: Sam Breit

Neuroimmunology
Candidate: Chen, Yiquan
Award: PhD
Title: Kynurenine pathway in amyotrphic lateral sclerosis
Supervisor: Gilles Guillemin

Neuroimmunology
Candidate: Lim, Edwin
Award: PhD
Title: Kynurenine pathway in pathology of multiple sclerosis
Supervisor: Gilles Guillemin

Neuroimmunology
Candidate: Specker, Elisa
Award: BSc Hons – German exchange student
Title: Regulation of tryptophan metabolism in neural stem cells
Supervisor: Juliana Lamoury

HIV Immunovirology
Candidate: Munier, Mee Ling
Award: PhD
Title: Role of HIV specific CD4+ T cells in acute primary HIV infection
Supervisor: Tony Kelleher

HIV Immunovirology
Candidate: Lim, Heidi
Award: PhD
Title: Virus suppression by dsRNA
Supervisor: Tony Kelleher

HIV Immunovirology
Candidate: Weatherall, Chris
Award: PhD
Title: Characterisation of B-lymphocyte responses in primary HIV infection - neutralising antibodies and immune tolerance
Supervisor: Tony Kelleher

HIV Immunovirology
Candidate: Distler, Oliver
Award: PhD
Title: HIV related Lipodystrophy
Supervisor: David Cooper

HIV Immunovirology
Candidate: McBride, Kristin
Award: PhD
Title: Effect of raltegravir on establishment and persistence of latent reservoir in HIV infection
Supervisor: David Cooper

HIV Immunovirology
Candidate: Swaminathan, Sanjay
Award: PhD
Title: SiRNA transcription: silencing of HIV by SiRNA
Supervisor: Tony Kelleher

Blood, stem cell and cancer
Candidate: Chung-Ching Hsu, Jean
Award: MSc
Title: To differentiate bone marrow derived stem cells into disc-like cells for treatment for intervertebral disc degenerative disorder
Supervisor: David Ma

Blood, stem cell and cancer
Candidate: Herbert, Andrea
Award: PhD
Title: Use of bone marrow stem cells for the treatment of myocardial ischaemia
Supervisor: John Moore

Blood, stem cell and cancer
Candidate: Parsi, Kurosh
Award: PhD
Title: Sclerosis, thromosis and fibrinolysis
Supervisor: Joanne Joseph

Blood, stem cell and cancer
Candidate: Bryant, Adam
Award: PhD
Title: MicroRNA profiling in acute myeloid leukaemia
Supervisor: David Ma

Structural biology
Candidate: Mynott, Andrew
Award: PhD
Title: Crystallographic and EPR studies of CLIC family proteins
Supervisor: Paul Curmi

Theses Passed in 2008

Neuro-immunology
Candidate: Ting, Kaka
Award: PhD
Title: Kynurenine pathway and Alzheimer's disease
Supervisor: Gilles Guillemin

HIV Immunovirology
Candidate: Sasson, Sarah
Award: PhD
Title: Investigate the expression of IL-7 and IL-7 receptor in HIV-1 infection ex vivo
Supervisor: Tony Kelleher

HIV Immunovirology
Candidate: Van Bockel, David
Award: PhD
Title: Comparison within the long-term non-progressors of T cell factors contributing to natural control of HIV
Supervisor: Tony Kelleher

Cell signalling
Candidate: Gold, Wendy
Award: PhD
Title: Elucidate the role of NLF-1 and NLF-2 in scleroderma
Supervisor: Keith Stanley

Blood stem cell and cancer
Candidate: Connor, David
Award: PhD
Title: A study of the procoagulant activity of platelets and platelet-derived microparticles in haematological disorders of platelet function
Supervisor: Joanne Joseph

Blood stem cell and cancer
Candidate: Loi, To Ha
Award: PhD
Title: Optimise the cDNA microarray technology to identify gene expression in Ph+ leukaemias and lymphoid malignancies
Supervisor: David Ma

Blood stem cell and cancer
Candidate: Khoo, Melissa
Award: PhD
Title: Define the mechanism underlying the differentiation of human bone marrow mesenchymal stem cells into dopaminergic neuronal-like cells
Supervisor: David Ma

Structural biology
Candidate: Smith, Phillip
Award: PhD
Title: Computational studies examining protein folding and structure
Supervisor: Paul Curmi

Structural biology
Candidate: Vincent, Kimberley
Award: PhD
Title: CLIC protein structure
Supervisor: Paul Curmi

Structural biology
Candidate: Thambiraj, Solomon
Award: PhD
Title: Membrane proteins
Supervisor: Paul Curmi

Teaching commitments of key academic staff

Inflammation
Sam Breit

University of NSW
PhD by research
Supervise research students

Neuroimmunology
Bruce Brew

University of NSW
PhD by research
Supervise research students

University of NSW
MBBS 3rd and 4th year medical students - clinical tutorials

University of NSW
MBBS 6th year medical students - lecture 'confusional states and dementia'
Registrar Clinical tutorials

University of NSW
MBBS 6th year medical students - Integrated session - 'headache'

FRACP
Registrar
Clinical tutorials, Sydney

BMedSc
Lecture - 'Neurological aspects of AIDS

UWS Master of HIV Neurological complication of HIV infection

Sydney Hospital
Post-RN (Nursing)
HIV infection and disease

HIV Immunopathology
Tony Kelleher

University of NSW
PhD by research
Supervise research students

FRACP
Registrar teaching
Clinical tutorials

FRCPA
Registrar teaching

University of NSW
Master Public Health Lecture - HIV: Immunology and Virology
Australian and international responses

University of NSW
Bachelor of Science - BSc
Lectures in Immunology 1 and 2

David Cooper

University of NSW
PhD by research
Supervise research students

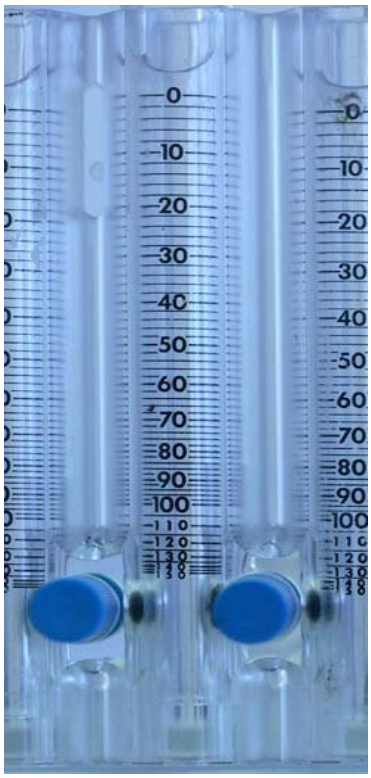
Blood, stem cell and cancer
David Ma

University of NSW
PhD by research
Supervise research students

Structural Biology
Paul Curmi

University of NSW
PhD by research
Supervise research students

University of NSW
Bachelor of Science - BSc
Lecture in Advanced Optics to 3rd year Physics students



Continuing Education Research Seminar Series - 2008

Wednesday's 1pm–1.45pm
CFI Library/Conference Room

February 20
Jim McBride
Rundown of IT for CFI Staff

February 27
Philip Cunningham
Occupational Health & Safety

March 12
David Booth
Genetics of Multiple Sclerosis Research Group, the Institute for Immunology and Allergy Research of Westmead Millennium Institute
IL7R genetics and autoimmune diseases
Sponsor: Genesearch

March 19
Gilles Guillemin
Involvement of tryptophan metabolism in neuroinflammatory diseases
Sponsor: BD Biosciences

March 26
Kersten Koelsch
HIV reservoirs
Sponsor: QIAGEN

April 2
David van Bockel
Definitive immunodominant T-cell response associated with control over HIV-1 infection: Relevance of diversity and function
Sponsor: Sigma

April 9
Oliver Distler
Molecular modeling and profiling of HIV protease inhibitor-induced dyslipidaemia
Sponsor: BIO RAD

April 16
David Brown
CEBPD in neuroinflammatory disease
Sponsor: LEICA

April 23
Prof Carolyn Geczy
Dept. of Pathology, School of Med Sciences, UNSW
S100 proteins: new regulators of inflammation. Implications in viral infection and chronic inflammation.
Sponsor: DKSH

April 30
Yiquan Chen
The involvement of the kynurenine pathway in amyotrophic lateral sclerosis
Sponsor: Edwards Instruments

May 7
A/Prof Gilda Tachedjian
Head, Macfarlane Burnet Inst. for Medical Research and Public Health
Novel drug resistance mutations in the HIV-1 reverse transcriptase
Sponsor: Interpath

May 14
Professor Georges E R Grau
Microparticles in immunopathology: Upstream and downstream
Sponsor: Merck

May 21
Wendy Gold
Localized scleroderma: A Th1 or Th2 driven disease
Sponsor: Corbett

May 28
Assoc Prof Reginald Lord
CFI studies on Barrett's oesophagus and oesophageal adenocarcinoma
Sponsor: Quantum Scientific

June 4
To Ha Loi
Post array analysis of Ph+ acute leukaemias treated with imatinib
Sponsor: Scientifix

June 11
Jean Hsu
Bone marrow mesenchymal stem cells and intervertebral disc cells
Sponsor: INVITROGEN

June 18
Melissa Khoo
Differentiation of human bone marrow mesenchymal stem cells into the neuronal lineage
Sponsor: Millipore

June 25
David Bowen
Centenary Institute
Mechanisms of hepatitis C virus persistence: virus and host
Sponsor: Pathtech

July 2
Sarah Pett
Small molecule antagonists of CCR5 and immune responses to common antigens
Sponsor: Geneworks

July 9
Heiko Johnen
Macrophage Inhibitory Cytokine-1 contributes to immune and food intake inhibition in mice.
Sponsor: Pacific Lab

July 16
Juliana Lamoury
The kynurenine pathway in stem cell biology
Sponsor: BioScientific

July 23
Kaka Ting
The effect of Quinolinic acid on human astrocytes with relevance to Alzheimer's disease pathogenesis
Sponsor: Miltenyi Biotech

July 30
Steve Carlin
In vitro generation of human T cells
Sponsor: In Vitro

August 6
Andrea Herbert
In vitro studies of endothelial progenitor cells
Sponsor: Sapphire Bioscience

September 24
Amy Weinmann
The coordinated recruitment of H3K27-demethylase and H3K4-methyltransferase activities is required for T-box protein-mediated activation of developmental target genes

Wednesdays 1.30pm–2.15pm

Level 4, Conference Room
Lowy-Packer Building

October 22
Ed Barker
HIV evasion of natural killer cells
Sponsor: Gilead

October 29
David Cooper
New drugs in development
Sponsor: Miltenyi Biotech

November 5
Torsten Juelich
Linage specific commitment to granzyme B expression by CD8+ is associated with distinct patterns of epigenetic modifications.

November 12
Christoph Boesecke
Are we ready to explore eradication?
Sponsor: TVRP

November 19
Mark Danta
Phylogenetic work?
Sponsor:Roche

November 26
Jonathan Anderson
Economics in HIV decision making
Sponsor: Tibotec

December 3
Sarah Sasson
Regulation and dysregulation of the IL-7/IL-7 receptor axis; implications for health and disease

Major Peer-Reviewed Grants awarded in 2008

Inflammation
Sam Breit
UNSW Goldstar
CLIC1 in immune and inflammatory responses
$40,000

Sam Breit
Prostate cancer foundation
Macrophage inhibitory cytocine-1 MIC-1 for the prediction of prostate cancer outcomes
$220,000

David Brown
St Vincent Clinic
Macrophage inhibitory cytokine - 1: a potential screening test for colonic polyps
$25,000

David Brown
UNSW faculty of Medicine
Molecular and cellular regulation of central nervous system immunity
$30,000

David Brown
MSRA
Molecular and Celluar regulation of CNS immune tolerance
$25,000

Neuroimmunology
Juliana Lamoury
UNSW faculty of Medicine
Role of chemokines in adult stem cell migration
$30,000

Bruce Brew
UNSW Goldstar
Role of chemokines in adult stem cell migration
$40,000

Bruce Brew
St Vincent Clinic
The kynurenine pathway of the metabolism of tryptophan influences stem cell proliferation and differentiation
$25,000

Bruce Brew
MS research
The kynurenine pathway of the metabolism of tryptophan influences stem cell proliferation and differentiation
$53,500

Gilles Guillemin
Alzheimer foundation
Involvement of the kynurenine pathway in the pathogenesis of Alzheimer's disease
$415,384

Michael Buckland
St Vincent Clinic
Epigenetic changes in human brain tumours
$50,000

HIV Immuno-virology
John Zaunders
NHMRC 510325
Processes underlying establishment & maintenance of latent HIV resevoir & potential impact of integrase inhibitors
$305,500

Blood, Stem cell and cancer
David Ma
Arrow Bone Marrow transplant foundation
Characterisation of a novel gene switch that regulates cell death in cancer
$40,000

David Ma
Arrow Bone Marrow transplant foundation
Pre-clinical in-vivo study to investigate the benefits of human bone marrow stem cells for treatment of severe degenerative intervertebral disc disease
$40,000

John Moore
St Vincent Clinic
The role of protein kinase C epsilon in Philadelphia positive acute leukaemia and its affect during glivec treatment
$25,000

Cancer
Megan Hitchins
NSW cancer Institute 07/CDF/1-17
Epimutations as a cause of familial cancer susceptibility syndromes fellowship and project grant
$600,000

Robyn Ward
NHMRC 510350
Epimutations as germ-line defects in hereditary cancer syndromes
$370,500

Cancer cell biology
Thomas Grewal
NHMRC 510293
Regulation of EGF receptor signaling
$317,250

Thomas Grewal
NHMRC 510294
Ras signalling and cholesterol efflux from late endosomes
$317,250

Structural Biology
Paul Curmi
NHMRC 488502
Integrons, mobile gene cassettes and pathogencity in vibrio chalerae
$510,000

Paul Curmi
ARC linkage LE0882295
X- ray crystallography resources for membrane proteins and large macromolecular complexes
$225,000

Paul Curmi
ARC discovery DP0881251
Ultrahigh resolution crystallography and ultrafast laser spectroscopy to uncover the evolution and mechanisms of a unique algal light harvesting system
$284,000

Paul Curmi
ARC linkage LP0883838
Structural and pharmaceutical studies on MIC-1
$514,074

Paul Curmi
ARC linkage LP0883403
Development of second generation chaperonin 10-based biologics for the treatment of inflammatory diseases
$360,000

Fellowships and scholarships

Neuroimmunology
Lucette Cysique
Brain Sciences
Brain Sciences UNSW postdoctoral fellowship
$123,000

Apsara Kandanearatchi
UNSW fellowship
UNSW postdoctoral
$220,719

Clinical
Andrew Carr
NHMRC 510301
Practitioner Fellowship
$400,000

Blood, Stem cell and cancer
Adam Bryant
NHMRC 510416
MicroRNA profiling in acute myeloid leukaemia
$94,266

Structural Biology
ARC linkage fellowship LX0881956
A rational approach to a high resolution structure of the multidrug transporter EmrE
$70,540

Memberships of Professional Societies

Inflammation
Sam Breit

- Fellow of the Royal Australasian College of Physicians
- Fellow of the Royal College of Pathologists of Austrasia
- Co-Founder and co-convenor of Society for Leukocyte and Inflammation
- Australian Rheumatism Association
- Australian Society for Immunology
- American Association of Immunologists
- American Collage of Rheumatology
- American Society for cell biology
- ANZ society for cell biology
- American Society for Biochemistry and molecular biology

Neuroimmunology
Bruce Brew

- Fellow of the Royal Australasian College of Physicians
- Member of Australian Association of Neurologists
- Appointed Corresponding Fellow of American Association of Neurologists
- New York Academy of Sciences
- American Association for the Advancement of Science
- Member of the Australasian Society of HIV Medicine
- International AIDS Society
- Australian Association of Neurologists 1995-
- Invited member of board of directors of International Society of Neurovirology

HIV
Tony Kelleher

- Fellow of the Royal Australasian College of Physicians
- Fellow of the Royal College of Pathologists of Austrasia

David Cooper

- Fellow of the Royal Australasian College of Physicians
- Fellow of the Royal College of Pathologists of Austrasia
- Australian Society of Immunology
- Australian Society of Medical Research
- American Academy of Allergy and Clinical Immunology
- American Association of Immunologists
- American Society of Microbiology

Cancer
Robyn Ward

- Fellow of the Royal Australasian College of Physicians
- Member, Gastroenterological Society of Australia
- Member, American Association of Cancer Research
- Medical oncology group of Australia
- Clinical oncology society of Australasia

Blood, Stem cell and cancer
David Ma

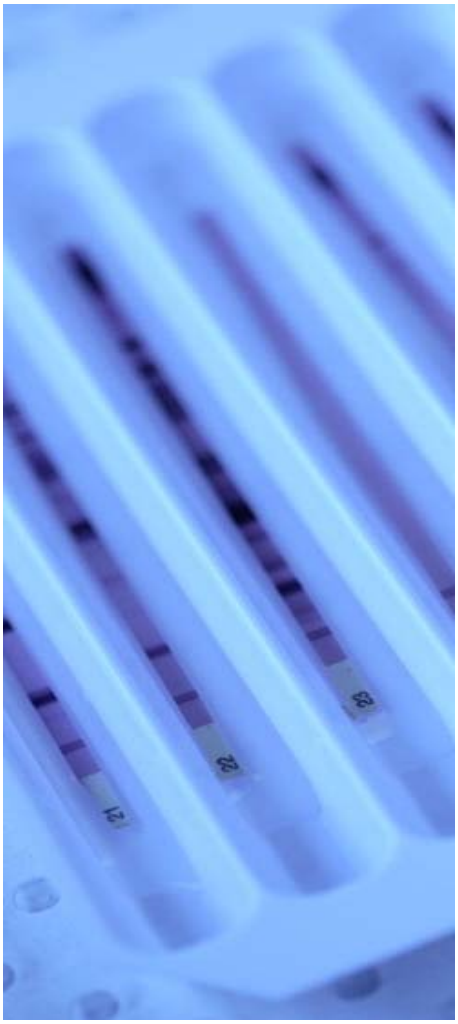
- Fellow of the Royal Australasian College of Physicians

Structural Biology
Paul Curmi

- Sydney Protein Group Committee Member of ASBMB

Gastro-oesophageal
Reginald Lord

- American Association for Cancer Research (AACR)
- Australian and New Zealand Gastric and Oesophageal Surgeons Association (ANZGOSA)
- Australasian Gastro-intestinal Trials Group (AGITG)
- Australian Medical Association (AMA)
- Clinical Oncological Society of Australia (COSA)
- Gastroenterological Society of Australia (GESA)
- International Federation for the Surgery of Obesity (IFSO)
- International Society for Diseases of the Esophagus (ISDE)
- Medical Guild of St Luke
- Obesity Surgery Society of Australia and New Zealand (OSSANZ)
- Society for Surgery of the Alimentary Tract (SSAT)
- Society of American Gastrointestinal Endoscopic Surgeons (SAGES)
- Sydney Gut Club
- Sydney Upper Gastrointestinal Surgery Society (SUGSS



Publications

Inflammation research program

Bauskin A, Brown DA, Breit SN. Macrophage inhibitory cytokine-1 in cancer. In: Schwab, Manfred ed. Encyclopedia of Cancer. 2nd Edition 2008. Berlin: Springer.

Boyle, G.M., Pedley, J., Martyn, A.C., Banducci, K.J., Strutton, G.M., Brown, D.A., Breit, S.N. and Parsons, P.G. Macrophage Inhibitory Cytokine-1 is overexpressed in malignant melanoma and is associated with tumorigenicity. J. Invest. Dermatol. 2008. 2008 Aug 28. Epub ahead of print

Paradisi S, Matteucci A, Fabrizi C, Denti MA, Abeti R, Breit SN,Malchiodi-Albedi F, Mazzanti M. Blockade of chloride intracellular ion channel 1 stimulates Abeta phagocytosis. J Neurosci Res. 2008:86:2488-98.

Rosemary H. Milton, Rosella Abeti, Stefania Averaimo, Silvia DeBiasi, Laura Vitellaro, Lele Jiang. Paul M. G. Curmi, Samuel N. Breit, Michael R. Duchen, and Michele Mazzanti. CLIC1 Function Is Required for b-Amyloid-Induced Generation of Reactive Oxygen Species by Microglia. J Neurosci. 2008.28:11488-11499.

Neuro-immunology research program

Owe-Young R, Mukhtar M, Pomerantz RJ et al. Kynurenine pathway metabolism in human endothelial cells. J Neurochemistry 2008;105(4):1346-57.

Maneglier B, Clayette P, Guillemin GJ, Rogez-Kreuz C, Brew BJ, Dormont D, Advenier C, Therond P, Spreux-Varoquaux O. Serotonin decreases HIV-1 replication in primary culture of human macrophages through 5-HT1A subtype receptors. B J Pharmacol 2008 154(1):174-82.

Cherry CL, Duncan A, Mackie K, Wesselingh SL, Brew BJ. A report on the effect of commencing enfuvirtide on peripheral neuropathy.AIDS Res Hum Retroviruses. 2008;24(8):1027-30.

Wright EJ, Brew BJ, Arayawichanont A, Robertson K, Sibmooh K, Kongsaengdao S, Lim M, Saphonn V, Lal L, Sarim C, Huffam S, Li P, Imran D, Lewis J, Lun W, Kamarulzaman A, Tau G, Ty Ali S, Kishore K, Bain M, Dwyer R, McCormack G, Hellard M, Cherry C, McArthur J, Wesselingh SL. HIV-associated Neurocognitive Impairment and Symptomatic Peripheral Neuropathy are Highly Prevalent in the Asia Pacific Region. Neurol 2008; 71 50-56.

Wright EJ, Brew BJ, Lal L et al. Antiepileptic drugs and HIV. Epilepsia 2008;49(3):541-3.

Pemberton LA, Stone E, Price P, Bockxmeer FM, Brew BJ. The Relationship Between Apoe, TNFa, IL1a, IL1b And IL12b Genes And HIV-1 Associated Dementia. HIV Med 2008; Jul 2. [Epub ahead of print].

Batmanian JJ, Lam M, Matthews C, Finckh A, Duffy M, Wright R, Brew BJ, Markus R. Tissue plasminogen activator for acute ischaemic stroke.Med J Aust. 2008;188(8):489-490.

Nady Braidy; Gilles J. Guillemin and Ross Grant Promotion of Cellular NAD Anabolism: Therapeutic Potential for Oxidative Stress in Alzheimer's Disease & Aging.. *Neurotoxicity Research,* 2008, VOL. 13(3,4). pp. 173-184

Benjamin Maneglier, Gilles J Guillemin, Odile Spreux-Varoquaux, Benoit Malleret, Christine Rogez-Kreuz, Stephane Prost, Charles Advenier, Patrice Therond, Dominique Dormont and Pascal Clayette Serotonin decreases HIV-1 infection of human macrophages. *Br J Pharmacol.* 2008 May;154(1):174-82

Brew BJ, Letendre S. Biomarkers of HIV related Central Nervous System Disease. Int Rev Psych 2008; 20(1):73-88.

Wright E, Brew BJ. Wesselingh S. Pathogenesis and diagnosis of viral infections of the nervous system. In Neurovirology. Neurologic Clinics. Eds Power C, Johnson R. 2008;26(3):617-633.

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Heaton, R. Cysique L., Jin, H., Franklin D, Shi C, Yu X, Marcotte T, Letendre S, Ake C, Grant I, Wu Z, & the HNRC group. Neurobehavioral Effects of HIV-1 Infection in Former Plasma Donors in Anhui, China. J Neurovirol 2008 7:1-14.

Brew BJ, Crowe SM, Landay A, Cysique LA, Guillemin G. Neurodegeneration and Ageing in the HAART Era. J Neuroimmune Pharmacol 2008;6:6.

Ismail AK, Milliken S, Buckland ME (2008). "Acute neutropenic diverticulitis: a case report" Pathology 40(4):423-5. 2.

Leecy T, Buckland ME, Turner J, Earls P. (2008) "The use of immunohistochemistry in the diagnosis of salivary duct carcinoma: three case reports." Pathology 40(4):434-7. 3.

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Books/chapters

Cysique LA, Brew BJ. The impact of long term HAART on cognition. In: HIV and the brain: new challenges in the modern era. Eds Paul R, Sacktor K, Tashima K, and Valcour V. (December 10 2008

Davies NWS, Brew BJ. HIV associated dementia and neuropathy. In HIV/AIDS, El-Gadi S, Gazzard B (eds) Mediscript Press (Sept 12, 2008

Brew BJ. Neurological complications of HIV. In The year in review – Neurology (March 10, 2008

Cysique LA, Brew BJ. Neuropsychological functioning and antiretroviral treatment in HIV/AIDS: an historical review. Neuropsychology (December 10 2008

Paul R, Sacktor N, Cysique LA, Brew BJ, Valcour V. The impact of clade diversity on neuropsychological outcomes. Eds Paul R, Sacktor K, Tashima K, and Valcour V. 2008

Letendre SL, Brew BJ. CSF biomarkers of HIV associated dementia. In: HIV and the brain: new challenges in the modern era. Eds Paul R, Sacktor K, Tashima K, and Valcour V. 2008

.Brew BJ. Opportunistic Infections in HIV. In: International Neurology, a clinical approach. Eds: Lisak R, Truong D, Carrol W and Bhidayasiri R. Blackwell International press 2008

Brew BJ. Primary central nervous system lymphoma. In: International Neurology, a clinical approach. Eds: Lisak R, Truong D, Carrol W and Bhidayasiri R. Blackwell International press 2008

Brew BJ. HIV and acquired immunodeficiency syndrome overview. In: International Neurology, a clinical approach. Eds: Lisak R, Truong D, Carrol W and Bhidayasiri R. Blackwell International press 2008

HIV Immuno-virology research program

Seddiki N, Kelleher AD – Review: Regulatory T cells in HIV-infection: Who's suppressing what? Published Current AIDS Reports 5:20-26 2008

Kelleher AD, Cooper DA, Infección primaria por HIV. Ramacciotti TPT In *SIDA y Enfermedades Asociadas, Diagnóstico, Clinica y Tratamiento,* 3ª Edición, Tomo 1 (2008), FUNDAI, 155-170 (Chapter Title: Primary HIV-1 infection; Book Title: AIDS and infectious diseases

Kestens L, Seddiki N, Bohjanen PR, Immunopathogenesis of the immune reconstitution disease in HIV patients responding to antiretroviral therapy, Current Opinion in HIV and AIDS 3(4):419-424, July 2008

Lewin SR, Murray JM, Solomon A, Wightman F, Cameron PU, Purcell D, Zaunders JJ, Grey P, Bloch P, Smith M, Cooper D, Kelleher AD, Virologic determinants of success after structured treatment interruptions of antiretrovirals in acute HIV-1 infection, J Acquir Immune Defic Syndr 47: 47 140-47 2008 ADD TO 2008

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Lim H, Suzuki K, Cooper DA, Kelleher AD. Promoter-targeted siRNAs induce silencing of Simian Immunodeficiency virus (SIV) infection in vitro. Molecular Therapy. 16 3, 565-570. November 2007

Kelleher AD, Cooper DA. Acute HIV Infection. In: 63-74. Volberding PA, Sande MA, Greene WC, Lange JMA., eds. Global HIV/AIDS Medicine. Philadelphia, PA: Elsevier Inc, 2008:

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Burton CT, Goodall RL, Samri A, Autran B, Kelleher A, Poli G, Pantaleo G, Gotch FM, Imami N. Restoration of Anti-Tetanus Toxoid Responses in Patients Initiating HAART with or without a Boost Immunisation: An INITIO Substudy. Clinical and Experimental Immunology (2008) 152: 252-257.
Kelleher AD, Purcell DF, HIV Co-receptor gets the finger ICD invited Commentary in Immunology and Cell Biology

Falster K, Gelgor L, Shaik A, Zablotska I, Prestage G , Grierson J, Thorpe R, Pitts M, Anderson J, Chuah J, Mulhall B , Petoumenos K, Kelleher A and Law M. Trends in antiretroviral treatment use and treatment response in three Australian states in the first decade of combination antiretroviral treatment. Sexual Health (2008) 5(2): 141–154

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Chessman, D., Kostenko, L., Lethborg, T., Purcell, A. W., Williamson, N. A., Chen, Z., Kjer-Nielsen, L., Mifsud, N. A., Tait, B. D., Holdsworth, R., Almeida, C. A., Nolan, D., Macdonald, W. A., Archbold, J. K., Kellerher, A. D., Marriott, D., Mallal, S., Bharadwaj, M., Rossjohn, J., and McCluskey, J. (2008). Immunity 28, 822.

Brumme, Z. L., Brumme, C. J., Carlson, J., Streeck, H., John, M., Eichbaum, Q., Block, B. L., Baker, B., Kadie, C., Markowitz, M., Jessen, H., Kelleher, A. D., Rosenberg, E., Kaldor, J., Yuki, Y., Carrington, M., Allen, T. M., Mallal, S., Altfeld, M., Heckerman, D., and Walker, B. D. (2008). J Virol 82, 9216

Clinical research program

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Calmy A, Carey D, Mallon PWG, Wand H, Cooper DA, Law M, Carr A, INITIO Trial International Co-ordinating Committee and HAMA study coordination team. Early changes in adipokine levels and baseline limb fat may predict HIV lipoatrophy over 2 years following initiation of antiretroviral therapy. HIV Med 2008; 9: 101-10.

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Blood, stem cell and cancer research program

Tao H, Shen B, Wei A, Kishen T, Diwan A, Ma D. Therapeutic potential of bone marrow mesenchymal stem cells to repair degenerative intervertebral discs. J Stem Cells 2008; 3(1):1-11.

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Gastro-oesophageal research group

Lord RVN, DeMeester SR, Peters JH, et al. Hiatal hernia, lower esophageal sphincter incompetence, and the effectiveness of Nissen fundoplication in the spectrum of gastroesophageal reflux disease. In press, J Gastrointest Surg.2008 December 3

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Conference publications

Inflammation research program

Breit SN, Johnen H, Lin S, Kuffner T, Brown DA, Tsai VWW, Bauskin AR, Wu L, Corey E, Sainsbury A, Herzog H. *The TGF-b superfamily cytokine MIC-1 causes tumour-induced anorexia/cachexia by modulating appetite control centres in the hypothalamus.* Cytokine 2008 Montreal Canada.

Neuro-immunology research program

Guillemin GJ, Cullen K, Brew BJ. Characterisation of the kynurenine pathway in human neurons. Australian Neuroscience Society 2008, Hobart January 23-27, 2008

Ting K, Brew BJ, Guillemin GJ. Effect of Quinolinic acid on gene expression in human Astrocytes. Australian Neuroscience Society 2008, Hobart January 23-27, 2008.

Lee M-C, Brew BJ, Guillemin GJ.Characterisation of the glutametergic system in primary human foetal astrocytes. Australian Neuroscience Society 2008, Hobart January 23-27, 2008.

Guillemin GJ, Cullen K, Ting K, Brew BJ. Involvement of the kynurenine pathway in Alzheimer's disease (oral). Kioloa Neuroscience Colloqium April 12-13, 2008

Ting KK, Brew BJ, Guillemin GJ. Effect of Quinolinic acid on gene expression in human Astrocytes. Kioloa Neuroscience Colloqium April 12-13, 2008.

Rossez H, Kandanearatchi A, Harman A, Donaghy H, Wilkinson J, Cunningham A, Brew BJ, Guillemin GJ. Characterisation of the kynurenine pathway in human dendritic cells. Kioloa Neuroscience Colloqium April 12-13, 2008.

Lim CK, Smythe G, Stocker R, Brew BJ, Guillemin GJ. Characterization of the kynurenine pathway in primary human oligodendrocytes. Kioloa Neuroscience Colloqium April 12-13, 2008

Michael Buckland Molecular FISH analysis of gliomas: The Sydney experience. Annual ANZSNP conference (Australian and New Zealand Society for Neuropathology), Brisbane, Australia, May 2008.

Michael Buckland Gene methylation in schizophrenia: A human post-mortem study. 82nd annual meeting of the American Association of Neuropathologists/FASEB, San Diego, CA, 2008.

Juliana Lamoury, Francois MJ Lamoury & Bruce J Brew. The kynurenine pathway of tryptophan metabolism modulates the differentiation potential of human and mouse stem cells obtained from bone marrow and CNS tissues. The 4th Australian Health Medical Research Congress, 16 November – 21st November 2008, Brisbane, Australia.

Juliana Lamoury, Francois MJ Lamoury & Bruce J Brew. Expression of the kynurenine pathway in human and mouse stem cells: role in differentiation. 18th St Vincent's Hospital Campus Research Symposium, Sydney, Australia, 19th September 2008.

Juliana Lamoury, Francois MJ Lamoury & Bruce J Brew. Expression and modulation of the kynurenine pathway in human and mouse stem cells obtained from bone marrow and CNS tissues: role in differentiation. 6th Annual meeting, International Society for Stem Cell Research (ISSCR), Philadelphia, USA, June 11-14, 2008.

Gilles J Guillemin, Karen Cullen, Edwin Lim, Brett Garner and Bruce J Brew. Characterization of the kynurenine pathway in human primary neurons.

Ming-Chak Lee, Bruce J. Brew and Gilles J. Guillemin Characterisation of the glutametergic system in primary human astrocytes

Nady Braidy; Ross Grant and Gilles J Guillemin A mechanism for quinolinic acid induced cytotoxicity in human astrocytes and neurons.

Chen Y, Stankovic R, Cullen K, Meininger V, Brett Garner, Brew BJ & Guillemin GJ.The involvement of inflammation and the kynurenine pathway (KP) in amyotrophic lateral sclerosis

Hidetoshi Akimoto, Syota Kagawa, Akiko Yamada, Gilles J Guillemin, and Osamu Takikawa. Amyloid Plaques-Associated Activated Microglial Cells are Primed for Expression of IDO and Production of Neurotoxin Quinolinic Acid toward Systemic Lipopolysaccharide-Induced Inflammation in a Tg2576 Mouse Model of Alzheimer's Disease. International Conference on Alzheimer's Disease (July 26-31, 2008), Chicago, USA

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Helene Rossez, Apsara Kandanearatchi, Andrew Harman, Heather Donaghy, John Wilkinson, Anthony Cunningham, Bruce J. Brew & Gilles J. Guillemin.Characterisation of the kynurenine pathway in human dendritic cells. Kioloa Neuroscience Colloquium 2008, Australia, (April 12 – 13, 2008

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HIV Immuno-virology research program

Zaunders J, Pett S, Bailey M, Seddiki N, Munier ML, Ip S, Kim M, Cunningham AL, Cooper DA, Kelleher AD. High Level Persistence of HIV Antigen-Specific CD4+ T Cells in Untreated Chronic Infection, Detected by a Novel Flow Cytometric Assay. 15th Conference on Retroviruses and Opportunistic Infections (CROI) Boston, 2008.

Weatherall C, Siebentritt C, Campbell S, Purcell D, Cooper DA, Kelleher AD. HIV-neutralizing Antibody Activity in a Large Primary Infection Cohort Correlates with Anticardiolipin Antibody Activity but is not Directed Against gp41 membrane Proximal Epitope Region. Keystone Symposia on Molecular and Cell Biology Canada, March 2008.

Kelleher A, Munier M, Zaunders J, Seddiki N, Brown K, Emery S, Cooper D, Pett S, Bailey M Persistence of HIV Antigen-Specific CD4 T Cells in Untreated Chronic Infection: Phenotypic and functional characterization. Keystone Symposia on Molecular and Cell Biology Canada, March 29, 2008

Brumme Z, C Brumme C, Carlson J, Streeck H, John M, Kadie C, Baker B, Eichbaum Q, Markowitz M, Jessen H, Kelleher A, E Rosenberg E, Kaldor J, Carrington M, Allen T, Altfeld M, Mallal S, Heckerman D, Walker B HLA class I-associated immune selection pressure drives a major portion of HIV-1 evolution in early infection Keystone Symposia on Molecular and Cell Biology Canada, March 28, 2008

Suzuki K, Heterochromatin structure is induced by silRNA targeting HIV-1 promoter region. RNAi Europe Conference and Exhibition, Stockholm, 16-18 September 2008

N Seddiki, K Brown, C Phetsouphanh, D Cooper, J Zaunders and A Kelleher. Identification of human antigen-specific regulatory T cells, phenotyping and functional analysis. Focis meeting (federation of clinical immunology), Boston 2008

N Seddiki, C Phetsouphanh, K Brown, John Zaunders, D Cooper and A Kelleher. Regulatory T cell abnormalities are associated with aberrant CD4+ T-cell responses in patients with immune inflammatory syndrome (IRIS). Focis meeting (federation of clinical immunology), Boston 2008

Lim HGW, Suzuki K, Cooper DA, Kelleher A. Promoter targeted siRNAs induce gene silencing of simian immunodeficiency virus (SIV) infection in vitro. UNSW International Research Workshop 20-22 February 2008

Zaunders J, Pett S, Bailey M, Seddiki N, Munier ML, Ip S, Kim M, Cunningham AL, Cooper DA and Kelleher A, High Level Persistence of HIV Antigen-Specific CD4+ T Cells in Untreated Chronic Infection, Detected by a Novel Flow Cytometric Assay UNSW International Research Workshop 20-22 February 2008

Brown KM, Seddiki N, Cooper DA, Kelleher AD Describing T-cell receptor [TCR] Repertoires Amongst Antigen-Specific CD4+ Regulatory T-cells. UNSW International Research Workshop 20-22 February 2008

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N Seddiki, C Phetsouphanh, K Brown, John Zaunders, D Cooper and A Kelleher. Regulatory T cell abnormalities are associated with aberrant CD4+ T-cell responses in patients with immune inflammatory syndrome (IRIS). SVH 2008 SVH Symposium 19 September 2008

Pett S, Emery S, Cooper DA, Zaunders JJ, Murray J, Bailey M, MacRae K, Kelleher AD. "Changes in CCR5+ cells and Antigen-specific CD4+ T-cells during monotherapy with a CCR5 antagonist SCH532706 compared with combination therapy" Ninth International Congress on Drug Therapy in HIV Infection 09-13 November 2008 Glasgow, UK

Puls R., Hemachandra A., Sirivichayakul S., Kerr S., Thaniworasit P., Cooper D.A., Emery S., Kellher A.D. and Ruxrungtham K. "A randomized Phase I/IIa trial of a Clade A/E Prime, Recombinant Fowlpox Virus Boost HIV-1 Vaccine in Low-risk Thai Population." Conference on Retroviruses and Opportunistic Infections (CROI) 2009 Montreal February 8-11 2009

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J Zaunders, ML Munier, S Ip, M Bailey, DA Cooper, and AD Kelleher Simple whole blood assay for antigen-specific CD4+ T cells using CD25 and CD134. 3rd Masir Conference Measuring Antigen-Specific Immune Responses (MASIR). La Plagne, France, February, 2008.

J Zaunders, S Pett, M Bailey, N Seddiki, ML Munier, S Ip, M Kim, AL Cunningham, DA Cooper and AD Kelleher. High Level Persistence of HIV Antigen-Specific CD4+ T Cells in Untreated Chronic Infection, Detected by a Novel Flow Cytometric Assay. *15th Conference on Retroviruses and Opportunistic Infections (CROI*). Boston, February, 2008.

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Zaunders JJ, Bailey M, Muiner ML, Seddiki N, Kim M, Pett S, Emery S, Cunningham AL, Cooper DA & Kelleher AD –persistence of high levels of HIV antigen specific CD4+ T cells in untreated chronic infection, detected by a novel flow cytometric assay ASHM abstract 17-20 September 2008 – Perth

Pett SL, Zaunders J, Bailey M, Murray J, Cooper DA, MacRae K, Emery S, Kelleher A changes in circulating CCR5+ T-cells and antigen specific CD4+ T-cells during monotherapy with a small molecule CCR5 antagonist SCH532706, compared with comination antiretroviral therapy (cART). ASHM abstract 17-20 September 2008 – Perth

Gelgor L, Anderson B, Baker, D, Finlayson R, McFarlane R, McMurchie M, Kelleher A, Kaldor J on behalf of the Long Term Non-progressor study group update of the Australian long-term non-progressor (LTNP) cohort ASHM abstract 17-20 September 2008 – Perth

Seddiki N, Phetsouphanh C, Brown K, Zaunders J, Cooper D and Kelleher A, Regulatory T Cell abnormalities are associated with aberrant CD4+ T-cell Responses in Patients with immune inflammatory Syndrome (IRIS). ASHM abstract 17-20 September 2008 – Perth

Seddiki N, Brown K, Phetsouphanh C, Cooper D, Zaunders J and Kelleher A, Identification of Human Antigen-Specific Regulatory T Cells, Phenotyping and Functional analysis.). ASHM abstract 17-20 September 2008 – Perth

Brumme C, Brumme Z, Walker B, Carlson J, Markowitz M, Jessen H, Kelleher AD, John M, Mallal S, Allen T, Heckerman D, Reversion of HLA-associated polymorphisms in Gag, Pol and Nef during the first year of HIV infection: Sites, rates and pVL Correlations, AIDS Vaccine 2008, Cape Town, South Africa, 13-16/10.

N Seddiki, K Brown, C Phetsouphanh, D Cooper, J Zaunders and A Kelleher. Identification of human antigen-specific regulatory T cells, phenotyping and functional analysis. Abstract in Clinical Immunology, Supplement 1, 127:S126, 2008

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Kelleher AD, "Reassessing Vaccine Responses" ASHM 2008

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Puls R., Hemachandra A., Sirivichayakul S., Kerr S., Thaniworasit P., Cooper D.A., Emery S., Kellher A.D. and Ruxrungtham K. "A randomized Phase I/IIa trial of a Clade A/E Prime, Recombinant Fowlpox Virus Boost HIV-1 Vaccine in Low-risk Thai Population." CROI 2009 Montreal February 8-11 2009

Seddiki N, Kai Brown K., Phetsouphanh C., Cooper D.A., Zaunders J.J. and Kelleher A.D. "Human antigen-specific regulatory T cells: New Strategy to identify and isolate them" Australian society of Immunology (ASI)

Clinical research program

Calmy A, Nguyen A, Montecucco F, Gayet-Ageron A, Burger F, Mach F, Carr A, Ubolyam S, Hirschel B, Ananworanich J, STACCATO Study Team. "HIV increases cardiovascular risk markers in a randomized treatment interruption trial: STACCATO". 15th Conference on Retroviruses and Opportunistic Infections, Boston, USA, February, 2008

Carr A, Amin J. "Reasons for treatment success with initial ART: an analysis of 22,635 participants in 64 randomized, controlled trials and 14 prospective cohorts". 15th Conference on Retroviruses and Opportunistic Infections, Boston, USA, February, 2008

Blood stem cell and cancer research program

Hsu J, Shen B, Tao H, Diwan A, Ma D. (2008)Bone marrow mesenchymal stem cells have distinct phenotypic characteristics compared to intervertebral disc cells and may be differentiated towards intervertebral disc cells via co-culture. Presented at the International Society for the Study of the Lumbar Spine Annual Meeting, Geneva, Switzerland. Abstract 116.

Wei A, Tao H, Chung S, Brisby H, Lin Z, Shen B, Ma D, Diwan AD. (2008)Differentiation of rodent bone marrow-derived mesenchymal stem cells into disc-like cells after co-cultured with intact intervertebral discs. Presented at the 6th Annual Meeting of International Society for Stem Cell Research. Abstract 424

Shen BJ, Wei AQ, Tao H, Diwan AD, Ma DDF. (2008) BMP-2 Enhances TGF-β3 - Mediated Chondrogenic Differentiation of Human Bone Marrow Multipotent Mesenchymal Stromal Cells (BM MSCs) *in vitro.* Presented at the Annual Scientific Meeting of Haematology Society of Australia and New Zealand. Abstract

Gastro-oesophageal research program

Samaras K, Hayward C, Lord RV. Arterial stiffness in morbid obesity and type 2 diabetes: the effects of weight loss and improved glucose metabolism. The Endocrine Society's 90th Annual Meeting. (Endo08). San Francisco June 2008

Botelho NK, Samaras K, Schneiders F, Chisholm DJ, Lord RV. Site-specific differential adipokine gene expression in visceral and subcutaneous adipocytes in obese and lean humans. The Endocrine Society's 90th Annual Meeting. (Endo08). San Francisco June 2008

Samaras K, Botelho NK, Schneiders F, Chisholm DJ, Lord RV. Proinflammatory adipokine gene expression is higher in visceral adipocytes in humans with Metabolic Syndrome. The Endocrine Society's 90th Annual Meeting. (Endo08). San Francisco June 2008

Samaras K, Botelho NK, Schneiders F, Chisholm DJ, Lord RV. Adipokine gene expression in subcutaneous and visceral fat in humans with type 2 diabetes mellitus compared to insulin sensitivity. The Endocrine Society's 90th Annual Meeting. (Endo08). San Francisco June 2008

Schneiders F, Botelho NK, Lord RVN. Barrett's Intestinal Metaplasia mRNA Expression Profile in Formalin-Fixed, Paraffin-Embedded Endoscopic Biopsy Specimens. Gastroenterology 2008; 134(4, Suppl. 1): A-911.

Lord RV, Oberg S, Peters JH, DeMeester SR, Hagen JA, DeMeester TR. Bile Reflux Induces Higher COX-2 Expression than Mixed Acid and Bile Reflux in a Rat Model of Esophagitis. Gastroenterology 2008; 134(4, Suppl. 1): A-875.

Cancer research program

Megan Hitchins Maternal transmission of 'reversible' germline MLH1 epimutation confers cancer susceptibility. International Society for Gastrointestinal Hereditary Tumours Yokohama, Japan January 2008

Megan Hitchins Coordinate epigenetic silencing of a cluster of 3p22 genes flanking MLH1 in sporadic microsatellite unstable colorectal cancer. American Association for Cancer Research Congress Los Angeles, USA April 2007

Robyn Ward Epimutations, mismatch repair and colorectal cancer Ludwig Institute for Cancer Research Colon Cancer Initiative Workshop Melbourne, Australia May 2008

Robyn Ward Genetic tests and reimbursement of pharmaceuticals – PBAC perspective ARCS (Association of Regulatory and Clinical Scientists) 17th Annual Scientific Congress Sydney Convention and Exhibition Centre, Austr

Conference Presentations

Inflammation research program

David Brown. Macrophage inhibitory cytokine-1 a novel therapeutic for cancer associated anorexia, 2008 The Australian health and medical research conference, Brisbane.

Neuro-immunology research program

Chen Y, Stankovic R, Cullen K, Meininger V, Brew BJ, Guillemin GJ. Investigating the kynurenine pathway in amyotrophic lateral sclerosis. Australian Neuroscience Society 2008, Hobart January 23-27, 2008.

Chen Y, Stankovic R, Cullen K, Meininger V, Brew BJ, Guillemin GJ. Investigating the kynurenine pathway in amyotrophic lateral sclerosis. Kioloa Neuroscience Colloqium April 12-13, 2008.

Brew BJ Progressive multifocal leukoencephalopathy and Natalizumab. Biogen Idec sponsored meeting Melbourne June 11, 2007

Brew BJ Progressive multifocal leukoencephalopathy. Australian and new Zealand Association of Neurologists Annual Scientific Meeting, Alice Springs May 21-25, 2007.

Brew BJ Progressive multifocal leukoencephalopathy. New Zealand Association of Neurologists. Queenstown New Zealand August 18, 2007.

Brew BJ Host and non-neuronal biomarkers in neuroAIDS. Methods in International NeuroAIDS Research, Conference and Training, University of California San Diego, October 26-29, 2007.

Brew BJ Biological markers of CNS injury in HIV infection. 8th International Symposium on Neurovirology San Diego, October 29-November 2, 2007.

Brew BJ Invited discussant. Strategic Planning Meeting for Domestic and International NeuroAIDS Research. July 24-25th, 2008 Bethesda, MD.

Brew BJ Update in HIV Neurology, Newcastle March 28, 2008.

Brew BJ Annual HIV Neurology Update, ASHM Ballina May 3, 2008.

Brew BJ Identifying And Managing HIV Dementia In The Primary Care Setting. Tibotec sponsored meeting Sydney August 13, 2008

Brew BJ HIV Neurology Update. The Burnet, August 27, 2008

Brew BJ Identifying And Managing HIV Dementia In The Primary Care Setting. Tibotec sponsored meeting Melbourne August 13, 2008.

Brew BJ Neurodegenerative diseases in the HAART era. ASHM annual meeting Perth Sept 17-20 2008

Brew BJ Current controversies in PML pathogenesis. PML investigator meeting, Chicago September 26-27, 2008.

Brew BJ Update on the neurological complications of HIV disease. 12th Asian Oceanian Congress of Neurology and 16th Annual Conference of the Indian Academy of Neurology, New Delhi, 23-26 October 2008.

Michael Buckland Molecular FISH analysis of gliomas: The Sydney experience. Annual ANZSNP conference (Australian and New Zealand Society for Neuropathology), Brisbane, Australia, May 2008.

Michael Buckland Gene methylation in schizophrenia: A human post-mortem study. 82nd annual meeting of the American Association of Neuropathologists/FASEB, San Diego, CA, 2008.

Juliana Lamoury and Bruce J. Brew. Tryptophan metabolism in the biology of stem cells - Invited speaker – Neural Stem Cells & Regenerative Neuroscience Workshop (Satellite meeting – 8th Scientific Meeting of the International College of Geriatric Psychoneuropharmacology), Scientia Building, University of New South

Wales, Sydney, Australia, 3-6 September 2008.

Juliana Lamoury and Bruce J. Brew. AusBiotech Business & Networking Seminar - Invited panellist: "Adult Stem Cell Research & Therapies of the Future" – NSW Dept State & Regional Development, Sydney, Australia, 8 July 2008.

Juliana Lamoury, Francois Lamoury and Bruce J. Brew. "Kynurenine pathway in stem cell biology". CFI Research Seminar, *Centre for Immunology, St. Vincent's Hospital*, Sydney, Australia, 14 July 2008.

Guillemin GJ, Karen Cullen, Abdur Rahman, Kaka Ting, and Brew BJ Involvement of the kynurenine pathway in Alzheimer's disease. 18th St Vincent's Hospital Campus Research Symposium, Sydney, Australia, 18 September 2008

Gilles J. Guillemin Kynurenine pathway, neuroprotection and neurodegeneration: role of astrocytes and microglia. Psychoneuroimmunology (**PNI**) workshop, Munich, Germany (July 11-13, 2008

Gilles J. Guillemin, Karen Cullen, Kaka Ting & Bruce J. Brew.Involvement of the kynurenine pathway in Alzheimer's disease. Kioloa Neuroscience Colloquium 2008, Australia, (April 12 – 13, 2008

Nady Braidy, Ross Grant and Gilles J Guillemin Effect of kynurenine pathway inhibition on NAD metabolism and PARP activity in human brain cells.. Kioloa Neuroscience Colloquium 2008, Australia, (April 12 – 13, 2008

Yiquan Chen, Roger Stankovic, Karen Cullen, Vincent Meininger, Bruce J. Brew and Gilles J. Guillemin Investigating the kynurenine pathway in amyotrophic lateral sclerosis. Kioloa Neuroscience Colloquium 2008, Australia, (April 12 – 13, 2008

Yiquan Chen, Roger Stankovic, Karen Cullen, Vincent Meininger, Bruce J. Brew and Gilles J Guillemin Investigating the kynurenine pathway in amyotrophic lateral sclerosis Australian Neuroscience Society 2008, Hobart (January 23-27, 2008

HIV Immuno-virology research program

Brumme Z, Brumme C, Carlson J, Heckerman D, Walker B, Kelleher AD, Jessen H, Streeck H, John M, Markowitz M. Kinetics of Escape Within HLA-restricted CTL Epitopes in the First Year of HIV Infection is Consisten With Early Immunodominant CTL Response Patterns-15th Conference on Retroviruses and Opportunistic Infections (CROI) Boston, 3-6 February 2008.

Zaunders J, Munier ML, Ip S, Bailey M, Cooper DA, Kelleher AD. Simple Whole Blood Assay for Antigen-Specific CD4+ T Cells and CD134. Measuring Antigen-Specific Immune Response (MASIR) Conference France, January/ February 2008.

Streeck H, Jolin J, Alter G, Meier A, Yassine-Diab B, Little S, Kelleher AD, Routy JP, Rosenberg ES, Sekaly RP, Hecht F, Walker BD and Altfeld M. Inter-epitope interference modulate HIV-1-specific CD8+ T cell immunodominance patterns in primary infection. XVII International AIDS Conference Mexico, 4 August 2008.

Brumme C; Brumme Z; Walker B; Carlson J; Markowitz M; Jessen H; Kelleher AD; John M; Mallal S; Allen T; Heckerman D; Reversion of HLA-associated polymorphisms in Gag, Pol and Nef during the first year of HIV infection: Sites, rates and pVL Correlations, AIDS Vaccine 2008, Cape Town, South Africa, 13-16/10.

Celine Yan, "Dried blood/plasma spots: Experience in HIV Immunovirology Lab" Treat Asia Quality Assurance Network Meeting, Bangkok Thailand 15th October 2008

Zaunders J, Simple whole blood assay for apthogen-specific CD4 + T cells. CFI Journal Club, 29 February 2008

Chan Phetsouphan, "Optimising Real-Time PCR Conditions for Detection of CD39, CD73 and the Adenosine Receptors A1, A2A, A2B and A3" Immunovirology and Pathogenesis Program Lab Presentation 6 March 2008

Kelleher AD, "That last step was a doosey"- the outcomes of STEP a Phase llb proof of a CTL inducing HIV-1 prophylactic vaccine. HIV immunology & Infectious disease journal club CFI, 14 March 2008

Sanjay Swaminathan, "Update on PhD" Immunovirology and Pathogenesis Program Lab Presentation 20 March 2008

Michelle Bailey, "Results from the (PO 4112 study) immunology substudy CCR5 blocker study Immunovirology and Pathogenesis Program Lab Presentation 27 March 2008

Ansari Shaik "Phaedra/ Core/ Phaedra extension data on Oracle Apex" Immunovirology and Pathogenesis Program Lab Presentation 3 April 2008

Chris Weatherall "Feedback on Keystone" Immunovirology and Pathogenesis Program Lab Presentation 10 April 2008

Heidi Lim "Feedback on Keystone" Immunovirology and Pathogenesis Program Lab Presentation 17 April 2008

Claudia Mische "An assay for detection of 2-LTR" circles Immunovirology and Pathogenesis Program Lab Presentation 1 May 2008

Nigel McCarthy " Development of reporter constructs for screening shRNA and a recombinant viral delivery system" Immunovirology and Pathogenesis Program Lab Presentation 29 May 2008

Kelleher AD, as invitee asked to comment Session 1 Medical Sciences Stream: Infection & Immunity (Group leader D Cooper & C Geczy) UNSW International Research Workshop 20 Feb 2008

Van Bockel D, T-cell response associated with control over HIV-1 infection: Relevance of diversity and function. CFI Research Seminar, 2 April 2008

Kersten Koelsch "Elite controllers of HIV infection" HIV/Immunology & Infectious Diseases Journal Club, 30 May 2008

Kelleher Anthony, "Review of STEP trial: that last step was a doosy!" NCHECRTrial Network Site Coordinator Meeting, Perth Tuesday 16 September 2008

Linda Gelgor "Current status of LTNP cohort" Immunovirology and Pathogenesis Program Lab Presentation 5 June 2008

Kersten Koelsch "New players in cytokine control of HIV infection" Immunovirology and Pathogenesis Program Lab Presentation 12 June 2008

Seddiki Nabila, "Immune regulation and profiling of HIV protase inhibitor-induced dyslipidaemia" Immunovirology and Pathogenesis Program Lab Presentation 19 June 2008

Distler Oliver, "Molecular modelling and profiling of HIV protase inhibitor induced dyslipidaemia" Immunovirology and Pathogenesis Program Lab Presentation 26 June 2008

Kirstin McBride, "The role of DNA on HIV-1 infection" Immunovirology and Pathogenesis Program Lab Presentation 10 July 2008

Seddiki "Tregs in health and disease" Garvan Lab Meeting Talk, July 2008

Chris Weatherall Basic Virology, diagnostics and monitoring of HIV infection lecture Masters of Community Health/ Master of Public Health course HIV/AIDS: Australian and International Responses UNSW, 26 August 2008

Tony Kelleher, Introduction to Immunopathogenisis of HIV infection lecture, Masters of Community Health/ Master of Public Health course HIV/AIDS: Australian and International Responses UNSW, 26 August 2008

Nabila Seddiki, "Regulatory T Cell abnormalities are associated with aberrant CD4+ T-cell Responses in Patients with immune inflammatory Syndrome (IRIS)". ASHM 17-20 September 2008 – Perth

Nabila Seddiki, "Identification of human antigen-specific regulatory T cells, phenotyping and functional analysis" ASHM 17-20 September 2008 – Perth

Chan Phetsouphan "Transcription factor expression in Naïve and activated Tregs" Immunovirology and Pathogenesis Program Lab Presentation 17 July 2008

Ansari Shaik "Demonstration of database" Immunovirology and Pathogenesis Program Lab Presentation 24 July 2008

John Zaunders, "T cell subsets in the PINT study" Immunovirology and Pathogenesis Program Lab Presentation 31 July 2008

Kate Marks, "CD4+ T cell isolation in from gut biopsies" Immunovirology and Pathogenesis Program Lab Presentation 7 August 2008

John Zaunders, " Simple whole blood assay for antigen-specific CD4+ cells using CD 25 and CD134 (OX40)", Oral Abstract Presentation, Australasian flow cytometry group 31st Annual Scientific meeting 14 August 2008

Claudia Mische "Intergrase inhibitor effects on a molecular level" Pathogenesis Program Lab Presentation 28 August 2008

Nabila Seddiki "Identification of human antigen-specific regulatory T cell phenotyping and functional analysis", ASHM 17 September 2008

Nabila Seddiki "Regulatory T cell abnormalities are associated with aberrant CD4+ T-cell responses in patients with immune inflammatory syndrome (IRIS), ASHM 17 September 2008

Nabila Seddiki "T-cell mediated suppression in immune function", UNSW 10 September 2008

Seddiki N, Regulatory T Cell Abnormalities Associated with Abberant CD4= T Cell Responses in HIV+ Patients with Immune Reconstitution Disease (IRD). CEA Centre de l'Energie Atomique Fontenay aux roses France, January 2008

Seddiki N, Regulatory T cell and immuno-suppression in HIV infection. Program Grant Meeting Double Bay 27 February 2008

Sasson S, Regilation and Dysregulation of the interleukin-7/ interleukin-7 receptor system: implications for B-cell oncogenesis Garvan Institute 2008

Kelleher AD, HIV Vaccines catch a cold: Implications of the STEP HIV vaccine trial. AIDS Council of NSW, Sydney 2007.

Zaunders JJ, Analysing the complexity of subsets of CD4 T lymphocytes UNSW statistics seminars 4pm, Friday, 2nd May UNSW

Seddiki N, Human Regulatory T cells in transplantation XXII International Congress of the Transplantation Society Sydney Convention and Exhibition Centre 10 August 2008

AD Kelleher. "State of play in HIV vaccine development and current studies? Arrested development?", Microbicides and HIV Biomedical Prevention Symposium, University of Sydney, 14 July, 2008.

AD Kelleher. "Review of STEP trial: that last step was a doosy!" NCHECR Trial Network Site Coordinator Meeting, Perth, 16 September 2008.

Kelleher AD, 20-minute "minilecture" to introduce a basic science proffered paper session (with an Immunology flavour). ASHM Conference Perth 15 September 2008

Kelleher AD, "State of play in HIV vaccine development and current studies? Arrested development?", Microbicides and HIV Biomedical Prevention Symposium, University of Sydney, 14 July, 2008.

Seddiki Nabila, "Antigen-specific Tregs in a CMV model" UNSW July 2008 – seminar for the centre infectious disease

Swaminathan Sanjay, "Clinical Pharmacology of HIV Drugs" Australian Society for HIV Medicine April 2008

Swaminathan Sanjay, "Immunomodulation" Roche, 9 July 2008

Chris Weatherall "Antibody responses in Primary HIV Infection" St George Hospital Dept of Immunology, Allergy and Infectious Diseases July 2008

Zaunders John, "Persistence of high levels of HIV antigen-specific CD4+ in untreated chronic infection, detected by a novel flow cytometric assay". ASHM Annual Conference, 17 September 2008

Kelleher AD, "Reassessing Vaccine Responses" ASHM Annual Conference, 17 September 2008

Linda Gelgor, "Update on the Australian Long-Term Non-Progressor Cohort" ASHM Annual Conference, September 2008

Koelsch Kersten, "Impact of raltergravir on HIV reservoirs" Garvan December 2008

Clinical research program

Carr A. "Fats, sugar, cardiovascular and renal disease: Changing causes of death and morbidity in the patients on HAART". 11th Bangkok Symposium on HIV Medicine. Organiser: The HIV, Netherlands Australia Thailand (HIVNAT) Research Collaboration, 17th January, 2008. Presentation to 1000 delegates.

Raboud J, Diong C, Carr A, Grinspoon S, Mulligan K, Sutinen J, Cavalcanti R, Walmsley S, Glitazones for Lipoatrophy Meta-analysis Group. A meta-analysis of five randomized, placebo-controlled trials of rosiglitazone for the treatment of HIV-associated lipoatrophy. 17th Annual Canadian Conference on HIV/AIDS Research, April 24-27, 2008

Carr A. "Management of HIV lipodystrophy". Invited presentation. Toronto General Hospital, Toronto, Canada. 27th May, 2008

Carr A. "HIV and cardiovascular disease – Summary of the American Heart Association / US HIV Medicine Association State-of-the-Science meeting". Sydney, June 2008.

Richardson R. "Issues for patients in clinical trial design". Presented at the National HIV Clinical Trials symposium, Perth, Western Australia, September 15, 2008

Blood stem cell and cancer research program

Carlin S, Moore J, Ma D. (2008)CD7+ Haemopoietic Stem Cells Presented at the St Vincent's & Mater Health Sydney Research Symposium

Shen B, Wei A, Tao H, Diwan AD, Ma DDF. (2008) BMP-2 enhances TGF-b3 mediated chondrogenic differentiation of human bone marrow multipotent mesenchymal stromal cells in vitro To be presented at the HAA Annual Scientific Meeting, 19-22 Oct 2008, Perth, Australia

Luterhborrow M, (2008) Acute myeloid leukaemia (AML) as a model to dissect microRNA transcription networks during myelopoiesis. presented at the HSA Annual Scientific Meeting

Cancer research program

Robyn Ward. Targeted drug therapy and their place in the management of breast cancer. Pharmaceutical Medicine and Drug Development Orientation Weekend University of New South Wales, Australia January 2008

Robyn Ward. Genetic disease and cancer 2008 Canberra Forum Service and Science Canberra, Australia April 2008

Robyn Ward Epigenetics and cancer a clinical perspective Department Health and Ageing Canberra, Australia May 2008

Robyn Ward Epimutations and colorectal cancer Lund University Lund, Sweden 17th September 2008

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